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# Higher Hospitalization Rates in Children Born HIV-exposed Uninfected in British Columbia, Canada, Between 1990 and 2012

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**Background:** Compared with children who are HIV-unexposed and uninfected (CHUU), children who are HIV-exposed and uninfected (CHEU) experience more clinical complications. We investigated hospitalizations among CHEU by antenatal antiretroviral therapy (ART) exposure, in British Columbia, Canada.

**Methods:** This retrospective controlled cohort study used administrative health data from 1990 to 2012. CHEU and CHUU were matched 1:3 for age, sex and maternal geographical area of residence. We determined adjusted odds ratios (aORs) via conditional logistic regression, adjusting for maternal risk factors.

**Results:** A total of 446 CHEU and 1333 CHUU were included. Compared with CHUU, more CHEU experienced one or more lifetime hospitalization (47.3% vs. 29.8%), one or more neonatal hospitalization (40.4% vs. 27.6%), and any intensive care unit admission (28.5% vs. 9.2%). In adjusted analyses, CHEU experienced higher odds of any lifetime hospitalization (aOR 2.30, 95% confidence interval 1.81–2.91) and neonatal hospitalization (aOR 2.14, 95% confidence interval 1.68–2.73), compared with CHUU. There was, however, no difference in infection-related hospitalizations (9.0% vs. 7.5%), which were primarily respiratory tract infections among both CHEU and CHUU. CHEU whose mothers-initiated ART preconception showed lower odds of infection-related hospitalizations than children whose mothers initiated ART during pregnancy or received no ART.

**Conclusions:** CHEU experienced increased odds of hospitalization relative to CHUU. A substantial number of CHEU hospitalizations occurred within the neonatal period and were ICU admissions. Initiating ART preconception may reduce the risk of infection-related hospitalizations. These findings reinforce the benefit of ART in pregnancy and the need for ongoing pediatric care to reduce hospitalizations.

**Key Words:** HIV-exposed uninfected, children who are HIV-exposed and uninfected, hospitalizations, maternal antiretroviral therapy, maternal HIV

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In the era of combination antiretroviral therapy (ART) for women living with HIV (WLWH), global vertical transmission rates have been substantially reduced, and there is a growing population of

children who are HIV-exposed but uninfected (CHEU).<sup>1</sup> Globally, there are an estimated 14.8 million CHEU, the majority of whom live in sub-Saharan Africa.<sup>2</sup> In Canada, between 200 and 250 HIV-exposed children are born every year, and the current rate of vertical transmission remains low at <1%.<sup>3,4</sup>

Although they experience fewer adverse outcomes than children who do acquire HIV perinatally, there is growing evidence that CHEU are at increased risk of complications compared with their HIV-unexposed and uninfected (CHUU) peers born to women without HIV. In low-, middle- and high-income settings, CHEU have been reported to experience a higher incidence of hospitalizations, infections and worse clinical outcomes compared with CHUU.<sup>5–13</sup>

The majority of infants born to WLWH are exposed to maternal ART antenatally,<sup>14,15</sup> and because ART agents may cross the placenta,<sup>16,17</sup> concerns have been raised about possible long-term effects in these children. We previously showed an increased risk of neurodevelopmental disease and preterm birth in CHEU born in British Columbia, Canada.<sup>18,19</sup> The risk of hospitalization and infections among CHEU, and the effects of antenatal exposure to ART and substances, has not been established in a Canadian setting, where access to ART and healthcare is high and infant mortality low.<sup>20</sup> However, a recent prospective study in Belgium reported a protective effect on infant hospitalizations and infections from maternal ART initiation preconception.<sup>8</sup> The purpose of our retrospective study was to assess hospitalization and infection outcomes among CHEU born in BC, while considering antenatal HIV and ART exposures. We hypothesized that CHEU would experience more hospitalizations in the early years of life compared with CHUU, and that this difference may be mediated by maternal ART and substance use.

## METHODS

### Study Design

This retrospective matched cohort study included all CHEU born in BC to WLWH between January 1, 1990, and December 31, 2012, with personal health numbers on record. CHEU were identified from Oak Tree Clinic, the provincial referral center for WLWH in BC and their children. Each CHEU was matched to three CHUU on age, sex and forward sortation area (first 3 digits of postal code). This study was approved by the Children's & Women's Health Centre of British Columbia Research Ethics Board (CWREB, H10-00992).

### Data Sources

Provincial administrative datasets were obtained from Population Data BC, and included data from the BC Ministry of Health (Medical Services Plan),<sup>21</sup> Perinatal Services BC,<sup>22</sup> BC Vital Statistics Agency<sup>23</sup> and medical charts in the Canadian Perinatal HIV Surveillance Program from BC Women's Hospital, Vancouver, BC.<sup>24</sup> Datasets were merged to create 2 cohorts for analysis. The first full cohort (cohort 1) included all CHEU and CHUU born between 1990 and 2012. The second cohort (cohort 2) included

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a subset of all CHEU and CHUU, born between April 2000 and December 2012 and for whom data on maternal substance use in pregnancy, collected only after April 2000, were available.

CHEU were classified based on HIV testing done as per Canadian pediatric guidelines whereby infants exposed to HIV are tested for HIV RNA at birth, 4 weeks, and 3–4 months of age. Two negative tests after 4 weeks of age and at least 4 weeks after the end of prophylactic ART exclude HIV infection. An additional confirmatory enzyme immunoassay test after 18 months of age is performed to document seroreversion after maternal antibody clearance.<sup>25</sup>

### Study Variables

The primary outcome of interest was one or more lifetime hospitalization, excluding those immediately related to delivery events, specifically 630–676.9, 760–779.9 and V30–V39.2 under the International Classification of Diseases, Ninth Revision (ICD-9), and O00–O99, P00–P96 and Z30–Z39 under ICD-10<sup>26,27</sup> (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/E561>). Readmission or transfer to a higher level of care was considered as a separate hospitalization.

Neonatal hospitalization was defined as any hospitalization between days of life 1–28. Postneonatal first-year hospitalization was defined as any hospitalization between days of life 29 and 365, to identify hospitalizations not related to neonatal conditions. Infection-related hospitalizations included those with a primary diagnosis of an infectious cause according to ICD-9 and ICD-10 codes, such as respiratory or urinary tract infections (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/E561>). These outcomes, as well as admission to the intensive care unit (ICU), were classified as a binary outcome. As children may have had more than one hospitalization, the sum of hospitalizations exceeds the total number of children within a cohort. The number of hospitalizations was defined as the total number of admissions for one child, while total hospitalization days was the sum of all days of admissions for a given child. These variables were classified as count variables.

From April 1, 2000, to March 31, 2008, maternal substance use during pregnancy was defined as documentation by a healthcare provider of prescription, nonprescription, or illicit drug use by the mother as a risk factor in their pregnancy. From April 1, 2008, to December 31, 2012, maternal substance use was defined as any of the following: heroin/opioids, cocaine, methadone, solvents or marijuana at any point during the pregnancy, in addition to prescription, “other,” or unknown drugs documented as a risk to the pregnancy. Maternal smoking (tobacco) was defined as any smoking during the pregnancy.

The timing of maternal ART was based on the gestational age at which the regimen was started in pregnancy and was classified as “before conception” when coded as zero in the database. CHEU exposure to maternal ART was categorized as “initiated ART before pregnancy and continued through pregnancy,” “initiated during pregnancy” or “no antenatal ART exposure.”

### Statistical Analysis

The proportion of CHEU and CHUU with each hospitalization outcome was compared using  $\chi^2$  tests. The number and length of admissions were compared using Wilcoxon rank-sum tests. Associations between CHEU and CHUU, hospitalization outcomes, and timing of ART initiation were estimated using odds ratios (ORs) for binary variables and relative rates (RRs) for count variables. Multivariable conditional logistic and negative binomial regressions were performed to adjust for preterm birth, maternal smoking and maternal substance use. Statistical analysis was performed using SAS 9.4 (Cary, NC).

## RESULTS

### Cohort 1: 1990–2012

Cohort 1 is the full cohort and includes all 446 CHEU and 1333 CHUU born from 1990 to 2012. CHEU were more likely to be born preterm compared with CHUU (19.1% vs. 7.1%) (Table 1). A significantly greater proportion of CHEU experienced  $\geq 1$  hospitalizations (47.3% vs. 29.8%),  $\geq 1$  neonatal hospitalizations (40.4% vs. 27.6%) and any ICU admission (28.5% vs. 9.2%), compared with CHUU. The proportions of CHEU versus CHUU experiencing  $\geq 1$  postneonatal first-year hospitalizations (10.8% vs. 8.0%) and infection-related hospitalizations (9.0% vs. 7.5%) were relatively small and not significant between the 2 groups. CHEU experienced more ICU admissions related to respiratory tract infections than CHUU (12.6% vs. 9.0%), but this difference was not significant. The most prevalent ICU diagnosis among CHEU was neonatal abstinence syndrome, while that among CHUU was dental caries and asthma.

There were significant associations between antenatal HIV exposure and hospitalization outcomes (Table 2). After adjusting for preterm birth, compared with CHUU, CHEU had significantly higher odds of having  $\geq 1$  lifetime hospitalization (adjusted OR [aOR] 2.30, 95% confidence interval [CI] 1.81–2.91) and  $\geq 1$  neonatal hospitalization (aOR 2.14, 95% CI 1.68–2.73). In particular, CHEU had 3.38 times the adjusted OR (95% CI 2.38–4.79) of ICU admission. Although CHEU experienced significantly more hospitalization days (adjusted RR [aRR] 2.10, 95% CI 1.87–2.36) than CHUU, the number of hospitalizations per child did not differ significantly (Table 3).

### Cohort 2: 2000–2012

The second cohort included the subset of CHEU and CHUU, born between April 2000 and December 2012, for whom information on maternal substance use was available. A significantly higher proportion of CHEU was exposed antenatally to maternal smoking and/or substance use compared with CHUU (Table 1). In this cohort, a greater proportion of CHEU experienced  $\geq 1$  lifetime hospitalization (48.6% vs. 24.4%), neonatal hospitalization (47.0% vs. 23.0%), postneonatal first-year hospitalization (12.6% vs. 6.6%) and ICU admissions (27.7% vs. 9.7%).

The association between antenatal HIV exposure and having  $\geq 1$  lifetime hospitalization (aOR 3.26, 95% CI 2.23–4.79) was strengthened in this cohort, as were the odds of neonatal hospitalization (aOR 3.11, 95% CI 2.12–4.57). Similar to the first cohort, the odd of infection-related hospitalizations was not significantly different between CHEU and CHUU (Table 2). Again, CHEU experienced more hospitalization days (aRR 1.74, 95% CI 1.49–2.03), but their rate of hospitalization did not differ (aRR 0.96, 95% CI 0.84–1.10), compared with CHUU (Table 3).

### Timing of Maternal ART Initiation

In the full cohort from 1990 to 2000, regardless of the timing of ART initiation, CHEU antenatally exposed to ART had significantly increased odds of  $\geq 1$  lifetime hospitalization, neonatal hospitalization and ICU admissions compared with CHUU (Table 4). CHEU with no antenatal ART exposure did not have significantly increased odds of any lifetime hospitalization, any neonatal hospitalization or any postneonatal first-year hospitalization, compared with CHUU (Table 4). With regard to the timing of ART initiation, CHEU born to women who initiated ART preconception had significantly decreased odds of infection-related hospitalizations, compared with CHEU whose mother-initiated ART during pregnancy (aOR 0.50, 95% CI 0.49–0.52) (Table, Supplemental Digital Content 2, <http://links.lww.com/INF/E562>).

The same analysis was performed in the second cohort from 2000 to 2012 (Table 5). Regardless of antenatal ART exposure,

**TABLE 1.** Cohort Characteristics, 1990–2012 and 2000–2012

	Cohort 1: 1990–2012			Cohort 2: April 2000–December 2012		
	CHEU	CHUU	P	CHEU	CHUU	P
N*	446	1333	—	253	739	—
Maternal age	30.3 ± 5.3	30.7 ± 5.6	0.23	30.3 ± 5.3	30.7 ± 5.6	0.26
Age at data collection†	8.4 ± 5.6	8.8 ± 5.7	0.28	5.9 ± 3.7	6.1 ± 3.6	0.46
Infant male sex	192 (46.7)	628 (47.1)	0.89	123 (48.6)	336 (45.5)	0.39
Preterm birth	85 (19.1)	94 (7.1)	<0.0001	51 (20.1)	49 (6.6)	<0.0001
Child with ≥1 lifetime hospitalization	211 (47.3)	397 (29.8)	<0.0001	123 (48.6)	180 (24.4)	<0.0001
Child with ≥1 neonatal hospitalization	180 (40.4)	368 (27.6)	<0.0001	119 (47.0)	170 (23.0)	<0.0001
Child with ≥1 postneonatal first-year hospitalization	48 (10.8)	107 (8.0)	0.07	32 (12.6)	49 (6.6)	0.003
Child with ≥1 ICU admission	127 (28.5)	122 (9.2)	<0.0001	70 (27.7)	72 (9.7)	<0.0001
Child with ≥1 infection-related hospitalization	40 (9.0)	100 (7.5)	0.32	21 (8.3)	44 (6.0)	0.19
Infection status						
Respiratory tract infections	31 (7.0)	77 (5.8)	—	17 (6.7)	32 (4.3)	—
Influenza	N < 6	N < 6	—	N < 6	N < 6	—
Urinary tract infections	N < 6	N < 6	—	N < 6	N < 6	—
Other infections	8 (1.8)	17 (1.3)	—	N < 6	8 (1.1)	—
No. infection-related hospitalizations	406 (91.0)	1233 (92.5)	—	232 (91.7)	695 (94.1)	—
No. hospitalizations	1.8 ± 2.1	1.6 ± 1.9	0.05	1.7 ± 1.7	1.5 ± 1.5	0.006
No. postneonatal hospitalizations	0.8 ± 1.8	0.6 ± 1.9	0.04	0.7 ± 1.7	0.5 ± 1.5	0.006
Total hospitalization days	12.8 ± 21.4	5.0 ± 16.1	<0.0001	12.3 ± 18.4	4.3 ± 13.8	<0.0001
Antenatal exposure						
Smoking	—	—	—	85 (33.6)	60 (8.1)	<0.0001
Substance use‡	—	—	—	56 (22.1)	14 (1.9)	<0.0001

CHEU and CHUU matched 1:3 on age, sex and forward sortation area. Data shown as mean ± SD or N (%). P value calculated from Pearson chi-squared test (proportions) or from Wilcoxon rank-sum test (continuous variables).

\*As children may have both a neonatal hospitalization and a postneonatal first-year hospitalization and thus fall into multiple hospitalization outcomes, the sum of children from each hospitalization outcome exceeds the total number of children within a cohort.

†Child age at data collection (years), as of December 31, 2012.

‡Any prescription, nonprescription or illicit drug use by the mother as a risk factor to pregnancy (2000–2008); OR any heroin/opioids, cocaine, methadone, solvents or marijuana at any point during pregnancy/whether provider indicated use of prescription, “other” or unknown drugs as a risk factor to the pregnancy (2008–2012).

CHEU had significantly increased odds of one or more lifetime hospitalization compared with CHUU. With regards to the timing of ART initiation, preconception ART was not significantly associated with lower odds of any postneonatal first-year hospitalization, ICU admission and infection-related hospitalizations, compared with ART initiation during pregnancy, although the effect was in the same direction as cohort 1 (Table, Supplemental Digital Content 2, <http://links.lww.com/INF/E562>).

## DISCUSSION

In this retrospective matched cohort study, we found that significantly more CHEU experienced ≥1 lifetime hospitalization and ICU admission, with the majority of hospitalizations occurring in the first 28 days of life. Compared with CHUU, CHEU also experienced 2.3 times the odds of any lifetime hospitalization, 2.1 times the odds of any neonatal hospitalization and 3.4 times the odds of any ICU admission. CHEU antenatally exposed to maternal ART had similarly higher odds of hospitalization outcomes, regardless of the timing of initiation of maternal ART. However, when maternal ART was initiated before pregnancy, CHEU had approximately half the odds of infection-related hospitalizations, compared with children mothers-initiated ART during pregnancy. Infections appeared to be a relatively infrequent cause of hospitalization, for both groups. As hypothesized, these findings suggest that antenatal HIV exposure may be a risk factor for hospitalizations early in life.

The majority of these results are consistent with previous research. CHEU in various settings have similarly experienced greater frequency and risk of hospitalizations, including infection-related admissions.<sup>8–13</sup> Existing literature show that globally, CHEU experience higher risks of hospitalizations compared with CHUU.<sup>6–8,11,28</sup> The finding of increased hospitalizations in our study (aOR 2.30) among CHEU from 1990 to 2012 is comparable with similar studies

from Belgium (adjusted hazard ratio 2.33),<sup>8</sup> South Africa (relative risk 2.74),<sup>13</sup> the United States (incidence rate ratio, IRR 2.25),<sup>28</sup> Denmark (IRR 3.49)<sup>10</sup> and Mozambique (IRR 1.45).<sup>29</sup> Of note, while the magnitudes are not directly comparable between different statistical measures, the direction of difference is the same with all studies reporting a higher measure of hospitalizations among CHEU, compared with CHUU. Furthermore, we found that the odds of any hospitalization among CHEU remained elevated at a similar magnitude when restricting the analysis to only the neonatal period, while they were reduced, but still higher than those of CHUU, for postneonatal first-year hospitalizations. Previous studies reported a similar increased risk of hospitalizations and infections early in infancy, ranging from 8 days to 2 years of life, particularly in the first 6 months of life, and waning after 2 years of age.<sup>9,11,13,30–32</sup>

As shown in this study, CHEU from 1990 to 2000 have 3.38 times the adjusted odds of being admitted to the ICU compared with their CHUU controls, even after adjusting for preterm birth. Consistent with the literature, this suggests that being born as CHEU may be associated with more severe illness requiring ICU management.<sup>5,11–13,30</sup> In particular, Slogrove et al<sup>13</sup> found that while their cohort of CHEU in South Africa did not experience a greater number of infection events, they were at higher risk for more severe events requiring hospitalization. This was reflected in our study, where the proportion of infection-related hospitalizations was not different between CHEU and CHUU, but CHEU did have increased odds of ICU admission and longer hospitalization lengths. Importantly, the association between antenatal HIV exposure and ICU admissions was no longer significant after adjusting for preterm birth, maternal substance use and maternal smoking during pregnancy. Along with our finding of neonatal abstinence syndrome as the most prevalent ICU admitting diagnosis among CHEU, this suggests that the majority of ICU care was likely not due to antenatal HIV exposure but coexisting maternal factors during pregnancy.

**TABLE 2.** Crude and aORs of Hospitalization Outcomes in CHEU, Adjusted for Preterm Birth, Maternal Substance Use and Maternal Smoking, 1990–2012 and 2000–2012

Cohort 1: 1990 – 2012*	N (%)	Crude OR (95% CI)	aOR (95% CI)
Child with ≥1 lifetime hospitalization			
CHUU (reference)	397 (29.8)	1	1
CHEU	211 (47.3)	2.14 (1.71-2.68)	2.30 (1.81-2.91)
Child with ≥1 neonatal hospitalization			
CHUU (reference)	368 (27.6)	1	1
CHEU	180 (40.4)	1.86 (1.48-2.35)	2.14 (1.68-2.73)
Child with ≥1 postneonatal first-year hospitalization			
CHUU (reference)	107 (8.0)	1	1
CHEU	48 (10.8)	1.39 (0.97-2.00)	1.36 (0.92-1.99)
Child with ≥1 ICU admission			
CHUU (reference)	122 (9.2)	1	1
CHEU	127 (28.5)	3.92 (2.94-5.22)	3.38 (2.38-4.79)
Child with ≥1 infection-related hospitalization			
CHUU (reference)	100 (7.5)	1	1
CHEU	40 (9.0)	1.22 (0.83-1.80)	1.11 (0.73-1.68)
Cohort 2: April 2000–December 2012*†‡			
Child with ≥1 lifetime hospitalization			
CHUU (reference)	180 (24.4)	1	1
CHEU	123 (48.6)	3.34 (2.39-4.67)	3.26 (2.23-4.79)
Child with ≥1 neonatal hospitalization			
CHUU (reference)	170 (23.0)	1	1
CHEU	119 (47.0)	3.22 (2.30-4.52)	3.11 (2.12-4.57)
Child with ≥1 postneonatal first-year hospitalization			
CHUU (reference)	49 (6.6)	1	1
CHEU	32 (12.6)	2.46 (1.47-4.13)	1.79 (0.99-3.23)
Child with ≥1 ICU admission			
CHUU (reference)	72 (9.7)	1	1
CHEU	70 (27.7)	3.45 (2.30-5.16)	1.63 (0.93-2.86)
Child with ≥1 infection-related hospitalization			
CHUU (reference)	44 (6.0)	1	1
CHEU	21 (8.3)	1.52 (0.86-2.69)	0.97 (0.46-2.01)

CHEU and CHUU matched 1:3 on age, sex and forward sortation area.

\*Adjusted for preterm birth.

†Adjusted for maternal smoking.

‡Adjusted for maternal substance use. Maternal substance use defined as any prescription, nonprescription or illicit drug use by the mother as a risk factor to pregnancy (2000–2008); OR any heroin/opioids, cocaine, methadone, solvents or marijuana at any point during pregnancy/whether provider indicated use of prescription, “other” or unknown drugs as a risk factor to the pregnancy (2008–2012).

**TABLE 3.** Crude and aRRs of Hospitalization Outcomes in CHEU, Adjusted for Preterm Birth, Maternal Substance Use and Maternal Smoking, 1990–2012 and 2000–2012

Cohort 1: 1990–2012*	Crude RR (95% CI)	Adjusted RR (95% CI)	Adjusted RR, P
No. hospitalizations			
CHUU (reference)	1	1	0.31
CHEU	1.13 (1.03–1.25)	1.05 (0.95–1.16)	
Total hospitalization days			
CHUU (reference)	1	1	<0.0001
CHEU	2.57 (2.27–2.92)	2.10 (1.87–2.36)	
Cohort 2: April 2000–December 2012*†‡			
No. hospitalizations			
CHUU (reference)	1	1	0.56
CHEU	1.15 (1.02–1.29)	0.96 (0.84–1.10)	
Total hospitalization days			
CHUU (reference)	1	1	<0.0001
CHEU	2.92 (2.51–3.39)	1.74 (1.49–2.03)	

CHEU and CHUU matched 1:3 on age, sex and forward sortation area.

\*Adjusted for preterm birth.

†Adjusted for maternal smoking.

‡Adjusted for maternal substance use. Maternal substance use defined as any prescription, nonprescription, or illicit drug use by the mother as a risk factor to pregnancy (2000–2008); OR any heroin/opioids, cocaine, methadone, solvents or marijuana at any point during pregnancy/whether provider indicated use of prescription, “other” or unknown drugs as a risk factor to the pregnancy (2008–2012).

**TABLE 4.** Crude and aORs of Hospitalization Outcomes in CHEU, by Timing of Maternal ART Initiation (Before Conception, During Pregnancy or None), Adjusted for Preterm Birth, 1990–2012

Health Outcome N†	CHEU: ART Before Conception	CHEU: ART During Pregnancy	CHEU: no ART	CHUU	Crude OR (95% CI)	Adjusted OR (95% CI)*
	95	255	61	1333		
Child with ≥1 lifetime hospitalization	48 (50.5)	121 (47.5)	29 (47.5)	397 (29.8)	CHUU 1	CHUU 1
					Before 4.03 (2.52–6.46)	Before 4.01 (2.50–6.44)
					During 2.44 (1.81–3.28)	During 2.42 (1.79–3.28)
Child with ≥1 neonatal hospitalization	48 (50.5)	112 (43.9)	20 (32.8)	368 (27.6)	CHUU 1	CHUU 1
					Before 4.13 (2.56–6.65)	Before 4.12 (2.56–6.65)
					During 2.26 (1.67–3.06)	During 2.25 (1.66–3.06)
Child with ≥1 postneonatal first-year hospitalization	9 (9.5)	29 (11.4)	10 (16.4)	107 (8.0)	CHUU 1	CHUU 1
					Before 1.53 (0.70–3.36)	Before 1.39 (0.63–3.06)
					During 1.63 (1.01–2.62)	During 1.47 (0.90–2.38)
Child with ≥1 ICU admission	21 (22.1)	78 (30.6)	16 (26.2)	122 (9.2)	CHUU 1	CHUU 1
					Before 2.85 (1.58–5.13)	Before 1.99 (1.01–3.93)
					During 4.85 (3.36–6.98)	During 3.88 (2.58–5.83)
Child with ≥1 infection-related hospitalization	N < 6	22 (8.6)	8 (13.1)	100 (7.5)	CHUU 1	CHUU 1
					Before 0.62 (0.61–0.64)	Before 0.61 (0.59–0.62)
					During 1.25 (1.24–1.26)	During 1.21 (1.20–1.22)
					No ART 1.44 (1.41–1.47)	No ART 1.39 (1.37–1.42)

CHEU and CHUU matched 1:3 on age, sex and forward sortation area.

Before, before conception; During, during pregnancy.

\*Adjusted for preterm birth. Data shown as N (%).

†As children may have both a neonatal hospitalization and a postneonatal first-year hospitalization and thus fall into multiple hospitalization outcomes, the sum of children from each hospitalization outcome exceeds the total number of children within a cohort.

**TABLE 5.** Crude and aORs of Hospitalization Outcomes in CHEU, by Timing of Maternal ART Initiation (Before Conception, During Pregnancy or None), Adjusted for Preterm Birth, Maternal Substance Use and Maternal Smoking, 2000–2012

Health Outcome N§	CHEU: ART Before Conception	CHEU: ART During Pregnancy	CHEU: No ART	CHUU	Crude OR (95% CI)	Adjusted OR (95% CI)*†‡
	75	164	14	739		
Child with ≥1 lifetime hospitalization	39 (52.0)	75 (45.7)	9 (64.3)	180 (24.4)	CHUU 1	CHUU 1
					Before 5.15 (2.91–9.09)	Before 4.94 (2.77–8.79)
					During 2.96 (2.00–4.36)	During 2.81 (1.82–4.35)
Child with ≥1 neonatal hospitalization	39 (52.0)	74 (45.1)	6 (42.9)	170 (23.0)	CHUU 1	CHUU 1
					Before 5.32 (2.99–9.45)	Before 5.11 (2.86–9.16)
					During 3.07 (2.07–4.55)	During 2.83 (1.82–4.41)
Child with ≥1 postneonatal first-year hospitalization	8 (10.7)	21 (12.8)	3 (21.4)	49 (6.6)	CHUU 1	CHUU 1
					Before 2.04 (0.81–5.14)	Before 1.63 (0.64–4.20)
					During 2.64 (1.43–4.85)	During 1.86 (0.93–3.73)
Child with ≥1 ICU admission	13 (17.3)	48 (29.3)	9 (64.3)	72 (9.7)	CHUU 1	CHUU 1
					Before 2.07 (0.96–4.46)	Before 1.07 (0.42–2.75)
					During 4.42 (2.74–7.13)	During 1.84 (0.97–3.51)
Child with ≥1 infection-related hospitalization	N < 6	13 (7.9)	N < 6	44 (6.0)	No ART 15.22 (4.22–54.98)	No ART 3.35 (0.65–17.23)
					CHUU 1	CHUU 1
					Before 0.75 (0.23–2.45)	Before 0.60 (0.17–2.06)
					During 1.53 (0.76–3.12)	During 1.02 (0.44–2.41)
					No ART 6.12 (1.41–26.55)	No ART 4.09 (0.84–19.85)

CHEU and CHUU matched 1:3 on age, sex and forward sortation area.

Before, before conception; During, during pregnancy.

\*Adjusted for preterm birth.

†Adjusted for maternal smoking.

‡Adjusted for maternal substance use. Maternal substance use defined as any prescription, nonprescription, or illicit drug use by the mother as a risk factor to pregnancy (2000–2008); OR any heroin/opioids, cocaine, methadone, solvents or marijuana at any point during pregnancy/whether the provider indicated use of prescription, “other” or unknown drugs as a risk factor to the pregnancy (2008–2012). Data shown as N (%).

§As children may have both a neonatal hospitalization and a postneonatal first-year hospitalization and thus fall into multiple hospitalization outcomes, the sum of children from each hospitalization outcome exceeds the total number of children within a cohort.

Previous studies report an inconsistent trend of infection-related hospitalizations among CHEU. Studies from South Africa, India and the United States found a higher rate of infection-related hospitalizations in the early years of life.<sup>7,9,28,33</sup> Other studies reported that the risk of infection-related hospitalizations is not different between CHEU and CHUU, similar to our study.<sup>10,13,34</sup> The higher proportion of infection-related hospitalizations among CHEU in this study, while not different from CHUU, is consistent with a higher frequency of infections reported globally among CHEU.<sup>32,35–37</sup> The increased frequency of infections in CHEU may be due to the effects of maternal HIV viral load on infant passive and innate immunity. Interestingly, Moseholm et al<sup>10</sup> noted that the excess risk of hospitalization among CHEU in Denmark was attributed to observation/nonspecific diagnoses, particularly a family history of HIV disease. The increased hospitalizations among CHEU in our study, even in those whose mothers received ART during pregnancy, may similarly reflect a lower threshold for admission by healthcare providers.

Our analysis compared hospitalization outcomes between CHEU whose mothers-initiated ART preconception, during pregnancy and those without antenatal ART exposure. While the analysis was likely insufficiently powered to detect a significant difference, our findings do suggest that earlier initiation of ART before conception may reduce the odds of ICU admission and infection-related hospitalizations, consistent with findings from Belgium.<sup>8</sup> Our analysis also suggest that initiation of ART preconception had a protective effect against infection-related hospitalizations. This protective effect was not demonstrated among CHEU with no antenatal ART exposure, where there was likely more exposure to maternal HIV milieu and possibly greater inflammation, early during development. This is consistent with studies reporting a lower level of placental transfer of maternal antibodies in mother-infant pairs with advanced maternal HIV infection, lower maternal CD4 count and higher maternal viral load at delivery.<sup>30,31,38,39</sup> Thus, the excess odds of infection-related hospitalization among CHEU may be attributable to late or no ART during pregnancy, consistent with the Belgian study<sup>8</sup> and the relationship of adverse CHEU outcomes with the severity of maternal HIV infection.<sup>30,31,38,39</sup>

The likelihood of a missed or late HIV diagnosis was low, given that since 1994, all pregnant women in BC are offered HIV testing as part of routine prenatal screening or testing at time of delivery if they did not have any prenatal care.<sup>40</sup> Inferences about the reason(s) excess hospitalization outcomes remain limited due to several reasons. For instance, we lacked data on other factors that may influence both infection-related and noninfectious hospitalizations, including pregnancy conditions, prenatal care, maternal HIV disease severity (CD4 nadir), medications other than ART, race/ethnicity and other socioeconomic and psychosocial factors.<sup>41–43</sup> WLWH receiving ART may be characteristically different from those who did not receive ART and may reflect the evolution in treatment guidelines from 1990 to 2012. The standard of care evolved from no ART available in the early 1990s, to monotherapy from 1994, then combination triple therapy starting in 1997; by the mid-2000s, the majority of WLWH were on combination therapy.<sup>18,20</sup> In the early years of the study period, preconception initiation of ART may have indicated more advanced disease. In the current era, WLWH who have not initiated ART preconception are more likely to have complex psychosocial factors and be affected by social determinants of health. Data on breast-feeding practices of WLWH were similarly unavailable for our study. While the WHO recommends breast-feeding by WLWH in resource-limited settings, the Society of Obstetricians and Gynaecologists of Canada and the Canadian Pediatric AIDS Research Group recommend against breast-feeding, regardless of ART usage and plasma viral load.<sup>25,44,45</sup> There are thus very few WLWH who breastfeed in Canada and BC. Within the general

population of BC, however, the rate of breast-feeding is high.<sup>46,47</sup> Breast-feeding may influence hospitalizations and infections, as it has been shown to decrease the incidence of hospitalization and mortality among CHEU.<sup>5,29,32,48</sup> Finally, our study included preterm birth and maternal substance use as covariates, which may be mediators of infection-related hospitalizations and whose inclusion may have masked the increased odds of hospitalization among CHEU. Given the different covariates included in the final models and varying outcome estimates, there is a need for standard statistical practices to minimize conflicting outcomes, such as infection-related hospitalizations, between studies.

In BC, WLWH have access to low-barrier, trauma-informed multidisciplinary care at Oak Tree Clinic at BC Women's Hospital. Their medical records, including substance use, may be more comprehensive than those of CHUU mothers, resulting in possible differential misclassification of these variables. Nevertheless, our findings are consistent with the direction and magnitude of excess risk in other studies investigating hospitalizations.

In conclusion, our study provides population-level evidence within a Canadian context of increased odds of hospitalizations among CHEU. An important insight is the increased odds of ICU admissions, suggesting that CHEU experience more severe conditions independent of preterm birth, maternal substance use and maternal smoking. Preconception initiation of ART may mitigate some risk of infection-related hospitalizations and ICU admissions. As the number of CHEU continues to rise in Canada and globally, further investigations of the multifactorial causes of hospitalizations and infections are warranted. Our findings support careful monitoring among CHEU for adverse health outcomes and the importance of early initiation of maternal ART, and may inform future care strategies of CHEU to reduce hospitalizations.

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