Changing Trends in Complications and Mortality Rates Among US Youth and Young Adults With HIV Infection in the Era of Combination Antiretroviral Therapy

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Background. Combination antiretroviral therapy (cART) has resulted in a dramatic decrease in human immunodeficiency virus (HIV)–related opportunistic infections and deaths in US youth, but both continue to occur.

Methods. We estimated the incidence of complications and deaths in IMPAACT P1074, a long-term US-based prospective multicenter cohort study conducted from April 2008 to June 2014. Incidence rates of selected diagnoses and trends over time were compared with those from a previous observational cohort study, P219C (2004–2007). Causes of death and relevant demographic and clinical features were reviewed.

Results. Among 1201 HIV-infected youth in P1074 (87% perinatally infected; mean [standard deviation] age at last chart review, 20.9 [5.4] years), psychiatric and neurodevelopmental disorders, asthma, pneumonia, and genital tract infections were among the most common comorbid conditions. Compared with findings in P219C, conditions with significantly increased incidence included substance or alcohol abuse, latent tuberculosis, diabetes mellitus, atypical mycobacterial infections, vitamin D deficiency or metabolic bone disorders, anxiety disorders, and fractures; the incidence of pneumonia decreased significantly. Twenty-eight deaths occurred, yielding a standardized mortality rate 31.5 times that of the US population. Those who died were older, less likely to be receiving cART, and had lower CD4 cell counts and higher viral loads. Most deaths (86%) were due to HIV-related medical conditions.

Conclusions. Opportunistic infections and deaths are less common among HIV-infected youth in the US in the cART era, but the mortality rate remains elevated. Deaths were associated with poor HIV control and older age. Emerging complications, such as psychiatric, inflammatory, metabolic, and genital tract diseases, need to be addressed.

Keywords. pediatric HIV; mortality; opportunistic infections; psychiatric; pregnancy.

An estimated 40 000 13–24-year-old children and youth in the United States were infected with human immunodeficiency virus (HIV) at the end of 2012 [1]. Introduction of combination antiretroviral therapy (cART) in the mid-1990s decreased the occurrence of opportunistic infections (OIs) in HIV-infected children and youth, with a subsequent decline in the mortality rate in that age group in the United States and Europe [2–8]. However, infectious (including OIs) and noninfectious conditions continue to contribute to the morbidity and mortality risk in this age group [9–11]. With improving access to cART, researchers in Asia [12–14] and Africa [15] are also reporting improved survival of

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HIV-infected children and youth. Treatment of aging youth with HIV in both resource-rich and resource-limited countries has led to the development of chronic and age-related problems, including dyslipidemia [16, 17], insulin resistance and diabetes mellitus [18, 19], decreased bone mineral density [20–22], renal disease [17], and psychosocial problems [23–25].

Longitudinal cohort studies have previously helped identify trends in HIV-associated infectious and noninfectious morbid conditions and deaths [7, 8]. The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network P1074 study is a US-based prospective, multicenter surveillance study of long-term outcomes in HIV-infected children and adolescents. We used data from P1074 to describe current infectious and noninfectious morbid conditions, pregnancy, and mortality rates among HIV-infected youth, in comparison with an earlier US-based cohort study, Pediatric AIDS Clinical Trials Group (PACTG) 219C [2–4, 11].

METHODS

Study Population

Data for this analysis were derived from the IMPAACT P1074 and PACTG 219C (P219C) studies. P219C was conducted between 2000 and 2007 to assess the long-term effects of cART on HIV-infected and HIV-exposed uninfected children in the United States, as described elsewhere [2–4]. To address changes in incidence over the past decade, we focused on the 2358 P219C participants with perinatally and nonperinatally acquired HIV in the study during 2004–2007. IMPAACT P1074 opened on 15 April 2009, after P219C closed, to continue long-term follow-up of those and other HIV-infected subjects. P1074 closed to accrual on 28 June 2013 and to follow-up on 30 June 2014. Of the 1201 P1074 participants, 782 (65%) had been enrolled previously in P219C, and the others had enrolled in IMPAACT interventional studies; age and other characteristics at P1074 entry were generally similar by prior P219C participation status. Institutional review board approval was obtained at all 39 participating clinical centers, and written informed consent was obtained from all participants and/or families, with assent obtained from minors according to local institutional review board guidelines.

Clinical and Laboratory Data

Clinical and laboratory data for the P1074 cohort were obtained from annual medical record reviews and included the 1-year period before study entry. Diagnoses were abstracted if resulting in hospitalization, persisting disability, or death; considered significant based on chronicity, recurrence, or major impact on quality of life; or potentially related to medication or indicative of underlying organ disease. Additional data obtained included pregnancy, height and weight, CD4 lymphocyte counts and HIV RNA viral load (VL) measurements, antiretroviral therapy (ART), and other medications used for >30 days. In P219C, medical history including infectious and noninfectious diagnoses, was recorded at enrollment and at study visits every 3 months thereafter. The HIV VL and CD4 lymphocyte counts were measured at each visit [2, 4].

Outcome Measures

The primary outcomes were occurrences of infectious or noninfectious conditions, pregnancy, and death. We considered incident events, defined as new events occurring between 1 year before study entry and the last chart abstraction. Each condition was counted only once per participant, at its earliest occurrence. Repeated pregnancies were also described. All clinical conditions were classified by the same coding team at the same data management center (Frontier Science Technology and Research Foundation) for P1074 and P219C, based on MedDRA (*Medical Dictionary for Regulatory Activities,* version 17.0) coding; MedDRA is a clinically validated international medical terminology created under the guidance of the International Conference on Harmonization to facilitate safety reporting [26] (see Supplementary Text 1 for further details).

Statistical Analyses

Incidence rates (IRs; per 100 person-years) and exact Poisson 95% confidence intervals (CIs) were calculated for the entire P1074 follow-up period (2008–2014, including the year prior to study entry) and during 2004–2007 for the P219C cohort. Participants with historical or prevalent events were excluded from the relevant risk sets. Subjects without a condition were censored as of their last chart abstraction date or death. We considered pregnancy only among female subjects aged ≥12.5 years, and genital tract infections among male and female subjects aged ≥12.5 years. We used Poisson regression models to evaluate trends in IRs for specific conditions over calendar years and over CD4 cell count strata for the P1074 cohort, and to adjust for age differences when comparing P1074 with P219C. The Poisson models yielded both unadjusted and age-adjusted IR ratios and corresponding 95% CIs [27]. A standardized mortality ratio was calculated comparing the mortality rate of P1074 participants with that of the general US population [28], standardized for age, sex, and race.

Demographic characteristics, HIV disease severity measures, and ART regimens at both entry and at final assessment (time of death or last chart abstraction) were compared between those who died during P1074 and those who survived. cART was defined as use of ≥3 ART drugs from ≥2 drug classes. We used χ^2, Wilcoxon rank sum, and 2-sample *t*-tests to compare characteristics between those who died and survivors, and Cox proportional hazards models to evaluate risk factors for mortality. Sensitivity analyses were conducted, accounting for overlap in subjects participating in P1074 and P219C and restricting to perinatally HIV-infected youth, to assess consistency in results.

Differences were considered statistically significant at $P < .05$ (2 sided). Owing to the exploratory nature of this study, no adjustments were made for multiple testing. All analyses were performed using SAS software (versions 9.2 and 9.4, SAS Institute).

RESULTS

Characteristics of Study Participants

A total of 1201 participants enrolled in P1074 and had ≥1 chart abstraction. Demographic and HIV disease characteristics are summarized in Table 1. The overall study population was 52% female, 58% black non-Hispanic, and 28% Hispanic; the majority (87%) had acquired HIV infection perinatally. The route of transmission for the nonperinatally infected group was primarily via sexual activity (74%), with other routes including blood transfusion or blood contact (14%), and sexual abuse (4%). At the first chart abstraction, participants' mean (standard deviation [SD]) age was 17.4 (5.4) years, their median CD4 cell count was 609 cells/mm^3, and their median VL was 1.88 log copies/mL. Most (85%) were receiving cART, and CD4 and VL measures remained relatively stable during a median follow-up of 3.7 years (Table 1). Among the 2358 P219C youth followed up between 2004 and 2007, their mean (SD) age in 2004 (or at enrollment, if after 2004) was 11.9 (5.0) years, with a median follow-up of 3.0 years. The P219C cohort was 52% female, 58% black, and 26% Hispanic, with 91% having perinatally acquired HIV infection; at start of the 2004–2007 follow-up period, their median CD4 was 720 cells/mm^3, their median VL 2.78 log copies/mL, and 75% were receiving cART.

Incidence of Conditions During P1074

Common incident infectious and noninfectious conditions occurring during P1074 follow-up (Table 2) included genital tract infections (including human papillomavirus [HPV]) and chlamydial infections), psychiatric conditions (particularly mood disorders and anxiety disorders), and neurodevelopmental disorders, especially learning and communication disorders. Asthma and pneumonia were also common. IRs were generally very similar when analysis was restricted to perinatally HIV-infected youth (Supplementary Table 1). First pregnancy occurred in 97 of 512 female subjects (19%); 18 pregnancies were associated with complications (preeclampsia, premature labor or delivery, fetal growth restriction, or fetal death) and 29 concluded with an abortion (elective in 13 and spontaneous in 16). Twenty-four (25%) of these 97 subjects also had ≥1 subsequent pregnancy during P1074. In P219C, first pregnancies occurred in 48 of 792 female subjects (6%) between 2004 and 2007.

Trends in Incidence by Calendar Year and CD4 for P1074

The IR for vitamin D deficiency and metabolic bone disorders in P1074 increased significantly from 2008 to 2014 (Figure 1). In contrast, IRs for asthma, cellulitis, learning and communication disorders, lipodystrophy, neutropenia, and pregnancy significantly decreased during this period. No significant temporal trends during 2008–2014 were observed for other diagnoses.

IRs showed a significantly increasing trend with decreasing entry CD4 levels for genital tract infections overall and for several specific genital infections, nongenital infectious conditions (all those shown in Table 2, except latent tuberculosis), mood disorders, iron deficiency anemia, hypertension, and wasting or failure to thrive (Supplementary Table 2). There was a decreasing trend in IRs with decreasing CD4 levels for learning and communication disorders.

Difference in IRs Between P219C and P1074

Numerous conditions had higher incidences in P1074 than in P219C, with IRs for substance or alcohol abuse, latent tuberculosis, diabetes mellitus, atypical mycobacterial infections, vitamin D deficiency or metabolic bone disorders, anxiety disorders, and fractures all ≥5-fold in P1074 (Table 3). The IR was significantly lower in P1074 than in P219C only for pneumonia. After adjustment for differences in age distributions between the 2 study populations, IRs remained significantly lower in P1074 than in P219C for pneumonia and significantly higher for all psychiatric and neurodevelopmental conditions shown in Table 3, as well as for all other conditions with the exception of pregnancy, genital tract infections, atypical mycobacterial infection, esophageal or pulmonary candidiasis, hepatitis, diabetes mellitus, and hypertension. IRs did not differ significantly between the 2 studies for other conditions shown in Table 2. Sensitivity analyses accounting for the overlap of subjects participating in P1074 and P219C yielded almost identical results (data not shown).

Mortality Rate in P1074

There were 28 deaths during P1074 follow-up (mortality rate, 0.66/100 person-years), including 3, 3, 14, 7, and 1 death in 2010, 2011, 2012, 2013, and 2014, respectively (trend $P = .24$). The standardized mortality ratio compared with the general US population was 31.5 (95% CI, 19.9–43.2). The mean (SD) age at death was 23.5 (3.3) years, compared with 17.8 (3.5) years in P219C; however, the mortality rate in P1074 was very similar to the rate of 0.63/100 person-years observed from 2004 to 2006 in P219C. Primary causes of death were characterized as unspecified pneumonia in 5 deaths; advanced AIDS and progressive multifocal leukoencephalopathy in 4 deaths each; sepsis in 3 deaths; *Pneumocystis jiroveci* pneumonia, lymphoma, and suicide in 2 deaths each; and disseminated *Mycobacterium avium intracellulare* infection, HIV-related cardiomyopathy, homicide, motor vehicle accident, hepatic failure, and tuberculosis meningitis in 1 death each (Supplementary Table 3). Most deaths (86%) were directly linked to infection or other

Table 1. Demographic and Human Immunodeficiency Virus Disease Characteristics, Overall and by Death Status, of P1074 Participants, Enrolled and Followed Up at 39 Sites in the United States, 2008–2014

Characteristic[a]	Total (N = 1201)	Patient Status		*P* Value[b]
		Alive (n = 1173)	Died (n = 28)	
Female sex, No. (%)	623 (52)	604 (52)	19 (68)	.09
Age (mean), SD, y				
First chart review	17.4 (5.4)	17.3 (5.4)	21.3 (3.0)	<.001
Last chart review	20.9 (5.4)	20.8 (5.4)	23.5 (3.3)	.01
Duration of study follow-up, median (IQR), y	3.7 (2.9–4.4)	3.7 (3.0–4.4)	2.3 (1.2–3.0)	<.001
Race/ethnicity, No. (%)				
White non-Hispanic	136 (11)	133 (11)	3 (11)	.98
Black non-Hispanic	698 (58)	681 (58)	17 (61)	
Hispanic	331 (28)	324 (28)	7 (25)	
Other or >1 race	31 (3)	30 (3)	1 (4)	
Perinatally HIV infected, No. (%)	1040 (87)	1015 (87)	25 (89)	.71
BMI *z* score, mean (SD)				
First chart review	0.41 (1.10)	0.41 (1.08)	0.22 (1.53)	.72
Last chart review	0.39 (1.15)	0.40 (1.13)	−0.01 (1.76)	.43
Change during follow-up	−0.02 (0.49)	−0.01 (0.48)	−0.24 (0.78)	.61
HIV disease severity measures				
CD4 cell count, median (IQR), cells/mm^3				
First chart review	609 (399–882)	618 (412–886)	28 (14–338)	<.001
Last chart review	580 (325–822)	593 (350–828)	20 (7–271)	<.001
CD4 cell count ≤200 cells/mm^3, No. (%)				
First chart review	123 (10)	104 (9)	19 (68)	<.001
Last chart review	171 (14)	151 (13)	20 (71)	<.001
CD4 cell count <200 cells/mm^3 during follow-up, mean (SD), %[c]	12.1 (28.2)	10.7 (26.3)	70.7 (43.1)	<.001
CD4 cell count <350 cells/mm^3 during follow-up, mean (SD), %[c]	22.8 (35.8)	21.5 (34.7)	76.0 (39.2)	<.001
HIV-1 RNA VL, median (IQR), log copies/mL				
First chart review	1.88 (1.68–3.30)	1.88 (1.68–3.21)	4.59 (2.69–5.14)	<.001
Last chart review	1.68 (1.30–3.47)	1.68 (1.30–3.37)	4.49 (2.85–5.40)	<.001
VL >1000 log copies/mL during follow-up, mean (SD), %[c]	30.9 (33.4)	29.9 (32.8)	75.1 (28.4)	<.001
ART regimen, No. (%)				
First chart review				.88
cART	1017 (85)	993 (85)	24 (86)	. . .
Non-cART ART	70 (6)	68 (6)	2 (7)	. . .
No ART	114 (10)	112 (10)	2 (7)	. . .
Last chart review				.02
cART	999 (83)	980 (84)	19 (68)	. . .
Non-cART ART	83 (7)	81 (7)	2 (7)	. . .
No ART	119 (10)	112 (10)	7 (25)	. . .

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; cART, combination ART (≥3 antiretroviral drugs from ≥2 drug classes); HIV, human immunodeficiency virus; IQR, interquartile range (25th–75th percentiles); SD, standard deviation; VL, viral load.

[a] Measures were unavailable for some characteristics, including race/ethnicity (n = 5), perinatal infection status (n = 5), BMI *z* score at first (n = 117) and last (n = 115) chart review, CD4 cell count at first (n = 4) and last (n = 2) chart review, and ART regimen at first (n = 22) and last (n = 11) chart review. Percentages are calculated among those with available information.

[b] *P* values comparing P1074 subjects who died with those who survived, using χ^2 test for categorical measures and Wilcoxon rank sum test for continuous measures.

[c] Mean percentage of measurements within an individual meeting the cutoff value.

HIV-associated medical conditions. Table 1 presents the characteristics of P1074 subjects who died compared with those of survivors. Subjects who died did not differ from survivors in sociodemographic background but were older and had lower CD4 cell counts and higher VLs. The percentages receiving cART at the first chart review were similar in the 2 groups,

Table 2. Common Incident Conditions in P1074 Participants and Their Relationships to CD4 Levels at Study Entry

Condition[a]	Participants at Risk, No.	Events, No.	Total Person-Years	IR/100 Person-Years	*P* Value[b]
Broad categories of conditions					
Genital tract infections	961	128	3760	3.405	.008
Psychiatric disorders	1061	124	4492	2.760	.10
Neurodevelopmental disorders	816	41	3520	1.165	.054
Specific conditions					
Infectious conditions					
Pneumonia	811	41	3508	1.169	<.001
Zoster	1042	35	4599	0.761	<.001
Oropharyngeal candidiasis	840	27	3732	0.723	<.001
Nongenital herpes simplex virus	1064	31	4724	0.656	<.001
Cellulitis	1082	24	4801	0.500	.002
Esophageal or pulmonary candidiasis	1160	23	5185	0.444	<.001
Latent tuberculosis	1196	21	5345	0.393	.52
Genital tract infections					
HPV	1024	79	4155	1.901	.006
Organism not specified	1035	48	4286	1.120	.003
Chlamydia	1064	36	4462	0.807	.66
Anogenital herpes simplex virus	1069	24	4502	0.533	<.001
Candidiasis	1064	19	4498	0.422	.18
Syphilis	1080	17	4571	0.372	.19
Gonorrhea	1072	16	4546	0.352	.25
Trichomoniasis	1072	16	4540	0.352	.33
Pregnancy	512	97	1896	5.117	.32
Psychiatric and neurodevelopmental disorders					
Mood disorders	1092	102	4696	2.172	.04
Learning and communication disorders	962	44	4170	1.055	.002[b]
Anxiety disorders	1172	38	5195	0.731	.80
Substance or alcohol abuse	1186	24	5290	0.454	.53
Trauma and stress-related disorders	1189	16	5318	0.301	.57
Other conditions					
Asthma	884	47	3844	1.223	.78
Iron deficiency anemia	1145	39	5076	0.768	<.001
Hypertension	1156	34	5147	0.661	.003
Eczema	1019	25	4501	0.555	.74
Vitamin D deficiency/metabolic bone disorders	1179	25	5281	0.473	.29
Renal disease	1162	24	5186	0.463	.54
Gastroesophageal reflux disease	1161	19	5195	0.366	.07
Lipodystrophy	1140	19	5089	0.373	.20
Neutropenia	1044	16	4644	0.345	.68
Dyslipidemia	1174	18	5242	0.343	.06
Wasting/failure to thrive	1031	15	4616	0.325	<.001
Fractures	1183	17	5311	0.320	.75
Hepatitis, nonspecific	1153	16	5151	0.311	.06

Abbreviations: HPV, human papillomavirus; IRs, incidence rates.

[a] IRs for all infectious and noninfectious conditions were calculated, and conditions with IRs >0.3 per 100 person years are included; conditions are defined in greater detail in Supplementary Text 1.

[b] *P* value for trend test computed from Poisson regression model comparing IRs across increasing baseline CD4 cell count categories of 0–199, 200–349, 350–499, and ≥500 cells/mm^3; all significant increases reflect higher IRs with lower CD4 cell counts with the exception of learning and communication disorders. (Additional details, including IRs by baseline CD4 cell count, are provided in Supplementary Table 2).

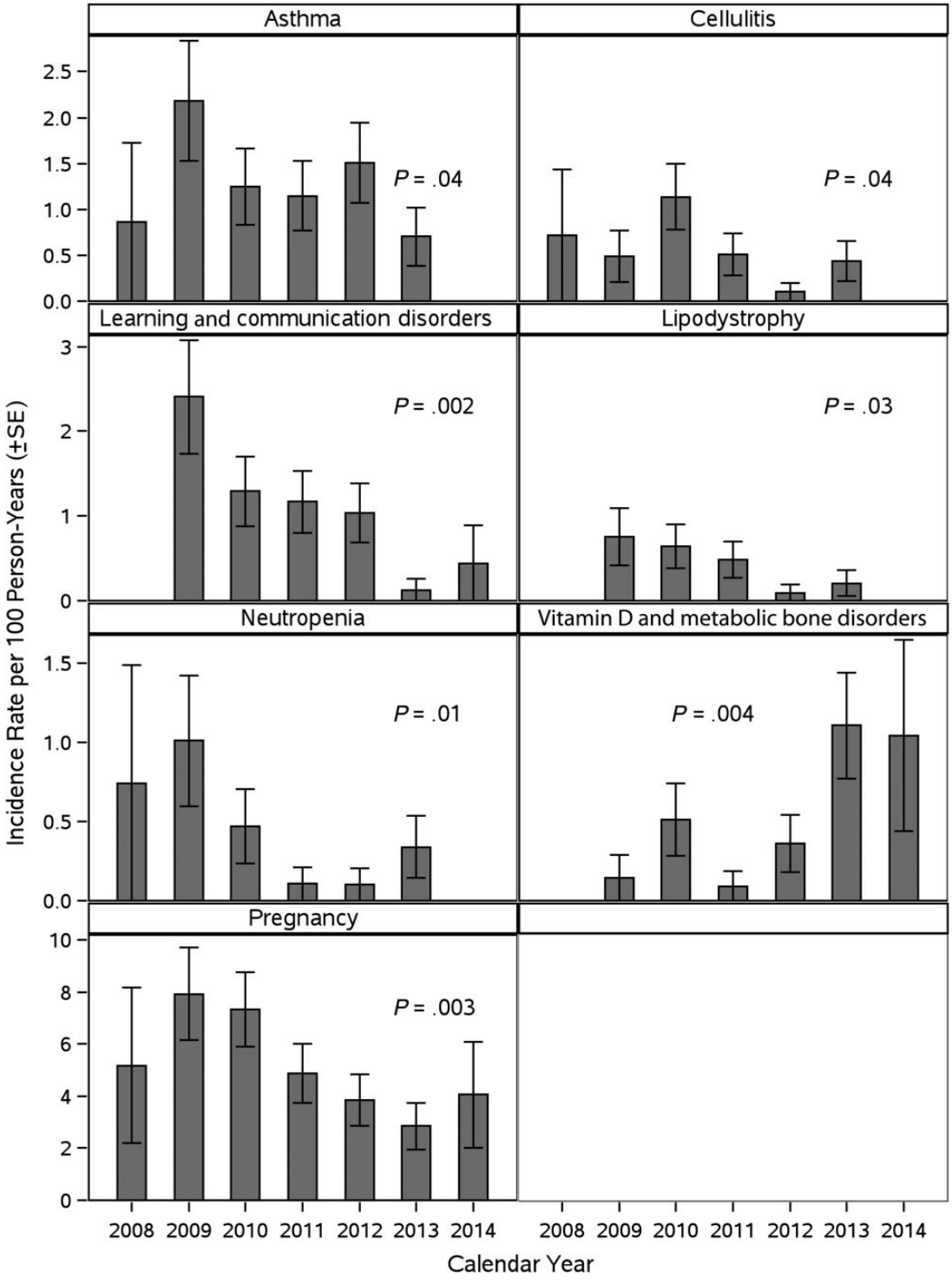

Figure 1. Significant temporal trends in diagnoses and pregnancy among P1074 participants between 2008 and 2014. Trends are based on Poisson regression models with number of events in a given year as the outcome, calendar year as a linear predictor, and offset term equal to log person-years of follow-up during that calendar year. Abbreviation: SE, standard error.

but a higher percentage of those who died were not receiving cART at the time of their death compared with survivors at their last review. (Table 1 and Supplementary Table 3).

In multivariable Cox proportional hazards models, the CD4 cell count at study entry was the strongest predictor of mortality risk, with a 22% decrease in risk of death for each 50 CD4 cell/mm^3

Table 3. Conditions With Significant Differences in Incidence Rates Between P1074 Participants in 2008–2014 and P219C Participants in 2004–2007[a]

	P219C (2004–2007)				P1074 (2008–2014)				P1074 vs P219C	
Category[a]	Participants at Risk, No.	Events, No.	Total Person-Years	Rate/100 Person-Years	Participants at Risk, No.	Events, No.	Total Person-Years	Rate/100 Person-Years	IRR (95% CI)	IRR, Age-Adjusted[b] (95% CI)
Significant Increases in IRs										
Infectious conditions										
Latent tuberculosis	2350	2	6443	0.031	1196	21	5345	0.393	12.66 (2.97–53.98)	12.62 (2.80–56.93)
Atypical mycobacterial infection	2325	1	6375	0.016	1183	8	5326	0.150	9.58 (1.20–76.56)	5.19 (.60–44.91)
Esophageal or pulmonary candidiasis	2279	7	6252	0.112	1160	23	5185	0.444	3.96 (1.70–9.23)	1.97 (.79–4.90)
Genital tract infections										
Anogenital herpes	1607	6	3597	0.167	1069	24	4502	0.533	3.20 (1.31–7.82)	1.54 (.62–3.87)
HPV infection or disease	1563	38	3463	1.097	1024	79	4155	1.901	1.73 (1.18–2.55)	0.94 (.62–1.41)
Pregnancy	792	48	1771	2.710	512	97	1896	5.117	1.89 (1.34–2.67)	1.31 (.91–1.88)
Psychiatric and neurodevelopmental conditions										
Substance abuse or alcohol abuse	2346	1	6441	0.016	1186	24	5290	0.454	29.22 (3.95–216.00)	10.72 (1.40–81.89)
Anxiety disorders	2347	7	6435	0.109	1172	38	5195	0.731	6.72 (3.00–15.06)	4.36 (1.83–10.42)
Trauma/stress-related disorders	2351	4	6445	0.062	1189	16	5318	0.301	4.85 (1.62–14.50)	4.27 (1.31–13.96)
Psychiatric disorders (any)	2260	58	6133	0.946	1061	124	4492	2.760	2.92 (2.14–3.99)	1.95 (1.39–2.74)
Disruptive/impulse control disorders	2343	5	6422	0.078	1188	12	5318	0.226	2.90 (1.02–8.23)	4.63 (1.59–13.48)
Mood disorders	2280	47	6196	0.759	1092	102	4696	2.172	2.86 (2.03–4.05)	1.74 (1.20–2.53)
Learning and communication disorders	2046	26	5547	0.469	962	44	4170	1.055	2.25 (1.39–3.66)	4.66 (2.83–7.66)
Other conditions										
Diabetes mellitus	2353	1	6454	0.015	1198	9	5381	0.167	10.79 (1.37–85.21)	4.94 (.57–42.70)
Vitamin D deficiency/metabolic bone disorders	2352	4	6444	0.062	1179	25	5281	0.473	7.63 (2.65–21.91)	6.56 (2.16–19.97)
Fractures	2343	4	6422	0.062	1183	17	5311	0.320	5.14 (1.73–15.27)	6.43 (2.06–20.11)
Appendicitis	2338	3	6407	0.047	1192	12	5349	0.224	4.79 (1.35–16.98)	4.55 (1.20–17.19)
Iron deficiency anemia	2305	14	6293	0.222	1145	39	5076	0.768	3.45 (1.88–6.36)	3.11 (1.60–6.04)
Gastroesophageal reflux disease	2313	7	6329	0.111	1161	19	5195	0.366	3.31 (1.39–7.87)	2.62 (1.00–6.84)
Hepatitis, nonspecific	2298	6	6308	0.095	1153	16	5151	0.311	3.27 (1.28–8.35)	2.54 (.96–6.77)
Eczema	2127	11	5811	0.189	1019	25	4501	0.555	2.93 (1.44–5.96)	4.22 (1.95–9.12)
Dyslipidemia	2349	8	6429	0.124	1174	18	5242	0.343	2.76 (1.20–6.35)	3.40 (1.37–8.42)
Hypertension	2328	16	6372	0.251	1156	34	5147	0.661	2.63 (1.45–4.77)	1.38 (.73–2.62)
Asthma	1935	27	5250	0.514	884	47	3844	1.223	2.38 (1.48–3.82)	3.07 (1.84–5.13)

Table 3 continued.

Category[a]	P219C (2004–2007)				P1074 (2008–2014)				P1074 vs P219C	
	Participants at Risk, No.	Events, No.	Total Person-Years	Rate/100 Person-Years	Participants at Risk, No.	Events, No.	Total Person-Years	Rate/100 Person-Years	IRR (95% CI)	IRR, Age-Adjusted[b] (95% CI)
Hypothyroidism	2356	0	6461	0.000	1191	8	5352	0.149	NC[c]	NC[c]
Hyperthyroidism	2358	0	6467	0.000	1200	5	5404	0.093	NC[c]	NC[c]
Significant decreases in IRs										
Pneumonia	1571	73	4201	1.738	811	41	3508	1.169	0.67 (.46–.99)	0.62 (.41–.95)

Abbreviations: CI, confidence interval; HPV, human papillomavirus; IRs, incidence rates; IRRs, IR ratios; NC, not calculated.

[a] Conditions are defined in greater detail in Supplementary Text 1.

[b] Age-adjusted models fit using Poisson regression models with effects for study and age group (<10, 10–14, 14–18, or ≥18 years).

[c] Not calculated because there were no events in the P219C study.

increase (adjusted hazard ratio, 0.78), and older age and higher VL at study entry were marginally associated with higher risk of death (Table 4). Sensitivity analyses restricted to youth with perinatal HIV infection (Supplementary Table 4), and exclusion of deaths considered unrelated to HIV disease yielded similar results.

DISCUSSION

The P1074 study allowed us to compare the incidences of complications of HIV infection, pregnancy, and death in a contemporary US cohort of HIV-infected youth with those in a younger cohort during an earlier period in the cART era [2–4]. Infected youth and young adults, including many survivors of perinatally acquired HIV infection, are now dealing with problems associated with chronic HIV infection and long-term complications of cART.

In the pre-cART era, the 5 most common OIs were serious bacterial infections, zoster, disseminated *M. avium intracellulare*, *P. jiroveci* pneumonia, and candidiasis, all with IRs >1 per 100 person-years [29]. In the cART era, IRs for *P. jiroveci* pneumonia, *M. avium intracellulare,* and other infectious conditions, such as lymphoid interstitial pneumonia, systemic fungal infection, cytomegalovirus retinitis, and tuberculosis disease, decreased to <0.50 per 100 person-years [3]. Although pneumonia was significantly less frequent in the P1074 cohort than in the P219C cohort, this and other infections, such as zoster continue to remain a significant disease burden. Importantly, we found an increase in the incidence of other infections, including latent tuberculosis, esophageal or pulmonary candidiasis, and atypical mycobacterial infections. The increased incidence of latent tuberculosis may reflect increased testing. Overall, these findings indicate that certain infections continue to occur in the era of widespread cART availability.

Among infectious complications, we observed particularly high rates of genital tract infections. These infections contribute to direct morbid effects and can increase HIV transmission [30]. Compared with the P219C cohort, P1074 participants had increased rates of genital HPV infection and anogenital herpes, as well as substantial rates of syphilis, chlamydia, gonorrhea, trichomoniasis, and yeast infections. Although these higher rates largely reflected an older age distribution in the P1074 population, they raise concern for development of cervical dysplasia in women, penile squamous cell carcinoma in men, and anal squamous cell carcinoma in women and in men who have sex with men [30]. Education about risk reduction strategies, including safe sex; administration of HPV vaccine; and cervical and anal screening for dysplasia are important preventive strategies for HIV-infected adolescents and young adults.

Chronic HIV infection and long-term cART present new challenges to HIV-infected youth. For example, we found

Table 4. Association of Demographic and Health Characteristics at Study Entry With Mortality Risk in P1074 Subjects

	Unadjusted Models			Adjusted Model[b] (n = 1197)	
Characteristic[a]	Subjects, No.	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age at first chart review	1201	1.18 (1.10–1.28)	<.001	1.09 (.98–1.22)	.10
CD4 cell count at first chart review (for each 50-cell/mm^3 increase)	1197	0.71 (.64–.79)	<.001	0.78 (.68–.88)	<.001
HIV RNA at first chart review (for each log_{10} copies/mL increase)	1201	3.02 (2.18–4.17)	<.001	1.45 (.99–2.13)	.054
Sex (female vs male)	1201	2.02 (.91–4.46)	.08	. . .	. . .
BMI *z* score at first chart review	1084	0.86 (.61–1.22)	.40	. . .	. . .
Black race	1201	1.10 (.51–2.38)	.81	. . .	. . .
Hispanic ethnicity	1201	0.85 (.36–2.00)	.71	. . .	. . .
Receiving cART at first chart review	1179	0.82 (.28–2.37)	.71	. . .	. . .
Perinatal HIV acquisition (yes vs no)	1196	1.15 (.35–3.80)	.82	. . .	. . .

Abbreviations: BMI, body mass index; cART, combination antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio.

[a] Characteristics were the latest available measurements prior to or on the date of the first chart abstraction.

[b] Adjusted model includes only those covariates with estimates provided (age, CD4 cell count, HIV RNA).

higher rates of dyslipidemia, asthma, eczema, hypertension, diabetes mellitus, and thyroid hormone abnormalities in P1074 than during the P219C period. Siberry et al [31] reported higher rates of asthma and atopic dermatitis in HIV-infected children receiving cART than in HIV-exposed children, suggesting immune dysregulation. Metabolic disorders, such as insulin resistance, diabetes mellitus, lipodystrophy, hyperlipidemia, and hypertension, probably have multiple causes, including effects of HIV and cART [32], inflammation, hypercoagulation, endothelial dysfunction [18], and genetic polymorphisms [33].

An emerging concern with chronic HIV infection and long-term cART is poor bone health [20]. We observed higher rates of vitamin D deficiency or metabolic bone disorders and fractures in P1074 than in P219C and increasing rates over time of vitamin D deficiency during P1074. These higher rates persisted after adjustment for the older age of P1074 participants. Increased osteoclast activity due to immune activation and cytokine release can lead to vitamin D deficiency and bone loss [20, 34]. ART regimens containing protease inhibitors and tenofovir may adversely affect bone mineral health [35], and tenofovir and efavirenz can contribute to vitamin D deficiency [34]. Additional causes of poor bone health and fractures include low weight, hypogonadism, hepatitis C virus infection, glucocorticoid use, and substance use. Although routine monitoring for bone loss in HIV-infected youth is not currently recommended, adequate nutrition, including sufficient calcium and vitamin D intake, exercise, and avoidance of substance abuse, may contribute to good bone health.

Adding to challenges facing HIV-infected youth are high rates of psychiatric and neurodevelopmental problems, which not only directly contribute to morbid conditions but also have secondary consequences such as medication nonadherence, risk-taking behavior, and increased HIV transmission. The mental health and neurodevelopmental conditions with the largest increases from P219C to P1074 are substance or alcohol abuse, anxiety disorders, trauma or stress-related disorders, impulse control and mood disorders, and learning and communication disorders. Previous studies showed high rates of mental health diagnoses, affecting as many as 30%–70% of youth with perinatally acquired HIV infection [36, 37]. Multiple biological and environmental risk factors for development of mental health problems occur in aging children with perinatally acquired HIV [36, 37]. A decreasing trend in IRs with decreasing CD4 levels for learning and communication disorders may reflect increased ascertainment among healthier youth. The 2 suicides in our cohort underscore the importance of recognizing depression and providing timely intervention. Strategies such as incorporating mental health assessments into routine health care, early linkage to mental health professionals, and cognitive behavioral treatment, together with structured medication algorithms, are important interventions that warrant further study [36, 38].

A higher rate of pregnancy was observed in P1074 than in P219C, as expected for a cohort reaching child-bearing age. Compared with the US population, P1074 pregnancy rates were lower for female subjects aged >20 years (61.3 vs 163.0 per 1000 women), similar for those aged 15–19 years (65.8 vs 69.8 per 1000), but higher for those aged <15 years (19.5 vs 1.4 per 1000) [39]. The frequent occurrence of pregnancy complications points to the need for early linkage to prenatal care.

The majority of subjects who died had infectious and other HIV-related conditions at the time of death, similar to previous findings in deaths among HIV-infected children [2, 5]. Although subjects who died were older in P1074 than in P219C, mortality rates in the 2 studies were similar, >30 times that in

the general population. Subjects who died had low CD4 cell counts, higher VLs, and lower usage of cART than survivors, presumably owing to lack of engagement in care, poor adherence to therapy, and/or limited treatment options [9, 40].

Strengths of our study include participation of a large number of experienced academic institutions and a 6-year follow-up period in P1074. Limitations include variability among sites in reporting significant diagnoses, lack of information about medication adherence, and a high proportion of subjects with perinatal HIV infection, which might limit generalizability to behaviorally infected populations. The frequency of screening for certain diagnoses (eg, tuberculosis, dyslipidemia, vitamin D deficiency, and genital tract infections) may have changed over time. Although a substantial proportion of the P219C and P1074 study populations overlapped, comparisons accounting for this overlap yielded almost identical results. In addition, although the 2 cohorts had different age profiles, most differences in IRs between P1074 and P219C persisted after adjustment for age. Furthermore, conditions that increase in incidence with increasing age require greater attention with the aging of the perinatally infected population.

HIV-associated OIs characteristic of earlier periods in the HIV epidemic have become uncommon in HIV-infected youth. Nevertheless, infections continue to occur and contribute to morbidity and mortality rates. Additional morbid conditions, including metabolic abnormalities, sexually transmitted infections, and psychiatric and neurodevelopmental disorders, are becoming more common and may reflect aging, chronic HIV infection, cART-related toxic effects, and chronic inflammation. Despite advances in cART, most deaths remain due to HIV-related conditions associated with virologic failure and immune suppression.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. MedDRA, the *Medical Dictionary for Regulatory Activities* terminology [26], is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

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