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HIV, SIDS, and Breastfeeding in the Pediatric Spectrum of HIV Disease Cohort

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HIV, SIDS, and Breastfeeding in the Pediatric Spectrum of HIV Disease Cohort

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2007

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Abstract

HIV, SIDS, and Breastfeeding in the Pediatric Spectrum of HIV Disease Cohort
By Kristen M. Little

Objective: Though the rate has declined significantly in the past two decades, Sudden Infant Death Syndrome (SIDS) remains the leading cause of death for infants in the post-neonatal period in the U.S. A number of studies have noted an elevated rate of SIDS among HIV-exposed infants. The objective of this analysis was to identify risk factors and trends in SIDS rates in HIV-exposed infants.

Methods: We analyzed data from the medical records of 13,084 HIV-exposed infants followed from birth from 1988-2004. Data was obtained from eight geographic sites in the United States involved in the Pediatric Spectrum of HIV Disease Project, which was conducted by the Centers for Disease Control and Prevention.

Results: Seventeen cases of SIDS were diagnosed during the study period, for a crude SIDS rate of 1.3 per 1,000 infants. Rates of SIDS were not statistically different among white, black, and infants of other races. Rates of SIDS were highest among HIV-status-indeterminate infants (6.2 per 1,000 infants), compared to HIV-infected infants (1.3 per 1,000 infants) and HIV-uninfected infants (0.4 per 1,000 infants).

Significant risk factors for SIDS included a lack of prenatal care (OR: 5.26; 95% CI: 1.493, 18.797), maternal drug use during pregnancy (OR: 4.2; 95% CI: 1.35, 12.93), low birth weight (OR: 2.60; 95% CI: 1.004, 6.753) and infant birth in 1994 or earlier (OR: 6.3; 95% CI: 2.0515, 19.3185). Breastfeeding, premature delivery, male gender, and black race were not significantly associated with SIDS. Among infants dying of all causes during the first year of life HIV-infected infants had a significantly higher risk of SIDS than HIV-uninfected infants, after controlling for age at death (aOR: 11.04; 95% CI: 1.660, 73.475).

Conclusions: The rate of SIDS in this cohort declined steadily from 1988-2004, a trend also observed in the general population during this period. Significant risk factors for SIDS for infants in this study included maternal drug use during pregnancy, no prenatal care, and low birth weight. Race, gender, and breastfeeding were not significantly associated with SIDS. HIV-infection was only a significant risk factor for SIDS among infants dying during the first year of life.

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Finally, this thesis is dedicated to my mom, Donna Little. The memory of your determination and enthusiasm has guided me through this process, and this year. Your dedication to making the world a better place for those around you has been a big part of my interest in public health. I hope I've made you proud!

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CHAPTER 1: INTRODUCTION

Rationale:

Perinatal HIV

The rate of mother-to-child transmission (MCT) of Human Immunodeficiency Virus (HIV) in the United States has fallen from approximately 25% [1] in 1991 to nearly 2% in 2007 thanks to interventions such as prenatal HIV testing for pregnant women, antiretroviral prophylaxis, elective Cesarean section, and avoidance of breastfeeding [2]. These interventions, with the addition of highly active antiretroviral therapy (HAART) have resulted in transmission rates as low as 1% in many European countries [3, 4].

Approximately 200-300 infants in the United States are perinatally infected with HIV each year [2]. The majority of these cases result from missed prevention opportunities, such as late or no prenatal HIV testing, inadequate or no prenatal care, less than 3 arms of antiretroviral prophylaxis (prenatal, intrapartum, and post-partum), or failure to avoid breastfeeding [5, 6].

HIV-infected women in the United States have been advised to avoid breastfeeding since 1985, when data emerged implicating breastfeeding in late postnatal HIV transmission from mother to child [7]. Though international guidelines still recommend exclusive breastfeeding for six months by HIV-infected women in resource-limited settings [8]. However, because acceptable, feasible, affordable, sustainable, and safe breastfeeding alternatives are available, HIV-infected women in the United States and they are still advised to avoid breastfeeding [9].

The benefits of breastfeeding, however, are well-known. They include infant benefits such as a reduced risk of otitis media and respiratory infections, decreased risk of overweight/obesity in adolescence, and a decreased risk of some childhood cancers and sudden infant death syndrome (SIDS) [10]. Women who breastfeed also return to pre-pregnancy weight more quickly and have decreased post-partum bleeding [10].

As HIV drugs, including HAART, continue to improve, questions have begun to arise regarding the need for HIV-infected mothers in the U.S. to avoid breastfeeding. Studies of HIV transmission from individuals on HAART with undetectable viral loads (viral load < 40 copies per ml) have found very small risks of sexual, prompting some Swiss officials to go so far as to conclude that "individuals with undetectable viral loads are sexually non-infectious" [11]. Similarly, researchers have found very low rates of late postnatal HIV transmission among breastfeeding women with suppressed viral loads as a result of effective antiretroviral therapy. Studies from Africa have found rates of perinatal transmission from mothers treated with HAART of less than 1% [12-17].

Sudden Infant Death Syndrome (SIDS)

Sudden Infant Death Syndrome (SIDS) is defined as the "unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history" [18]. While SIDS has decreased significantly since the mid-1990s, it remains the leading

cause of post-neonatal death among infants in the United States and other developed countries [19]. SIDS, along with the two other leading causes of infant death—congenital malformations and low birth weight—accounted for 46 percent of all infant deaths in 2006, the most recent year such data was available [20]. SIDS risk factors include the prone infant sleep position, maternal prenatal smoking and drug use, low birth weight, race, gender, and bed sharing [21].

Recent research has also found a significant reduction in the risk of SIDS among infants who are ever breastfed. A meta-analysis by the Agency for Health Research Quality (AHRQ) found an OR for breastfeeding of 0.64 [22]. A lack of breastfeeding remains a somewhat controversial independent risk factor for SIDS, however. While a number of recent studies have supported this conclusion [10, 23-26], others have found that breastfeeding is no longer a statistically significant risk factor after controlling for other confounders [27-29]. However, recently a well-respected German study found that breastfeeding reduced the risk of SIDS by more than 50% [23] after controlling for other confounders.

Among HIV-exposed infants[1] [30] in the developed countries—the vast majority of whom were never breastfed—studies have observed an increased rates of SIDS [31-34]. Though these elevated rates have been noted, no studies have yet examined the factors that account for the increase in SIDS deaths observed among HIV-exposed infants.

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[1] *An HIV-exposed infant is defined as "an infant born to a mother infected with HIV and exposed to HIV during pregnancy, childbirth, or breast-feeding" HIV-exposed infants may be HIV-infected, HIV-uninfected, or HIV-status unknown.* (30. Women Children and HIV. *Glossary of HIV/AIDS Terms*. 2011 [cited 2011 March 1]; Available from: http://www.womenchildrenhiv.org/wchiv?page=gl-h.)

The Issue:

The risk factors for SIDS among HIV-exposed infants have yet to be examined, though a number of studies have postulated a number potential risk factors, including elevated levels of maternal substance abuse [35], cardiac dysfunction as a result of infant HIV-infection [31], and in-utero cardio-respiratory developmental delays and/or slowed fetal growth resulting from maternal HIV infection [31]. It has also been suggested that the relationship between SIDS and HIV is confounded by the increased rates of prematurity, low birth weight, black and Hispanic race, maternal smoking, and young maternal age, which are all common among HIV-exposed infants in addition to being risk factors for SIDS [36]. Since more than 98% of HIV-infected mothers in the United States avoid breastfeeding [37], the risk associated with formula feeding could also potentially play a role in the increased rates of SIDS observed among HIV-exposed infants.

Study Aims:

This study set out to identify risk factors for SIDS among a cohort of HIV-exposed infants followed through the first year of life. While major risk factors, including infant sleep position, maternal smoking, and infant sleep environment were unavailable in the cohort, the study was able to assess the effects of variables including maternal drug use, prenatal care, HIV status, gestation, birth weight, race, gender, and maternal age, all of which have been identified as SIDS risk factors [21, 38-43].

This study also sought to predict the potential effects of breastfeeding on both SIDS deaths and late postnatal HIV transmission among infants in this cohort. Because

HAART reduces, but does not fully eliminate, the risk for MCT through breastfeeding, allowing HIV-infected mothers to breastfeed may significantly reduce the risk of SIDS deaths while also increasing the risk of HIV transmission. This study aimed to evaluate the potential effects of a reversal of CDC's breastfeeding recommendations for HIV-infected women in the U.S.

Study setting:

The Perinatal Spectrum of HIV Disease (PSD) cohort was a CDC-funded longitudinal follow-up study of 19,025 HIV-exposed infants followed from 1988-2004. Infant medical records from 41 hospitals in eight geographic areas across the U.S. were abstracted at regular intervals from birth or entry into the study through the first year of life. Data collected included infant HIV status, race, gender, gestation, birth weight, post-natal and pediatric visits, drugs prescribed, primary caretaker, number of siblings, viral loads and cell counts, and cause of death (if applicable).

If available, maternal characteristics were abstracted from the pediatric medical records. Data collected on maternal factors included age, race, parity, drug use, prenatal care, and healthcare reimbursement. Data collected on infant factors included gender, race, birth weight, number of siblings, type of birth, source of medical insurance, and HIV status.

For the purposes of this study, analysis was limited to those infants followed from birth. Infants born before the start of data collection in 1988 were excluded from the analysis. From 1988-2004, 19,025 infants were enrolled in PSD and 13,084 (68.8%) met the inclusion criteria above.

This analysis was limited to de-identified secondary data collected by the PSD study. As such, this analysis did not involve human subject research, and was classified as non-research. It did not require IRB approval.

CHAPTER 2: EXPLANATION OF STUDENT INVOLVEMENT

Members of the Perinatal HIV Transmission Team (Team Leader: Dr. Steven Nesheim) at the Centers for Disease Control and Prevention (CDC) Division of HIV/AIDS Prevention (DHAP) wanted to investigate the relationship between breastfeeding and infant morbidity/mortality in the context of perinatal HIV exposure. DHAP had begun to receive questions regarding HIV-infected mothers' continued need to avoid breastfeeding in light of recent research on HIV-transmission in the context of highly active antiretroviral therapy (HAART) [11, 15-17]. This research indicated that individuals on HAART with a stably suppressed viral load had significantly decreased risk of transmitting HIV both perinatally and/or sexually.

After a 2009 article linked breastfeeding with a reduced risk of SIDS [38], Dr. Nesheim suggested I explore this topic further in order to evaluate the benefits/risks associated with altering current recommendations on avoidance of breastfeeding by HIV-infected mothers on both SIDS and perinatal HIV transmission.

For this project I was responsible for drafting a concept sheet and submitting it to the Pediatric Spectrum of HIV Disease Cohort (PSD) research committee in order to request access to the PSD data set. I was responsible for examining the data dictionary, identifying the necessary variables, and outlining the research question and forming a data analysis plan. Upon receiving the data, I was responsible for cleaning the data, creating new variables, and performing descriptive statistics using SAS 9.2 (Cary, North Carolina). Additional statistical approaches to adjust for an unstable rate (due to a very small number of SIDS cases each year), including LOESS regression and multiple

imputation, were suggested by DHAP statistician Craig Borkowf, PhD and Senior Associate Professor of Biostatistics Patrick Kilgo, MS. I obtained resources in order to learn about these statistical techniques, wrote the appropriate SAS code, and interpreted the results.

I also consulted with members of the perinatal transmission team and CDC subject matter experts in SIDS on the analysis and interpretation of results. Through these discussions and a growing familiarity with the dataset, it became clear that the scope of the study would need to be narrowed. Due to the small number of cases and a significant degree of missing data, logistic regression could not be used to examine risk factors for SIDS among these infants while controlling for important factors such as HIV status, gender, and race. Instead I used descriptive statistics to evaluate bivariate relationships between risk factors and SIDS. Given the limitations inherent in SIDS diagnostics and the long time-period encompassed by the study, the team and I also decided to forego building a model to predict the effects on SIDS and perinatal HIV transmission had the women in the study breastfed their infants.

After making these decisions, I wrote the manuscript, which was then edited by DHAP epidemiologists Dr. Nesheim and Dr. Kenneth Dominguez. The manuscript underwent a series of revisions on which Dr. Nesheim, Dr. Dominguez, and I collaborated. Future changes during the CDC clearance process will involve a number of DHAP employees and researchers, in addition to SIDS subject matter specialists.

CHAPTER 3: REVIEW OF THE LITERATURE

Sudden Infant Death Syndrome:

Despite a significant reduction in the rate of sudden infant death syndrome (SIDS) since 1994, SIDS remains the leading cause of death for infants in the post natal period in the United States [19]. Currently SIDS is defined as the "unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history" [18]. This definition of SIDS will be used throughout this analysis unless stated otherwise.

Extensive epidemiologic research into the risk factors for SIDS has been carried out since the mid-1980s, and has implicated a number of risk factors, most notably the prone sleeping position [43]. While prone sleeping was the focus of risk reduction interventions such as the Back-to-Sleep Campaigns that began in 1994 [44] , more recent studies have identified a variety of risk factors including maternal smoking during pregnancy, bed-sharing, and cushioned sleep surfaces, among others [18, 21] (**Appendix: Table 1**).

Causative Theories of SIDS

Though no single cause of SIDS has ever been satisfactorily demonstrated, a number of researchers have developed multiple-risk hypotheses, in which multiple, over-lapping risk factors combine and interact to cause sudden infant death. A 1972 presentation by Dr. RJ Wedgewood outlined a "triple risk hypothesis" which involved:

> "3 classes of risk factors: 1) general factors that increase the probability of death from any cause, including poverty, prematurity, gender, and race; 2) age-specific risks relating to the infant's developmental status; and 3) precipitating factors, including sleep state, position, and infection." [45]

This definition was adapted slightly in 1994 by Filiano and Kinney, who wrote that "SIDS results from the intersection of 3 overlapping factors: 1) a vulnerable infant; 2) a critical developmental period in homeostatic control; and 3) an exogenous stressor." [46] The authors emphasized that all three of these factors needed to be present for an infant to die of SIDS [46].

Unfortunately, evidence for these models is variable and largely inconclusive. SIDS appears to be the result of multiple causes. The advantage of these "triple risk hypotheses" lies largely in their ability to incorporate a number of risk factors and the interactions that occur between them [47].

SIDS Risk Factors

Since the late 1960s studies have identified a number of factors that increase an infant's risk of SIDS [18, 40, 43]. The predominant focus has been on the infant sleep environment, including infant sleep position, type of sleep surface, bedding, bed-sharing, room-sharing, and temperature, all of which have been significantly associated with SIDS [18, 40, 43]. Studies have also found links between SIDS and a variety of infant characteristics, including prematurity, low birth weight, gender, and race/ethnicity [40, 41]. Modifiable maternal risk factors have also grown in importance as the proportion of infants placed to sleep in the prone or side positions decreased. Risk factors including maternal age, parity, maternal smoking status, drug dependency during pregnancy, and breastfeeding have accounted for an increased proportion of

SIDS deaths in recent years as fewer infants are placed to sleep in the prone or side positions [39, 43, 48].

Infant Sleep Environment: Studies have consistently identified the prone sleeping position as a risk factor for SIDS. A case-control study in Scotland by Brooke et al, which included 201 SIDS cases and 276 controls recruited between 1992-1995, found that the prone sleeping position was independently associated with SIDS (aOR 6.96 (95% CI: 1.51-31.97)) [28]. The study also found that parental smoking was strongly associated with SIDS, especially if both parents smoked (aOR: 5.19 (95% CI: 2.26-11.91)) [28].

Similarly, a population-based case-control study by Fleming et al. concluded that prone sleeping, side sleeping, bed sharing, and maternal smoking were all significantly associated with SIDS [49]. The study included 195 SIDS cases and 780 age-matched controls from England between 1993-1995 and used a multi-session caretaker questionnaire that included data on demographic variables and infant care practices. When adjusting for maternal age, parity, maternal smoking, gestation, and birth weight, the prone sleeping position had a multivariate adjusted odds ratio of 9.00 (95% CI: 2.84-28.47) and the side sleeping position at last sleep had an aOR of 1.84 (95% CI: 1.02-3.31) [49].

A case-control study by Schlaud et al. verified sleep environment risk factors such as sleep position [41]. The study analyzed specific sleep-environment risk factors including pillow use, face covered by bedding, and the use of duvets or underlays. The study included 52 SIDS cases and 154 matched controls from Germany from 1998-2001.

Using multiple logistic regression, the authors found an adjusted OR of 4.3 (95% CI: 1.6-11.6) for pillow use, an aOR of 4.4 (95% CI: 1.5-13.3) for the use of a heavy duvet, an aOR of 3.0 (95% CI: 1.1-8.7) for the use of a soft underlay, and an aOR of 15.8 (95% CI 2.5-102.1) for the face being covered by bedding. Using standard protocols and measurements, this study found strong associations between infant sleep environment and SIDS [41].

A variety of review articles and meta-analyses have supported the significance of infant sleep environment risk factors described above. Gunn et al. performed an extensive meta-analysis on 17 case-control studies and calculated pooled odds ratios for the major risk factors [50]. In addition to prone sleeping, parental smoking, and side sleeping, the study found bed sharing with a smoker and low birth weight to be independent risk factors for SIDS [50]. Their results indicated that simply changing the sleep environment may not be enough to reduce the risk of SIDS further in the future.

In a 2007 paper Moon et al. found similar results after reviewing recently published literature [21]. The authors concluded that as the proportion of infants put to sleep in the prone position has declined, other SIDS risk factors are emerging. These include side sleeping, soft bedding/sleep surfaces, and overheating. Most importantly, however, they argue that maternal smoking during the prenatal period remains an important modifiable risk factor for SIDS. This was especially true for mothers who shared a bed with their infants, though bed sharing itself was a SIDS risk factor, even among women who did not smoke. Bed sharing was especially hazardous for infants less than eleven weeks of age, if bed-sharing lasted through the whole night, or if the

parent had consumed alcohol or was especially tired [21]. The authors also posit that the cause of SIDS is multifactorial and support a "triple risk hypothesis" of SIDS, outlined above and comprising: "a vulnerable infant, a critical development period, and an exogenous stressor". These results were based on a review of the literature, however, and no meta-analysis was performed.

Physiological Factors: Additional review papers hypothesized similar multifactorial causes for SIDS, including a paper by Mage et al. which outlined a quadruple risk model for SIDS [51]. The model included "X-linked genetic susceptibility, respiratory infection, neurological prematurity, and physiological anemia of infancy and apnea" [51]. This model included the ideas of infant vulnerability, a critical developmental period, and outside stressors, but differed from previous triple risk hypotheses by incorporating genetic susceptibility. The authors used Centers for Disease Control and Prevention (CDC) data on live births and deaths from 1979-2005 to evaluate the applicability of their model. They concluded that the model explains the gender, age, and seasonal variations seen in the SIDS surveillance data. Infant susceptibilities, including apnea, respiratory infections, and neurological prematurity could also be connected to one another mathematically through use of the model. This theory has not been tested on additional data, however [51].

Physiological predisposition has also been explored by other studies, including a review article by Martin Samuels on the role of viral infections in SIDS [52]. Though he did not test them, Samuels hypothesized that an interaction between infant smoke

exposure, breastfeeding, and viral respiratory infections may put infants at risk for SIDS. Such a model would also explain the fact that SIDS has historically been most common in the winter months, and why SIDS appears to be related to exposure to cigarette smoke [52].

A comprehensive literature review and policy statement by the Task Force on Sudden Infant Death Syndrome in 2005 summarized the significant risk factors for SIDS and made a series of recommendations to reduce risk [40]. The study found 2.5 times greater risk for SIDS among black infants compared to their white counterparts. Additionally, black infants were almost twice as likely as white infants to be placed to sleep in the prone position (21% vs. 11%). The study also concluded that the prone sleep position, overheating, sleeping on a soft surface, maternal smoking, young maternal age, low birth weight, and male gender were significantly associated with SIDS. Interestingly, the study also identified a lack of prenatal care as a risk factor. According to the task force, as incidence of prone sleeping falls in the United States, interventions targeting these and other modifiable risk factors (such as maternal smoking) will become increasingly important [40].

Maternal Factors: A number of maternal characteristics have been recognized as risk factors for SIDS, including maternal age, parity, receipt of prenatal care, smoking during pregnancy, and prenatal drug dependency [40].

A number of studies have also found an association between maternal drug use and the risk of Sudden Infant Death Syndrome [35, 53-58]. Early reports of increased

rates of sudden infant death among the children of drug-abusing women began emerging in the 1960s and 1970s [55]. The relationship between maternal illicit drug use and the risk of SIDS began to be explored more fully in the early 1970s, and a number of articles were published on the topic in the 1970s through the early 1990s. An early study of 13,372 infants born at two hospitals in the Bronx, New York from 1972-1974 found a significantly higher rate of SIDS among infants born to narcotic-dependent mothers compared to infants whose mothers were not dependent on narcotics during pregnancy [58]. The incidence of SIDS among infants of narcotic-dependant mothers was 20.9 per 1,000 live births, 5.5 times higher than the rate observed in the general hospital population ($p<0.0001$) and 8.7 times greater than the rate observed in the hospitals' borough in New York City ($p<0.0001$) [58]. While these results are suggestive, the authors performed only univariate analysis of the data and were unable to control for other potential confounders including infant sleep position, premature birth, gender, or race.

A similar relationship between maternal drug dependency and SIDS risk was observed in a population of over one million infants born in New York City from 1979-1989 [56]. While SIDS rates declined among both drug-exposed and the drug-unexposed infant, SIDS rates were higher among drug-exposed infants compared to their drug-unexposed counterparts during the entire study period. Prenatal drug exposure remained a significant risk factor even after controlling for race, maternal age, parity, maternal smoking, year of birth, and low birth weight. The study found particularly strong associations with prenatal opiate exposures and rate of SIDS. Infants

exposed to methadone or heroin in utero had a 3.2 times greater risk of SIDS (95% CI: 1.2-8.6), after controlling for potential confounders [56].

A 2001 case-control study from southern California, however, did not find an association between maternal recreational drug use and SIDS after controlling for maternal smoking during pregnancy. The study did find a relationship between SIDS and paternal marijuana use around the time of conception, during pregnancy and the prenatal period, and the postnatal period, which remained significant after controlling for paternal smoking and alcohol use [59].

The role of prenatal smoking in SIDS risk has also been explored by a number of studies. Prenatal smoke exposure has been associated with developmental delays, brainstem alterations, respiratory problems, and impaired arousal patterns in infants, which may explain the heightened risk of SIDS among infants whose mothers smoked during pregnancy [48, 60, 61].

A study of the U.S. Linked Birth/Infant Death Data Set, 2002 cohort examined the proportion of SIDS deaths that were attributable to smoking among 3,352,756 live births in the United States in 2002 [62]. The study found that 11.5% of all births were to women who smoked during the prenatal period. In multiple logistic regression analysis, smoking resulted in an adjusted odds ratio of 2.7 for SIDS (95% CI: 2.4, 3.0). Significantly, the study also found that 23.2-33.6% of SIDS cases were attributable to prenatal smoking. Even after adjusting for the continued decline in prenatal smoking rates, the study estimated that 20.2-29.3% of all SIDS deaths in 2009 would have been attributable to prenatal smoking [62].

Maternal smoking may also be an effect modifier for bed-sharing, another known risk factor for SIDS and Sudden Unexpected Infant Death (SUID). A 2004 study of 745 SIDS cases and 2411 live controls from 20 regions in Europe found that among infants whose mothers smoked, bed-sharing in the first two weeks of life was associated with a 27 times greater odds of SIDS (95% CI: 13.3, 54.9) [63]. For women who did not smoke, the effects of bed sharing were smaller, though still significant (OR: 2.4; 95% CI: 1.2-4.6) [63].

Racial Disparities: As the rate of SIDS has fallen in the United States, the pre-existing racial disparities among SIDS deaths have actually increased. A retrospective cohort study by Unger et al. compared the differences in SIDS deaths between African American (AA) and non-African American (non-AA) infants, as well as racial differences in infant sleep environments [39]. The study included 119 infant deaths (81 AA and 38 non-AA) occurring between 1994-1997 in St. Louis City and St. Louis County. The rate of SIDS among AA infants was found to be significantly higher than among non-AAs (2.08 vs. 0.06 per 1000 live births, p=0.001). Analysis of data from death scene investigations and caretaker interviews conducted for all cases found that, while prone sleeping position was similar between the two groups, significantly more AA SIDS cases were found on non-standard sleep surfaces (defined as a surface other than a crib, playpen, or bassinet) (79.0% vs. 49.0%, p-value=0.001). Risk factors such as bed sharing were also more common among AA cases than non-AA cases. The authors concluded that the racial disparities persisting among SIDS deaths in the United States may be a product of

these differences in infant sleep practices between AA and non-AA populations, and believe risk-reduction messages should be specifically targeted to these groups [39].

A longitudinal cross-sectional study by Colson et al. also found racial differences in infant sleep position [43]. The nationally representative telephone survey was carried out annually from 1993-2007, interviewed caretakers of infants ages 7 months or less at the time of the survey, and included at least 1000 participants each year. Demographic data on both mother and child were collected in addition to infant sleep variables. The authors found that the proportion of infants put to sleep in the supine position has increased over time but leveled off during the latter part of the survey period. Using logistic regression analysis the study found that whites and Hispanics were more likely to place their children prone to sleep than African Americans, even after controlling for other behavioral variables (aOR AA versus white: 1.83 (95% CI: 1.52-2.19) AA versus Hispanic: 1.73 (95% CI: 1.91-1.50-2.42)). The study also observed statistically significant regional differences in usual supine sleep position, with individuals living in the South being the least likely to place infants to sleep supine and those in the West the most likely. While recall bias may affect the results of phone surveys, these results support the conclusions of previous studies and indicate the racial disparities in SIDS deaths may be the result of racial differences in infant sleep habits [43].

Protective Factors against SIDS

Breastfeeding: The protective effects of breastfeeding and its relationship with Sudden Infant Death Syndrome have been debated extensively over the past decade.

Researchers have been divided on whether breastfeeding is an independent risk factor for SIDS. While a number of studies have been published that found statistically significant relationships between breastfeeding and SIDS [22, 25, 38, 64], others have been unable to find an association after controlling for other risk factors [27-29].

A prospective, multi-center cohort study in 2002 explored the association between breastfeeding and infant arousal [64]. The authors hypothesized that physiological mechanisms—namely arousal—are responsible for the effects of SIDS risk factors, including breastfeeding. Infant arousal is affected by a number of factors, including developmental state, medical conditions, and environmental exposures. The study recorded data on sleep stages, arousal scoring, and cardio-respiratory function of over 20,000 infants during one night of sleep in a sleep laboratory. Infants were then followed during the first year of life to determine if SIDS deaths occurred. Of the 20,000 infants, 40 eventually died of SIDS, for a rate of 2 per 1,000 infants. The authors found that breastfeeding was associated with a lower infant arousal threshold compared to infants who were bottle fed. While the authors did not find a direct association between infant feeding type and SIDS, they postulated that the lower arousal thresholds observed among breastfed infants may put them at a decreased risk of SIDS [64].

A meta-analysis of six studies on SIDS and breastfeeding by the Agency for Health Research and Quality in 2007 found a crude odds ratio of 0.41 (95% CI: 0.28, 0.58) in support of ever breastfeeding [22]. This association remained significant after controlling for infant sleep position, socioeconomic status, and maternal smoking (aOR 0.64; 95% CI: 0.51, 0.81). While the methods of this meta-analysis, and the weaknesses

of some of the studies included have been criticized, the results indicate the potential protective effects of breastfeeding on SIDS deaths [22].

A meta-analysis from 2000 also found an association between breastfeeding and a reduction in SIDS risk when compiling the results of 23 case-control and cohort studies [25]. The authors found that bottle-fed infants were more than twice as likely to die of SIDS in comparison to breastfed infants (OR: 2.11; 95% CI: 1.66, 2.68). While this association was statistically significant, the authors did note that a large number of the studies were of either "fair" or "poor" quality. The study was also unable to consider the effects of confounding variables on this relationship.

A 2005 population-based case-control study of 333 SIDS cases from Germany found a statistically significant relationship SIDS and breastfeeding for less than two weeks [65]. SIDS deaths occurred between 2002-2005, and cases and controls were matched on age, gender, region, and sleep time. The study found that infants who were breastfed for less than two weeks had 1.7 times greater risk of SIDS (aOR: 1.71, 95% CI: 1.06-2.77) after controlling for other covariates including sleep position, maternal smoking during pregnancy, family status, socioeconomic status, maternal age at delivery, ethnicity, bed sharing, previous live births, birth weight and extra heating of the infants [65].

A strong 2009 study from Germany also found that breastfeeding significantly reduced the risk of SIDS, even after controlling for a number of other potential confounders, including infant sleep position [38]. This population-based case-control study included 333 infants who died of SIDS and 998 age-matched controls from

Germany from 1998-2001. The study used a standardized definition of SIDS, and all cases were autopsy-confirmed. Any breastfeeding at two weeks of age was associated with an adjusted 0.43 odds of SIDS death compared to infants who had no breastfeeding (95% CI: 0.27, 0.69). Exclusive breastfeeding at one month of age also significantly reduced the risk of SIDS death (aOR: 0.48; 95% CI: 0.28, 0.82), though partial breastfeeding at one month was not statistically significant. The most striking effects of breastfeeding on the reduction of SIDS risk were seen in infant feeding mode in the month before death/interview. Infants who were exclusively breastfed in the months before death were over 73% less likely to die of SIDS (aOR: 0.27; 95% CI: 0.13, 0.56) compared to infants who were exclusively bottle-fed. Similarly, infants who were at least partially breastfed in the month before death/interview were 3.4 times less likely to die of SIDS than infants who were exclusively bottle-fed (aOR: 0.29; 95% CI: 0.16, 0.53) [38]. While this is a case-control design and based on retrospective surveys, this study controlled for a large number of known confounders and compared exclusive, partial, and no breastfeeding at multiple age points using a standardized definition of SIDS.

Pacifier Use: A number of studies have also found an association between pacifier use and SIDS. It appears that pacifier use during sleep is protective against SIDS deaths in infants. A 2010 matched case-control study of 195 black infants examined racial disparities and interactions between bed sharing and other SIDS risk factors, including pacifier use [66]. When examining SIDS risk factors among bed-sharing infants, non-use

of a pacifier was among the strongest predictors of SIDS. Among bed-sharing infants, non-use of a pacifier was associated with more than 2.7 greater risk of SIDS (aOR: 2.7; 95% CI: 1.1-7.0) after controlling for other covariates [66].

In the 2005 Germany SIDS study (methods above), Vennemen et al. observed a similar protective effect for infants using a pacifier during last sleep. After controlling for a number of known confounders, pacifier use during last sleep resulted in an adjusted odds ratio of 0.39 (95% CI: 0.25-0.59) [67].

Room sharing (without bed sharing): The German Sudden Infant Death Syndrome Study also found that room sharing—without bed sharing—was protective against SIDS. Compared to sleeping in the parental room, infants sleeping in the living room had more than twice the risk of SIDS (aOR: 2.41; 95% CI: 1.06, 5.51) [65]. Sleeping in a bedroom at a friend's house put infants at a particularly high risk of SIDS compared to sleeping in the parental bedroom (aOR: 38.67; 95% CI: 3.89-384.05) [65].

HIV and SIDS:

Several cohort studies have identified higher rates of SIDS among HIV-exposed infants than in the general population. A paper by the European Collaborative Study in 1991 explored the natural history of perinatal HIV infections among a cohort of 600 children born to HIV-infected mothers before June 1990 [32]. Children were followed up every three months from birth until 18 months of age. During the follow up period, 3 HIV-indeterminate children in this cohort died of SIDS, resulting in a rate of 4.5 per 1000

births. The study noted that this rate was significantly higher than that observed in the general population. The definition of SIDS used and the method of diagnosis, however, were not explained in the paper [32] .

A cohort study by Mayaux et al. and the French Pediatric HIV Infection Study Group examined maternal risk factors for perinatal HIV transmission. The longitudinal study of 848 HIV-exposed infants and their HIV-infected mothers began in 1986, and noted 6 cases of sudden unexpected infant death (SUID), for a rate of 7.1 per 1,000 infants [33]. A study by Kind et al. and the Swiss Neonatal HIV Study Group analyzed data from 286 perinatally exposed infants in Switzerland. While a strict definition of SIDS was not used in this study, the researchers did observe a high incidence of sudden unexpected infant deaths (SUID) deemed unrelated to HIV. Four of the 286 infants died suddenly during the follow-up period, and were classified as sudden infant deaths [34]. Overall the study observed a rate of 2 cases per 100 of sudden infant death unrelated to HIV disease. This was a 15-fold increase over unexpected sudden infant deaths observed in the general population [34].

A multiple cohort study by the Perinatal Safety Review Working Group explored the effects of prenatal exposure to antiretroviral drugs on mitochondrial toxicities in infants [36]. The study included five U.S. cohorts and over 20,000 HIV-exposed infants. During the study period 37 of these infants died of SIDS, for a rate of 1.8 per 1000 births. Given the increased risk of SIDS among minority populations, and the racial makeup of the cohort which was 55% African American, the authors concluded that this rate was not outside of the range observed in the general population [36].

A 1993 study by Bulterys et al. postulated that SIDS in a cohort of 410 HIV-exposed Rwandan infants could be caused by cardiac abnormalities [31]. During the study period researchers observed a rate of sudden infant deaths of 7.3 per 1000 live births among HIV-exposed infants. Because no autopsies were performed after the deaths in Rwanda, deaths were classified as Sudden Unexpected Infant Deaths (SUID) rather than SIDS. None of the 426 children born to HIV-uninfected women in the control group died suddenly and unexpectedly during this same period. Exposure to HIV infection in utero could have an adverse impact on fetal growth and development, causing abnormalities in "infant cardiac autonomic regulation" [31]. This impact would occur regardless of the infection status of the infant, and could explain the unusually high rate of SIDS among HIV-exposed infants according to the authors, though this has not yet been confirmed in the literature.

In addition to HIV exposure, the use of opiates during pregnancy can put infants at higher risk of SIDS. A study by Kahlert C et al. in 2007 explored the role of opiate use in SIDS risk among HIV-exposed infants in Switzerland [35]. The prospective Swiss HIV and Cohort Study (SHCS) and the Swiss Mother and Child HIV Cohort Study (MoCHiV) included 466 perinatally HIV-exposed infants followed from birth through 2 years of age. Seven of these infants died of SIDS during the study period. Compared to the general population in Switzerland, infants perinatally exposed to HIV had 18 times greater risk of SIDS (95% CI: 9-38). Those infants who were exposed to both HIV and intrauterine opiods had 69 times greater risk of SIDS (95% CI: 33-141) than infants in the general population. The study did not find any bivariate associations between SIDS and risk

factors such as prematurity, low birth weight, HIV status, or ARV drug exposure, though no model was constructed [35].

HIV and Breastfeeding:

Since 1985 HIV-infected mothers in the United States have been advised not to breastfeed their infants [7]. The Centers for Disease Control and Prevention (CDC) published recommendations for preventing perinatal HIV transmission in an article from the Center for Disease Control and Prevention's (CDC) Morbidity and Mortality Weekly Report (MMWR) that concluded "HIV infected women should be advised against breastfeeding to avoid postnatal transmission to a child who may not yet be infected." [7]

Bertolli et al. found that a small proportion of HIV-infected mothers in the United States still chose to breastfeed after these recommendations were put forward [68]. A cohort study of 1193 HIV-infected mothers in Massachusetts and Los Angeles between 1998-1993 enrolled in the Perinatal Spectrum of HIV Disease cohort found that 79 women (3%) reported breastfeeding. Women who did not know their HIV status before delivery were more than 8 times as likely to breastfeed their infant than women who knew that they were HIV-infected before birth. However, receipt of prenatal care was not significantly associated with avoidance of breastfeeding [68]. The proportion of HIV-infected women choosing to breastfeed appears to have decreased. More recent studies found a smaller proportion of HIV-infected mothers reported breastfeeding their infants—as low as 1.3% in 1999-2008 [37].

However, in the absence of acceptable, feasible, affordable, sustainable, and safe (AFASS) breastfeeding alternatives in resource-limited settings, HIV-infected women have been advised to exclusively breastfeed their infants for six months [69]. The latest WHO recommendations have also added extended infant and/or maternal ARV prophylaxis in addition to breastfeeding in order to prevent MCT at all periods before, during and after pregnancy, including late postnatal HIV transmission through breastfeeding [70].

Without ARV prophylaxis, the risk of HIV transmission through breastfeeding is substantial. A prospective cohort study by Mayaux et al. explored the rate of mother-to-child (MTC) HIV transmission from breastfeeding [33]. The study included a cohort of 848 mother/infant pairs in which the mother was HIV-infected at the time of delivery, from 62 obstetric facilities in France. The rate of mother-to-child transmission in this cohort was approximately 20.2%. The rate of transmission among breastfeeding infants, however, was twice as high as among bottle fed infants (40 versus 19%, $p<0.04$). Multivariate analysis found that low CD4 counts and elevated maternal age were associated with HIV transmission through breastfeeding [33].

A randomized control trial in Tanzania by Fawzi et al. assessed the risk of mother-to-child HIV transmission through breastfeeding [71]. Breastfeeding resulted in an additional risk of HIV transmission of 18% among women with uninfected infants at 6 weeks. Late post-natal transmission was significantly associated with maternal viral load, CD4 count, high erythrocyte sedimentation rates, maternal stage of HIV disease, and nipple/breast lesions [71].

A review article by Fowler and Newell in 2002 summarized the effects of breastfeeding on mother-to-child HIV transmission. The study found that, in the absence of other preventative interventions, breastfeeding accounted for ⅓ - ½ of all MTCT in resource poor settings. The study also supported previous findings that maternal viral load is significantly associated with late postnatal HIV transmission through breastfeeding [72]. Kourtis et al. explored new and emerging strategies for preventing HIV transmission through breastfeeding. The study found the risk of HIV transmission through breastfeeding to be approximately 15% if continued through the first 2 years of life [73]. The authors also calculated that breastfeeding accounted for up to half of all infant HIV infections worldwide [73].

However, maternal and/or infant antiretroviral therapy can significantly reduce the risk of MCT through breastfeeding. A Cochran review by Horvah et al. in 2010 examined interventions to avoid mother-to-child transmission (MTCT) of HIV through breastfeeding [74]. The review included 6 randomized clinical trials and 1 cohort study. The study found that ARV drugs were effective in reducing the risk of late postnatal HIV transmission through breastfeeding. The study also found that the reduction in risk was significantly associated with the lowering of maternal viral loads and the amount of virus in the breast milk. Rates of late postnatal transmission below 1% have been achieved in a number of randomized clinical trials of various ARV therapies [12, 74, 75].

SIDS and Breastfeeding in the Context of Perinatal HIV Transmission and HAART:

It should be noted, however, that despite the significant decrease in the MCT rate as a result of effective ARV therapy, the risk of late postnatal mother-to-child HIV transmission cannot be completely eliminated [75]. In areas such as the United States, where acceptable, feasible, affordable, sustainable, and safe breastfeeding alternatives are available, HIV-infected mothers should avoid breastfeeding their infants [9]. These recommendations still apply to those women who have stably suppressed viral loads due to effective HAART [9].

While breastfeeding has been associated with a reduced risk of a number of infant diseases and conditions—including sudden infant death syndrome—the risk of perinatal HIV transmission through breastfeeding likely still outweigh the benefits. Given the relatively low rate of SIDS, a risk of MCT through breastfeeding of 1% would likely still result in a number of perinatally HIV-infected infants for every case of SIDS prevented.

In addition to an examination of the risk factors for SIDS among perinatally HIV-exposed infants, this study sought to predict the effects of breastfeeding among a cohort of HIV-infected women on both late-postnatal HIV transmission and their infants' risk of SIDS.

CHAPTER 4: MANUSCRIPT

HIV, SIDS, AND BREASTFEEDING IN THE PEDIATRIC SPECTRUM OF HIV DISEASE COHORT

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The findings and conclusions of this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention

ABSTRACT

Objective: Sudden Infant Death Syndrome (SIDS) remains the leading cause of post-neonatal death among infants in the United States. However, the rate of SIDS has declined significantly in the past two decades, due in large part to interventions such as the National Back to Sleep Campaign. A number of studies have noted an elevated rate of SIDS among cohorts of HIV-exposed infants both before and after the launch of the Back to Sleep Campaign. The objective of this analysis was to identify trends in SIDS rates among a cohort of HIV-exposed infants from 1988-2004, as well as risk factors for SIDS among HIV-exposed infants.

Methods: We analyzed data from the medical records of 13,084 HIV-exposed infants followed from birth during 1988-2004. Data was obtained from eight sites in the United States involved in the Pediatric Spectrum of HIV Disease (PSD) Project, which was conducted by the Centers for Disease Control and Prevention (CDC). The study population included HIV-infected, HIV-uninfected, and HIV-status-indeterminate infants.

Results: During the study period 17 cases of SIDS were diagnosed among infants in this cohort, for a crude SIDS rate of 1.3 per 1,000 infants. Rates of SIDS were highest during 1988-1994 at 2.9 per 1,000, but dropped to 0.5 per 1,000 from 1995-2004. Rates of SIDS were not statistically different among white, black/African American, and infants of other races. Rates of SIDS were highest among HIV-status-indeterminate infants (6.2 per 1,000 infants), who presumably died before their HIV status could be determined,

compared to HIV-infected infants (1.3 per 1,000 infants) and HIV-uninfected infants (0.4 per 1,000 infants).

Significant risk factors for SIDS among members of this cohort included a lack of prenatal care (OR: 5.26; 95% CI: 1.493, 18.797), maternal illicit drug use during pregnancy (OR: 4.2; 95% CI: 1.35, 12.93), low birth weight (OR: 2.60; 95% CI: 1.004, 6.753) and infant birth in 1994 or earlier (OR: 6.3; 95% CI: 2.0515, 19.3185). Breastfeeding, premature delivery, male gender, black/African American race were not significantly associated with SIDS in this cohort. On univariate analysis HIV-status-indeterminate infants also had a greater risk of SIDS compared to HIV-uninfected infants (OR: 15.3; 95% CI: 4.853, 48.0), and HIV-infected infants (OR: 4.704; 95% CI: 1.041, 21.26). Among infants dying of all causes during the first year of life, however, HIV-infected infants had a significantly higher risk of SIDS than HIV-uninfected infants, after controlling for age at death (aOR: 11.04; 95% CI: 1.660, 73.475).

Conclusions: The rate of SIDS among this cohort of HIV-exposed infants declined steadily from 1988-2004, a trend also observed in the general population during this period. At the beginning of the study period the adjusted rate of SIDS in this cohort was 4.9 per 1,000 infants—approximately 3.5 times higher than the overall rate of SIDS in the United States. By 2004, however, the adjusted rate had fallen to 0.4 per 1,000 infants, a rate similar to that observed in the general population. Significant risk factors for SIDS for infants in this study included maternal drug use during pregnancy, lack of prenatal care, and low birth weight. Race, gender, and breastfeeding were not

significantly associated with SIDS. HIV-infection was only a significant risk factor for SIDS among infants dying during the first year of life.

INTRODUCTION:

SIDS: The term "Sudden Infant Death Syndrome" (SIDS) has been used since 1969 to describe unexpected infant deaths of unknown etiology [1]. SIDS has also been known as "cot death" or "crib death," terms more common in Europe, Australia, and New Zealand. Today SIDS is defined as the "unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history" [1]. As such, SIDS is fundamentally a diagnosis of exclusion, making death scene investigations and autopsies crucial components of a SIDS diagnosis. Clinical and/or autopsy findings often include intrathoracic petechiae, mild pulmonary edema, and minor inflammatory changes to the airway, though these are not always present. There are no positive autopsy findings that definitively indicate a diagnosis of SIDS; rather, post-mortem examinations allow investigators to rule out other potential causes of death [1].

SIDS belongs to a larger category of conditions known as "Sudden Unexpected Infant Death" (SUID). SUID is a broad diagnostic category used for infant deaths for which the cause of death is "unapparent or multifactorial [2]." The term is increasingly being used by clinicians or death scene investigators, and a number of researchers have documented a shift in SIDS diagnoses, with a growing preference for SUID or "undetermined" for cases of sudden infant death that remained unexplained by other diseases or conditions [3]. The rates of both SUID and SIDS have decreased significantly

since the mid-1990s. Despite this decrease, SIDS remains the leading cause of post-neonatal death among infants in the United States and other developed countries [4].

The majority of SIDS cases occur during the first six months of life, with incidence peaking between the ages of 2-4 months. SIDS is also more likely to affect boys than girls, and rates remain highest among infants who are African American, or Native American/Alaska Native, even after controlling for socioeconomic status [5]. A number of studies have also identified a higher rate of SIDS during the winter months of December, January, and February, though this trend seems to have dissipated as the rate of SIDS has fallen [6]. Rates of SIDS in the U.S. were approximately 1.4 per 1,000 live births in 1989, but dropped to 0.55 per 1,000 live births by 2006 [7].

Since the late 1980s SIDS has been strongly associated with the prone infant sleep position in epidemiologic studies. As a result the American Academy of Pediatrics (AAP) has been recommending the non-prone sleep position for infants since 1992 [8]. Interventions such as the “Back to Sleep” campaign are largely credited with the successful reduction of both infant prone sleeping and the annual rate of SIDS deaths among infants in the U.S. [7]. The “Back to Sleep” campaign began in 1994 as a joint effort between a number of institutions including the US Public Health Service, the AAP, and the National Institute of Child Health and Human Development, and has worked to promote “infant back sleeping and other risk-reduction strategies to parents, family members, child care providers, health professionals, and all other caregivers of infants” [9].

The campaign appears to have been successful in promoting infant back sleeping. According to the National Infant Sleep Position Study, the percent of infants back sleeping during their last sleep rose from 13% in 1992 to nearly 76% in 2006. However, the proportion of infants sleeping supine has remained largely the same since 2001 [7]. Racial disparities also continue to persist, with black infants being nearly 2 times more likely to have been placed to sleep prone or in the side sleep position during their last sleep when compared to white infants [7]. Similarly, the rates of SIDS among black infants remain more than three times higher than the rates among white infants [10].

In addition to infant sleep position, a number of factors have been identified which increase infants' risk of SIDS, including preterm birth/low birth weight, infant side sleeping, maternal smoking, maternal illicit drug use during pregnancy, soft infant sleep surfaces or redundant soft bedding, overheating, and sharing a sleep surface with an adult [5, 11]. Research has also identified a number of factors protective against SIDS, including pacifier use, room sharing without bed sharing, a lack of prenatal care, and, more recently, breastfeeding [11, 12].

Many countries including Germany and New Zealand have included breastfeeding promotion in their SIDS prevention and infant sleep campaigns [13, 14]. The benefits of breastfeeding include reduced risk of infectious diseases such as otitis media, respiratory infections and conditions such as childhood leukemia and overweight/obesity [15]. A number of studies have also found a significant relationship between breastfeeding and a reduced risk of SIDS. This association, however, has not

been consistently documented, and a number of studies have found that breastfeeding is no longer significant after controlling for other potential confounders including maternal smoking [16-18]. Recent analyses have found 50% or greater reduction in the risk of SIDS at all ages among infants who were breastfed, a relationship that remained significant after controlling for potential confounders such as maternal smoking during pregnancy, maternal age at delivery, family socioeconomic status, infant's birth weight, bed sharing, sleep position, and pacifier use during last sleep [12, 19].

Perinatal HIV: Since 1985 the Centers for Disease Control and Prevention has advised women infected with human immunodeficiency virus (HIV) to avoid breastfeeding in order to prevent late postnatal mother-to-child transmission (MCT) of HIV through breastfeeding [20]. Studies have shown that only a small proportion of HIV-infected mothers in the U.S. breastfeed their infants against recommendations. This proportion appears to be declining, from about 3% from 1988-1993, to 1% from 2005-2008 [21, 22]. Most of these women did not receive adequate prenatal care, and many were not diagnosed with HIV until labor and delivery, or later [21, 22].

Advances in HIV treatment including the use of highly active antiretroviral therapy (HAART) have greatly reduced the risk of both sexual and late postnatal HIV transmission in individuals with stably suppressed viral loads. While the risk cannot be entirely eliminated, a number of studies from Africa have shown HIV transmission rates through breastfeeding of approximately 1% among women being treated with HAART

[23]. These results have prompted questions regarding the need for HIV-infected mothers in the United States on HAART to continue avoiding breastfeeding.

Several large cohort studies in the developed world have also noted an increased rate of SIDS among infants perinatally exposed to HIV[2]. The European Collaborative Study identified 3 SIDS deaths among 600 HIV-exposed infants born before 1990 and followed from 0-18 months, for an overall rate of 5 per 1,000 infants [24]. A study from the French Pediatric HIV Cohort Study also found 6 cases of SIDS among a cohort of 994 HIV-exposed infants born between 1986-1990, a rate of 6.03 per 1,000 infants [25]. A 1992 prospective study from Switzerland found an even higher rate of SIDS in their cohort of 286 perinatally exposed infants. Four of these infants died of SIDS, for an overall rate of 13.99 per 1,000 infants [26]. A later study of the Swiss HIV Cohort found a rate of 14.9 per 1,000 infants followed from 1989-2002 [27]. A study in the United States in 1990-1998 found a rate of SIDS of 2.6 per 1,000 infants [28].

The reasons for the heightened rate of SIDS among infants perinatally exposed to HIV is unknown, though researchers have hypothesized that it could be related to the negative effects of maternal HIV infection on infant fetal growth and development, or cardiac complications associated with infant HIV infection [29]. This study will examine risk factors associated with SIDS deaths among perinatally HIV-exposed infants in the Pediatric Spectrum of HIV Disease (PSD) cohort, as well as trends in the rate of SIDS by HIV status during the study period.

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[2] Perinatal HIV exposure is defined as any infant born to an HIV-infected woman. A perinatally HIV-exposed infant may be HIV-infected, uninfected, or HIV-status indeterminate/unknown. (Women Children and HIV. (2011). Glossary of HIV/AIDS Terms. Retrieved March 1, 2011, from http://www.womenchildrenhiv.org/wchiv?page=gl-h)

METHODS:

The Pediatric Spectrum of HIV Disease Cohort: The PSD cohort was a CDC-funded longitudinal study of 19,025 HIV-exposed infants followed from birth during 1988-2004 in 41 hospitals from eight geographic locations across the United States. HIV-exposed infants were defined as those born to women known to be HIV-infected during pregnancy. Detailed reviews of medical records were conducted for all infants, including HIV-infected, HIV-uninfected, and HIV status-unknown infants. Chart reviews were carried out at regularly scheduled intervals through the first two years of life for those infants still receiving care at the site. HIV-infected infants were followed for the duration of their pediatric treatment. For the purposes of this analysis, data are limited to those gathered during the first year of life.

Definitions: HIV status was determined based on the CDC definition [30], and children lost to follow-up before their HIV status could be determined were classified as indeterminate. For the purposes of this analysis, infants classified as "Definitely HIV-infected" or "Probably HIV-infected" were defined as HIV-infected. Infants classified as "Definitely HIV-uninfected" or "Probably HIV-uninfected" were defined as uninfected. All other "Unclassified" infants were defined as indeterminate. Any maternal drug use was defined as a report of any of the following in the pediatric medical records: maternal use of intravenous drugs, street drugs, crack cocaine, symptoms of withdrawal in the infant, or a positive infant urine toxicology screening. Race was categorized as white, black/African American, or "other", which included all other and multiple races.

Data for both women and infants were abstracted from the pediatric medical records. Infant characteristics included gender, race, birth weight, number of siblings, type of birth, source of medical insurance, and HIV status. Data collected on maternal characteristics included age, race/ethnicity, no prenatal care, drug use, decision to breastfeed, parity, and weeks of gestation.

Inclusion Criteria: The present analysis was limited to perinatally HIV-exposed infants followed from birth. Infants born before the beginning of data collection in 1988 were excluded from this analysis. Analysis was limited to data gathered during the first year of life. From 1988-2004, 19,025 infants were enrolled in PSD and 13,084 (68.8%) met the inclusion criteria.

Statistical Analysis: We analyzed trends in SIDS diagnoses from 1988-2004 among HIV-exposed births. We used χ^2 tests for proportions and the Mantel-Haenszel chi-squared test for trends, and t-tests to compare quantitative variables. We calculated odds ratios to determine the magnitude of association between SIDS deaths and SIDS risk factors among HIV-exposed infants in the cohort. In order to evaluate risk factors for SIDS, odds ratios (ORs) were calculated in Univariate analysis for all exposures of interest. Using LOESS regression we estimated the rate of SIDS deaths per 1,000 infants in the cohort. In a separate analysis using multiple logistic regression, we evaluated factors associated with SIDS deaths while controlling for HIV status. 95% confidence

intervals were calculated and a 0.05 significance level was used. All data was analyzed using SAS 9.2 (Cary, North Carolina).

RESULTS:

Characteristics of Infants and Mothers: 6,696 (51.2%) of the infants were male (**Table 1**). 9,796 (74.9%) were classified as HIV-uninfected, 1,512 (11.6%) of infants were diagnosed with HIV infection, and 1,776 (13.6%) were status unknown or indeterminate. The majority of infants (7,728 [84.7%]) were black/African American. 1,133 (12.4%) were white, and 264 (2.9%) were classified as "other". Over 25% of infants had a low birth weight, and 82% had a biologic parent as their primary caretaker. Mothers in the cohort averaged 28 years of age with a parity of 1.7. Approximately 11.2% of women in the cohort had not received any prenatal care, and nearly 42% had documented illicit drug use during pregnancy. Over 93% had healthcare reimbursement through a public payer system such as Medicaid.

SIDS was diagnosed in a total of 17 infants in the cohort between 1988 and 2004 (**Table 2**). The majority of these infants (11 [64.7%]) were male (p-value: 0.2643). Two infants with SIDS were diagnosed as HIV-infected (11.8%), 4 were classified as HIV-uninfected (23.5%), and 11 (64.7%) were HIV status indeterminate (p-value <0.0001). Thirteen of the infants dying of SIDS (81.3%) were black/African American, two were white (12.5%), and one was classified as other (6.3%) (p-value: 0.8332).

Only 1,741 (13.3%) infant records contained data on breastfeeding. Of these, only 25 (1.4%) women reported breastfeeding their infants, a rate that is consistent with findings from other studies. The single SIDS case with data on infant feeding practices denied breastfeeding. Seventeen (100%) of the infants diagnosed with SIDS were singleton births, compared to 12,024 (95.8%) of infants who were not diagnosed with SIDS. Six (37.5%) of infants diagnosed with SIDS were born premature (<=37 weeks gestation), compared to 2,431 (21.0%) of non-SIDS infants (p-value 0.1228). Overall, 21.1% of the cohort was born premature. Premature birth was not significantly more common among infants diagnosed with SIDS (37.5%) compared to infants without SIDS (21.0%) (p-value: 0.1228). On average, infants dying of SIDS did not weigh significantly less at birth (2612.5 grams) compared to other infants in the cohort (2887.3 grams) (p-value: 0.1058) (**Data not shown)**.

Infant and Maternal Factors Associated with SIDS Deaths:

A number of infant characteristics were significantly associated with SIDS diagnosis (**Table 2**). Infants born before 1995 were more than six times more likely to die of SIDS than those infants born in 1995 or later (95% CI: 2.05, 19.25). Maternal drug use—a significant risk factor for SIDS in this cohort—was also more common in the period before 1994. Between 1988-1994 approximately 62% of infant records reported maternal drug dependency during pregnancy, compared to only 31% of records between 1995-2004. Maternal illicit drug use during pregnancy was 3.7 times more likely to occur before 1995 than after (OR: 3.72; 95% CI: 3.4287, 4.0398). Even after

controlling for maternal drug use during pregnancy, however, infants born before 1995 were still significantly more likely to die of SIDS compared to infants born in 1995 or later (aOR: 4.123; 95% CI: 1.272, 13.366).

Infants born premature were more than twice as likely to die of SIDS as infants born at >= 32 weeks gestation, though this relationship was not statistically significant. However, low birth weight infants (birth weight ≤ 2500 grams) had a greater risk of being diagnosed with SIDS. Low birth weight infants had 2.6 times greater risk of SIDS compared to infants of normal birth weight (95% CI: 1.0035, 6.7531). Male infants were also 1.75 times more likely to die of SIDS than female infants, though again this result was not statistically significant. Despite the fact that more than 83% of the infants diagnosed with SIDS were black/African American, race was not a significant risk factor for SIDS. When compared to white infants, black/African American race (OR: 1.05, 95% CI: 0.237, 4.657) or "other" race (OR: 0.465, 95% CI: 0.042, 5.148), were not significantly associated with SIDS in this cohort.

Several maternal characteristics were also significant risk factors for SIDS deaths among infants, including maternal drug use and no prenatal care (**Table 2**). Prenatal care appeared to be a protective factor against SIDS in this cohort. Infants whose mothers did not receive any prenatal care were more than five times more likely to be diagnosed with SIDS than infants whose mothers did not receive any prenatal care (OR: 5.26; 95% CI: 1.4928, 18.7970). This relationship may be confounded by race, however, as black women were significantly less likely to receive prenatal care compared to women of other races (OR: 0.61; 95% CI: 0.4904, 0.7488).

Overall 41.8% of infant records indicated some type of maternal drug use during pregnancy. Infants whose mothers reported drug use during pregnancy were significantly more likely to be diagnosed with SIDS than infants whose mothers had not used illicit substances while pregnant. Infants whose mother reported injection drug use were 4.6 times more likely to be diagnosed with SIDS than infants whose mothers did not report injection drug use (95% CI: 1.38, 15.14). Similarly infants whose mothers reported the use of street drugs were 4.37 times more likely to be diagnosed with SIDS than infants of mothers not reporting the use of street drugs (95% CI: 1.16, 16.47) Overall, infants whose mothers reported the use of any illicit substances were 4.2 times more likely to be diagnosed with SIDS than other infants (95% CI: 1.35-12.93).

Changes in the Rate of SIDS: Overall the cohort had a crude SIDS rate of 1.3 per 1,000 infants enrolled (95% CI: 0.81, 2.09). The crude rate of SIDS amongst black/African American infants in the cohort was 1.68 per 1,000 infants (95% CI: 0.98-2.90). The crude SIDS rate among white infants was 1.77 per 1,000 infants (95% CI: 0.44-7.06), and 3.8 per 1,000 among infants classified as "other" (95% CI: 0.53, 26.89) (**Figure 1**). Rates of SIDS were highest among HIV-status indeterminate infants (6.2 per 1,000 infants; 95% CI: 3.43, 11.18) compared to HIV-infected infants (1.3 per 1,000 infants; 95% CI: 0.33, 5.29) and HIV-uninfected infants (0.4 per 1,000 infants; 95% CI: 0.15, 1.09), though these rates were not significantly different (**Figure 2**).

The rate of SIDS was highest in the period before the advent of perinatal ARV prophylaxis and the launch of the 'Back to Sleep' Campaign, both of which began in

1994. Between 1988-1994, thirteen infants died of SIDS, for a rate of 2.91 per 1,000 infants (95% CI: 1.69-5.02). Only four infants died of SIDS between 1994-2004, for a rate of 0.46 (95% CI: 0.17, 1.24).

LOESS regression revealed a significant reduction in the rate of SIDS in the cohort from 1988-2004 (**Figure 3**). Overall the rate of SIDS dropped between 1988 and 2004. The rate of SIDS in 1988 was estimated to be 4.87 per 1,000 infants (95% CI: 0.3569, 9.3898), and fell to approximately 0.42 per 1,000 infants (-4.098, 4.935) in 2004.

Risk Factors for SIDS among Infants Dying during the First Year of Life: 429 infants (3.3%) died during the follow-up period (**Table 3**). Of these 183 (42.7%) died during their first year of life. 17 of these deaths (4.0%) were attributable to SIDS based on medical and/or autopsy records. Thirteen of 14 SIDS diagnoses were autopsy-confirmed. Autopsy data was missing for 3 cases. Infants dying of SIDS were over 9 times more likely to have received an autopsy than infants who died of other causes during the first year of life (OR: 9.68; 95% CI: 1.2139, 77.2579). Compared to infants who died of other causes, SIDS deaths were also more likely to occur during the autumn months of September, October, and November (OR: 2.77; 95% CI: 1.044, 7.35) (**Figure 2**).

Infants diagnosed with SIDS survived for an average of 3.2 months, while infants who died of other causes during the first year of life survived significantly longer, living for an average of 4.6 months (p 0.0146). Infants dying from causes other than SIDS also weighed significantly less at birth (2232.5 grams) than infants with SIDS (2728.3 grams,

p: 0.0469), and were born earlier on average (33.9 weeks versus 37.6, p: 0.0004). Infants with SIDS were also more than 11 times more likely to be classified as HIV-indeterminate when compared to infants dying from other causes during the first year of life (OR: 11.3, 95% CI: 1.72, 75.12). However, this relationship is confounded by age at death. Among infants dying during the first year of life, HIV-status-indeterminate infants are no longer significantly more likely to die of SIDS than HIV-uninfected infants after controlling for age at death (aOR: 1.6; 95% CI: 0.345, 7.541). After controlling for age at death, HIV-infected infants had significantly greater risk of SIDS than HIV-uninfected infants (aOR: 11.04; 95% CI: 1.660, 73.475).

DISCUSSION:

Interventions including the National Back to Sleep Campaign, have contributed to the significant decrease in the rate of Sudden Infant Death Syndrome in the United States. Today the proportion of children back-sleeping has risen from approximately 13% in 1992, to almost 76% in 2006 [7]. Additional research on modifiable risk factors, including maternal smoking and drug use, bed-sharing, redundant bedding, and formula feeding have informed policy recommendations by organizations such as the American Academy of Pediatrics [8].

Several studies from the late 1990s observed a much higher rate of SIDS among HIV-exposed and HIV-infected infants. The increased rate of SIDS among HIV-exposed infants was supported by the results of our study. Our analysis of SIDS deaths before

1995 found a SIDS rate of approximately 3 per 1,000 infants, more than 2 times higher than the national average during that period.

Encouragingly, this study found that the rate of SIDS among HIV-exposed infants declined between 1988 and 2004, from an estimated 4.87 per 1,000 infants in 1988 to 0.42 per 1,000 infants in 2004 (**Figure 1**). This decline coincided with the national reduction in SIDS rates observed in the U.S. general population, which fell from 1.4 per 1,000 live births in 1988 to 0.56 per 1,000 live births in 2004 [7].

The risk of SIDS was also significantly higher among infants born before 1995. It is not known if this difference is attributable to improved HIV treatments—which likely improved the health of HIV-infected pregnant women and prevented perinatal HIV transmission—or to interventions like the national Back to Sleep Campaign which reduced the rate of SIDS nationally.

The drop in the rate of SIDS deaths observed in the United States has been attributed largely to educational interventions such as the National Back to Sleep Campaign, which educated parents and healthcare providers on the risks associated with the infant prone sleep position. Racial and ethnic disparities, however, remain in both the rate of SIDS and the proportion of infants sleeping prone. Black/African American infants are still more likely to be placed to sleep in the prone position compared to infants of other races [7]. Though this study did not find a statistically significant relationship between race and an infant's risk of SIDS, on a population level black/African American infants are both disproportionately impacted by HIV/AIDS [31]

and are more likely to be placed to sleep in the prone position [7], making targeted interventions particularly important for this group.

This study did find a number of significant risk factors for SIDS among HIV-exposed infants, including maternal drug use during pregnancy, low birth weight, and not receiving any prenatal care, which have been noted in other studies [11]. However, unlike previous research, this study did not find a significant relationship between SIDS and gender or premature delivery. Because premature birth is associated with both prenatal HIV-exposure and SIDS, however, confounding may have obscured the relationship between SIDS and premature delivery.

A number of studies in from the 1970s through the 1990s identified a significant relationship between maternal drug use during pregnancy and an infant's risk of SIDS [32-35]. Maternal substance abuse during pregnancy was common among women in this cohort, in which nearly 42% of infant care records documented some type of maternal drug use during the prenatal period. Maternal drug use was significantly more common in the period before 1994, when more than 62% of mothers in the cohort used drugs, compared to approximately 31% from 1995-2004 (OR: 3.72; 95% CI: 3.4286, 4.0398) (**Figure 4**). While any maternal drug use was a significant risk factor for SIDS, this study did not find a statistically significant relationship between crack use and SIDS (OR 3.51; 95% CI: 0.587, 21.039), though both IV drug use and street drug use were significantly associated with an increased risk of SIDS.

While an indeterminate HIV status was a significant risk factor for SIDS, this is likely due to the fact that infants dying during the first year of life were less likely to

have had their HIV status assessed. If analysis is limited to infants dying during their first year of life, HIV-status-indeterminate infants were not significantly more likely to be diagnosed with SIDS than HIV-uninfected infants if age at death is controlled for. Among infants dying during their first year of life, HIV-infection was a significant risk factor for SIDS, increasing the risk of a SIDS diagnosis more than 11 times.

Our analysis did not find a significant relationship between SIDS and breastfeeding, though only a small proportion of infant medical records contained data on infant feeding modality. HIV-infected pregnant women in the United States have been advised to avoid breastfeeding since 1985 [20]. However, studies have shown that a small proportion of HIV-infected women—between 1.3-3.0%--report breastfeeding despite recommendations [36, 37]. This study found that approximately 1.4% of infants with data on feeding practices had been breastfed. Given the efficacy of Highly Active Antiretroviral Therapy (HAART) in preventing perinatal HIV transmission [38], some have begun to speculate that HIV-infected pregnant women with undetectable viral loads may be able to safely breastfeed. However, research indicates that the risk of HIV transmission through breastfeeding cannot be completely eliminated, even when viral loads are undetectable [38]. While breastfeeding has a variety of beneficial effects, including substantially reducing the risk for SIDS, the Centers for Disease Control and Prevention (CDC) continues to recommend that HIV-infected women in the United States avoid breastfeeding, given the availability of acceptable, feasible, affordable, sustainable, and safe breastfeeding alternatives [39].

Concerning SIDS, it is likely that the risk of late postnatal HIV transmission likely still outweighs the benefits of breastfeeding in the United States, even for women with stably suppressed viral loads as a result of HAART treatment. Given the low rate of SIDS, many more infants would likely be late postnatally infected with HIV through breastfeeding for every case of SIDS prevented.

HIV-infected mothers may reduce their infants' risk of SIDS by creating a safe infant sleep environment that avoids high temperatures, redundant bedding, and the prone or side sleep positions. The use of a pacifier and room-sharing without bed-sharing may also reduce the risk, as well as the avoidance of smoking. The results of this study indicate that HIV-infected mothers can also lessen their infant's risk by avoiding drug use, and obtaining prenatal care.

Limitations: The results of this study are limited by several factors. First, the definition of SIDS evolved during the years this cohort was followed, and diagnostic criteria changed [8]. Studies have indicated that the criteria for a SIDS diagnosis are not applied uniformly to cases of sudden unexpected infant death, and that SIDS diagnostics differ from state to state. Additionally, resources for death scene investigation, autopsy, and training vary widely across the country [3, 11].

Because the study was based on pediatric hospital chart review data, researchers were unable to determine the criteria used for diagnosing each case of SIDS. In at least one case, a SIDS diagnosis was applied to an infant who did not have a documented post-mortem examination. Because data was abstracted from the pediatric records,

maternal information, including smoking status and socioeconomic status were unavailable.

This analysis was also limited by our inability to examine several known risk factors for SIDS, namely infant sleep position. The role of other modifiable risk factors, including bed-sharing and infant sleep environment, could not be considered. The lack of these variables in addition to a large proportion of missing observations for variables of interest—e.g. breastfeeding—meant that we were unable to determine if the decline in SIDS rates was associated with national trends in infant sleep position, advancements in HIV drugs, or other potentially confounding factors. Finally, this analysis was limited by the small number of cases of SIDS which occurred in this cohort. The relatively small number of cases caused instability in the annual rate of SIDS.

However, this study is the first to examine trends in the rate of SIDS among HIV-exposed infants and to assess risk factors for SIDS in the context of perinatal HIV-exposure. Data was obtained from a large, multi-center cohort which contained a large proportion of all HIV-exposed births in the U.S. during this period.

CONCLUSIONS:

This study found that the rate of SIDS among HIV-exposed infants has declined steadily since 1988. While the rate of SIDS among HIV-exposed infants was substantially higher than the rate in the general population in the period before 1995, by 2004 rates had fallen to the level of those seen among infants in the general population.

This study also found associations between SIDS and a number of known risk factors, including maternal drug use during pregnancy, no prenatal care, and low birth weight. We also found significantly greater risk of SIDS among infants born before 1995 compared to those born in 1995 or later. Male gender, black/African American race and breastfeeding were not significant risk factors for SIDS among infants in this cohort. While not significantly associated with SIDS among all infants in the cohort, HIV-infection was a significant risk factor for SIDS among infants dying during the first year of life.

Table 1: Demographic Maternal and Infant Characteristics, PSD Cohort 1988-2004

Variable	% Responding	n	%
Infant Characteristics			
Male	100	6696	51.2
HIV Status			
Uninfected	100	9796	74.9
Infected		1512	11.6
Unknown		1176	13.6
Race			
White	69.7	1133	12.4
Black		7728	84.7
Other		264	2.9
Low birth weight	90.9	3032	25.5
Breastfed	13.3	25	1.4
Born before 1994	100	4462	34.1
Singleton Birth	96.1	12041	95.8
Total Siblings (mean, SD)	75.3	1.8	1.7
Biological parent as primary caretaker	86.5	9297	82.2
Positive Urine Toxicology Screen	22.2	1625	56.0
Symptoms of withdrawal	65.3	951	11.1
Maternal Characteristics			
Age (mean, SD)	11.3	27.9	6.2
Parity (mean, SD)	12.7	1.7	1.6
Gravida (mean, SD)	12	3.3	2.1
No Prenatal Care	85.0	1246	11.2
Preterm Delivery	88.5	2437	21.1
Crack use	52.4	2053	29.9
IV drug use	57.2	2281	30.5
Street drug use	56.4	2793	37.9
Any maternal drug use	84.7	4632	41.8
Public Payer	85.3	10417	93.3

Table 2: Risk Factors for SIDS among 13,084 HIV-Exposed Infants Followed from Birth: PSD, 1988-2004

Characteristic	SIDS (n=17) n (%)	No SIDS (n=13067) n(%)	Crude OR	95% CI
Infant Characteristics				
Male	11 (64.7)	6685 (51.2)	1.75	(0.647, 4.735)
HIV Status				
Uninfected	4 (23.5)	9792 (74.9)	Ref.	--
Infected	2 (11.8)	1510 (11.6)	0.31	(0.056, 1.685)
Unknown	11 (64.7)	1765 (13.5)	**0.07**	**(0.021, 0.206)**
Race				
White	2 (12.5)	1131 (12.4)	Ref.	--
Black	13 (81.3)	7715 (84.7)	0.95	(0.215, 4.228)
Other	1 (6.3)	263 (2.9)	2.15	(0.194, 23.802)
Low Birth Weight	8 (47.1)	3024 (25.5)	**2.60**	**(1.004, 6.753)**
Breastfed	0 (0.0)	25 (1.4)	--	--
Born before 1994	13 (76.5)	4449 (34.05)	**6.30**	**(2.052, 19.319)**
Singleton Birth	17 (100.0)	12024 (95.7)	--	--
Biological Parent As primary Caretaker	12 (80.0)	9285 (82.2)	0.87	(0.245, 3.079)
Positive Infant Urine Toxicology Screen	1 (33.3)	1624 (56.1)	0.39	(0.036, 4.327)
Symptoms of Withdrawal	2 (16.7)	949 (11.1)	1.6	(0.350, 7.304)
Maternal Characteristics				
No Prenatal care	4 (40.0)	1242 (11.2)	**5.3**	**(1.493, 18.797)**
Preterm delivery	6 (37.5)	2431 (21.0)	2.25	(0.818, 6.206)
Crack use	3 (60.0)	2050 (29.9)	3.51	(0.587, 21.039)
IV drug use	8 (66.7)	2273 (30.4)	**4.58**	**(1.377, 15.216)**
Street drug use	8 (72.7)	2785 (37.8)	**4.38**	**(1.162, 16.537)**
Any maternal drug use	12 (75.0)	4620 (41.8)	**4.18**	**(1.348, 12.974)**
Public payer	17 (100.0)	10400 (93.3)	2.51	(0.151, 41.814)

Figure 1:

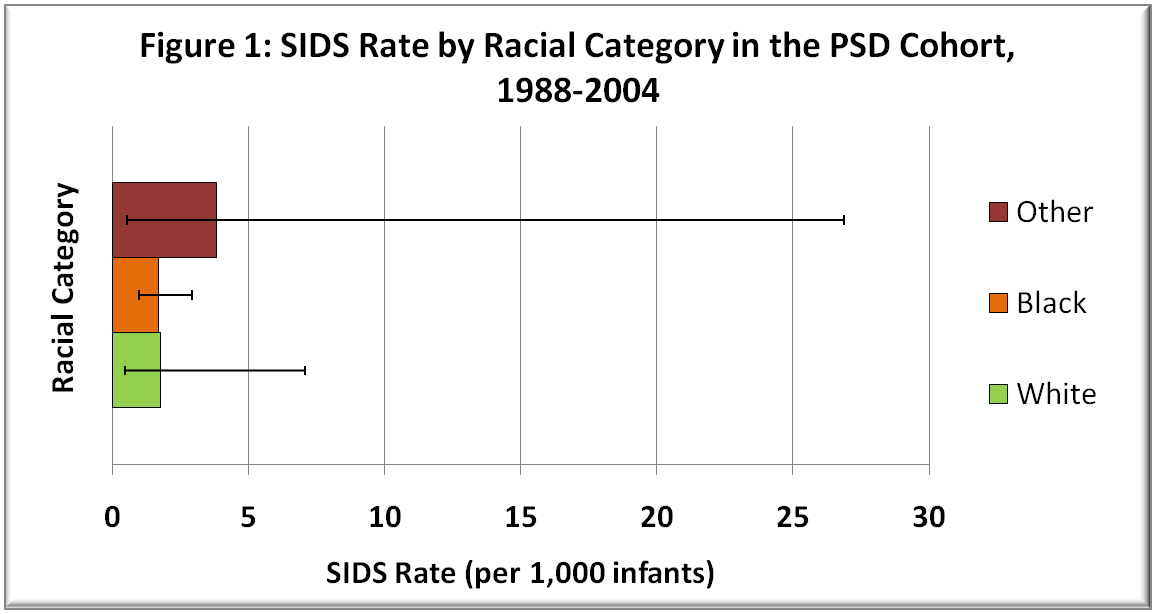


Figure 1: SIDS Rate by Racial Category in the PSD Cohort, 1988-2004
Racial Category
Other
Black
White
0
5
10
15
20
25
30
SIDS Rate (per 1,000 infants)

Figure 2:

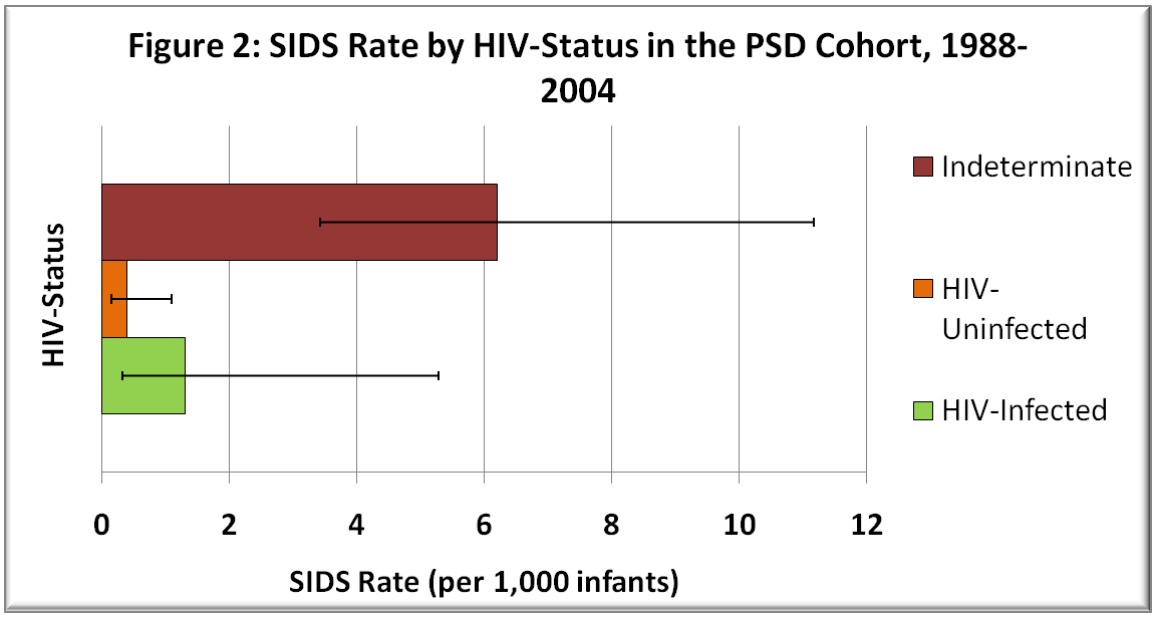
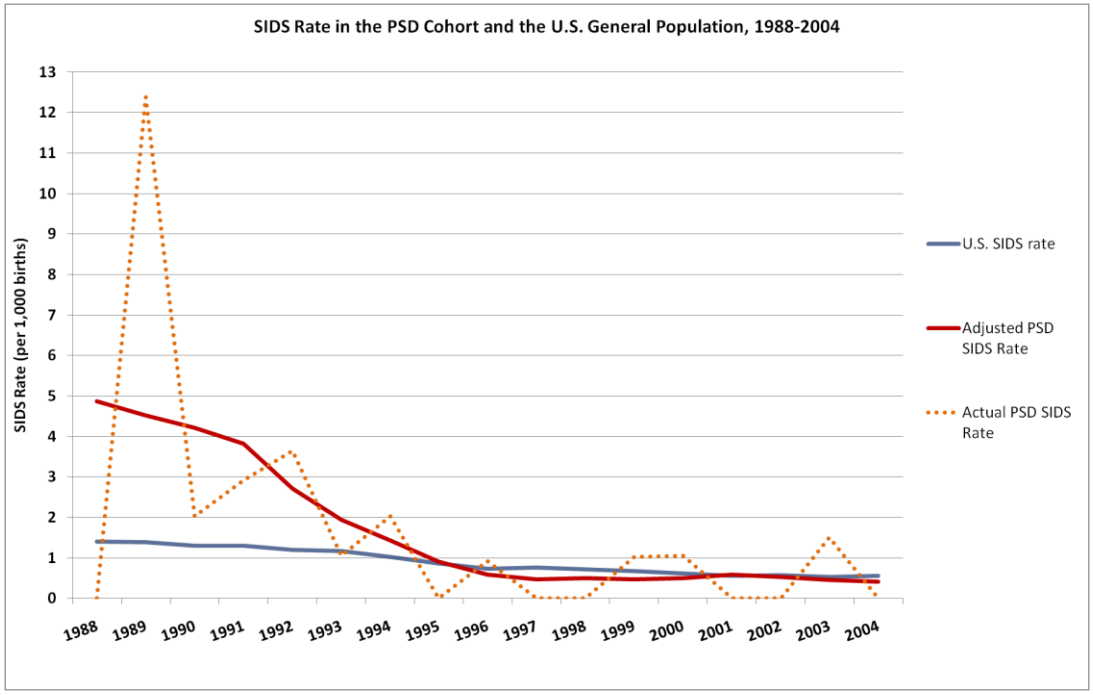


Figure 2: SIDS Rate by HIV-Status in the PSD Cohort, 1988-2004
HIV-Status
Indeterminate
HIV-Uninfected
HIV-Infected
0
2
4
6
8
10
12
SIDS Rate (per 1,000 infants)

Figure 3: SIDS Rate among HIV-Exposed Infants in the PSD Cohort and the U.S. General Population*, 1988-2004



*US SIDS rate obtained from: Colson ER, et al., *Trends and Factors Associated With Infant Sleeping Position.* Arch Pediatr Adolesc Med, 2009. **163**(12): p. 1122-1128.

Table 3: Characteristics of Infants Dying during the First Year of Life, by SIDS Status

Variable	SIDS (n, %) n=17	No SIDS (n, %) n=172	OR	95% CI
Autopsy	12 (92.3)	1 (7.7)	**9.68**	**(1.2139, 77.2579)**
Death in the Autumn	9 (56.3)	46 (27.5)	**3.38**	**(1.1901, 9.6110)**
Male	10 (62.5)	95 (56.9)	1.26	(0.4388, 3.6366)
Race				
White	2 (13.3)	14 (11.4)	1	ref
Black	12 (80.0)	107 (87.0)	1.27	(0.258, 6.292)
Other	1 (6.7)	2 (1.6)	0.29	(0.017, 4.797)
HIV Status				
Uninfected	3 (18.8)	12 (7.2)	1	ref
Infected	2 (12.5)	91 (54.5)	**11.37**	**(1.722, 75.118)**
Unknown	11 (68.8)	64 (38.3)	1.46	(0.352, 6.004)
Breastfed	0 (0)	0 (0)	--	--
Singleton Birth	16 (100.0)	147 (91.3)	3.24	(0.1849, 56.9152)
Preterm Delivery	5 (33.3)	78 (50.65)	0.4872	(0.1591, 1.4917)
Low Birth Weight	7 (43.8)	86 (56.6)	0.5696	(0.2113, 1.6862)
Maternal Drug Use	11 (73.3)	84 (60.9)	1.77	(0.5355, 5.8364)
No Prenatal Care	6 (60.0)	95 (74.8)	0.51	(0.1340, 1.9048)
Public Payer	16 (100.0)	137 (94.5)	2.04	(0.1125, 36.9833)
Born before 1994	12 (75.0)	101 (60.5)	1.96	(0.6064, 6.3375)

Figure 2: SIDS and Non-SIDS Deaths by Season, PSD Cohort 1988-2004

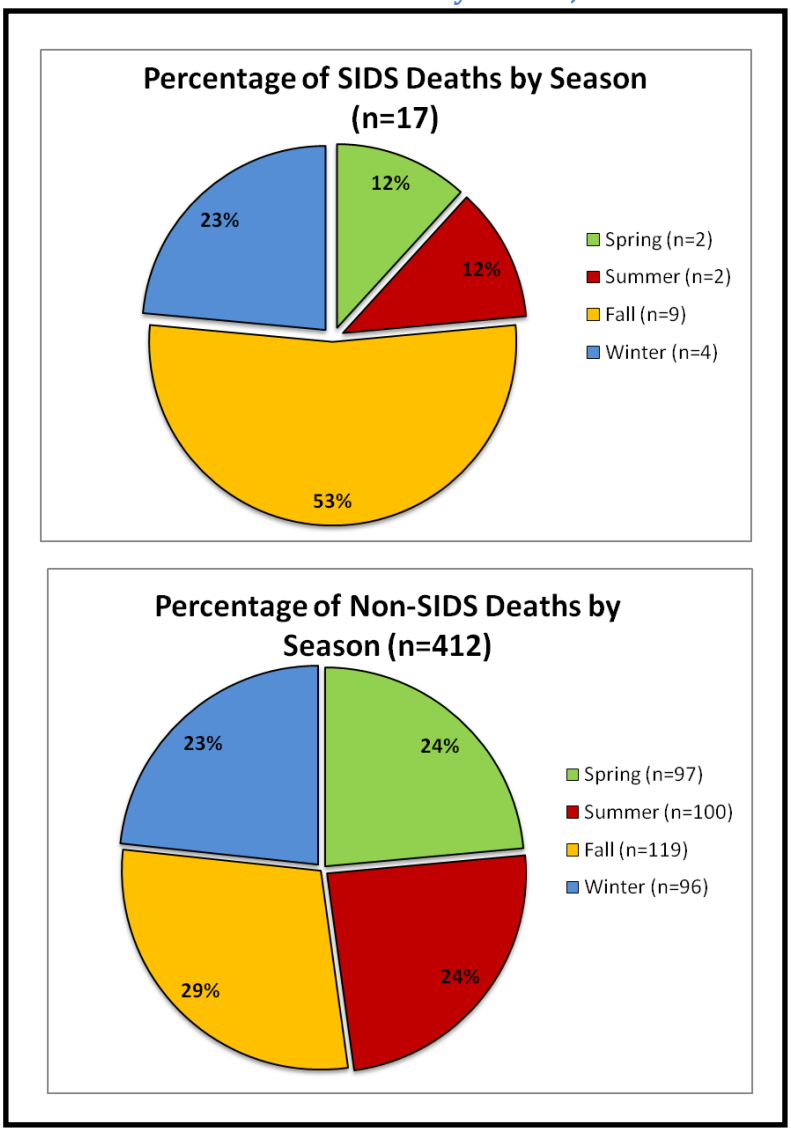
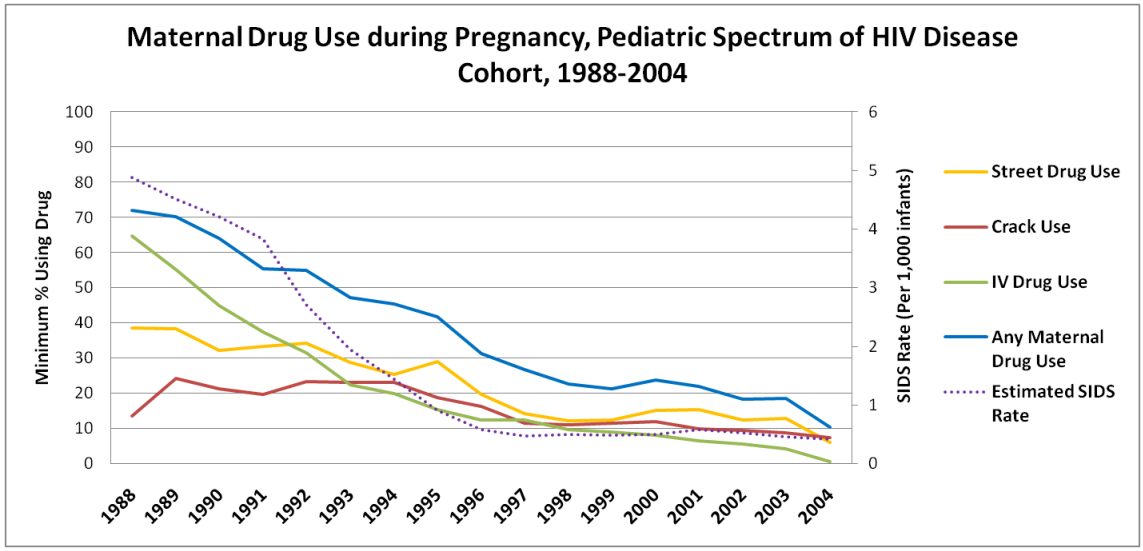


Figure 4: Maternal Drugs Use and SIDS Rate, PSD Cohort 1988-2004



RESOURCES

1. Krous HF, et al., *Sudden Infant Death Syndrome and Unclassified Sudden Infant Deaths: A Definitional and Diagnostic Approach.* Pediatrics, 2004. **114**(1): p. 234-238.
2. Randall B, Wilson A, and Regional Infant and Child Mortality Review Committee, *Regional Infant and Child Mortality Review Committee: 2009 final report.* S D Med, 2010. **63**(10): p. 343-7.
3. Shapiro-Mendoza CK, et al., *Recent National Trends in Sudden, Unexpected Infant Deaths: More Evidence Supporting a Change in Classification or Reporting.* Am J Epidemiol, 2006. **163**(8): p. 762-9.
4. Matthews TJ and Macdorman MF, *Infant mortality from 2004 period linked birth/death data set.* Natl Vital Stat Rep, 2007. **55**(14): p. 1-32.
5. Moon RY, Horne RSC, and Hauck FR, *Sudden infant death syndrome.* Lancet, 2007. **370**: p. 1578-87.
6. Leach CE, et al., *Epidemiology of SIDS and explained sudden infant deaths.* Pediatrics, 1999. **104**(4): p. e43.
7. Colson ER, et al., *Trends and Factors Associated With Infant Sleeping Position.* Arch Pediatr Adolesc Med, 2009. **163**(12): p. 1122-1128.
8. Task Force on Sudden Infant Death Syndrome, *The Changing Concept of Sudden Infant Death Syndrome: Diagnostic Coding Shifts, Controversies Regarding Sleeping Environment, and New Variables to Consider in Reducing Risk.* Pediatrics, 2005. **116**(5): p. 1245-1255.
9. NIH. *Back to Sleep Public Education Campaign*. 2010 [cited 2010 June 17, 2010]; Available from: http://www.nichd.nih.gov/sids/.
10. Unger B, et al., *Racial Disparity and Modifiable Risk Factors Among Infants Dying Suddenly and Unexpectedly.* Pediatrics, 2003. **111**(2): p. e127-e131.
11. Task Force on Sudden Infant Death Syndrome, *The Changing Concept of Sudden Infant Death Syndrome: Diagnostic Coding Shifts, Controversies Regarding the Sleeping Environment, and New Variables to Consider in Reducing Risk.* Pediatrics, 2005. **116**(5): p. 1245-1255.
12. Vennemann MM, et al., *Does Breastfeeding Reduce the Risk of Sudden Infant Death Syndrome?* Pediatrics 2009. **123**(3): p. e406-e410.
13. Kiechl-Kohlendorfer U, et al., *Epidemiology of sudden infant death syndrome (SIDS) in the Tyrol before and after an intervention campaign.* Wien Klin Wochenschr, 2001. **113**(1-2): p. 27-32.
14. Mitchell EA, et al., *Risk factors for sudden infant death syndrome following the prevention campaign in New Zealand: a prospective study.* Pediatrics, 1997. **100**(5): p. 835-840.
15. Bartlick M and Reinhold A, *The burden of suboptimal breastfeeding in the United States: a pediatric cost analysis.* Pediatrics, 2010. **125**(5): p. e1048-56.

16. Kraus JF, Greenland S, and Bulterys M, *Risk factors for sudden infant death syndrome in the US Collaborative Perinatal Project.* Int J Epidemiol, 1989. **18**: p. 113-120.
17. Gilbert RE, et al., *Bottle feeding and the sudden infant death syndrome.* BMJ, 1995. **310**: p. 88-90.
18. Hauck FR, et al., *Sleep environment and the risk of sudden infant death syndrome in a an urban population: the Chicago Infant Mortality Study.* Pediatrics, 2003. **111**: p. 1207-1214.
19. US Department of Health and Human Services, *Breastfeeding and Maternal and Infant Health Outcomes*. 2007, Agency for Healthcare Research and Quality: Rockville, MD. p. 93-97.
20. Centers for Disease Control and Prevention, *Recommendations for assisting in the prevention of perinatal transmission of human T-lymphotrophic virus type III/lymphophadenopathy-associated virus and acquired immunodeficiency syndrome.* MMWR Morb Mortal Wkly Rep, 1985. **34**: p. 721-726, 731-732.
21. Whitmore SK, et al., *Mother-to-Child Transmission of HIV in the United States: Correlates of Transmission in 15 areas during 2005 to 2008, Enhanced Perinatal Surveillance.* CDC Unpublished Data.
22. Bertolli JM, et al., *Breastfeeding among HIV-Infected Women, Los Angeles and Massachusetts, 1988-1993*, in *XI International Conference on AIDS*. 1996: Vancouver, Canada. p. Abstract #158.
23. Kilewo C, et al., *Prevention of Mother-to-Child Transmission of HIV-1 Through Breastfeeding by Treating Mothers with Triple Antiretroviral Therapy in Dar es Salaam, Tanzania: The Mitra Plus Study.* J Acquir Immune Defic Syndr, 2009. **52**(3): p. 406-416.
24. European Collaborative Study, *Children born to women with HIV-1 infection: natural history and risk of transmission.* Lancet, 1991. **337**(8736): p. 253-260.
25. Mayaux MU, et al., *Maternal factors associated with perinatal HIV-1 transmission: the French Cohort Study: 7 years of follow-up observation.* J Acquir Immune Def Syndr, 1995. **8**(2): p. 188-94.
26. Kind C, et al., *Epidemiology of vertically transmitted HIV-1 infection in Switzerland: results of a nationwide prespective study.* Eur J Pediatr, 1992. **151**(6): p. 442-8.
27. Kahlert C, Rudin C, and Kind C, *Sudden infant death syndrome in infants born to HIV-infected and opiate-using mothers.* Arch Dis Child, 2007. **92**: p. 1005-1008.
28. Bulterys M, et al., *Lack of evidence of mitochondrial dysfunction in the offspring of HIV-infected women. Retrospective review of perinatal exposure to antiretroviral drugs in the Perinatal AIDS Collaborative Transmission Study.* Ann N Y Acad Sci, 2000(918): p. 212-21.
29. Bulterys M, et al., *Sudden Infant Death Among Children Born to Women With Human Immunodeficiency Virus Type 1 Infection.* The Pediatric Infectious Disease Journal, 1993. **12**(2): p. 172.
30. Schneider E, et al., *Revised Surveillance Case Definitions for HIV Infection Among Adults, Adolescents, and Children Aged <18 Months and for HIV Infection and*

AIDS Among Children Aged 18 Months to <13 Years --- United States, 2008. MMWR Morb Mortal Wkly Rep, 2008. **57**(RR10): p. 1-8.

31. Lampe MA, et al., *Racial/Ethnic Disparities Among Children with Diagnoses of Perinatal HIV Infection -- 34 States, 2004--2007.* MMWR Morb Mortal Wkly Rep, 2010. **59**(04): p. 97-101.
32. Peterson DR, *SIDS in infants of drug-dependent mothers.* J Pediatr, 1980. **96**(4): p. 784-5.
33. Chavez CJ, et al., *Sudden infant death syndrome among infants of drug-dependent mothers.* J Pediatr, 1979. **95**(3): p. 407-9.
34. Rajegowda BK, Kandall SR, and Falciglia H, *Sudden unexpected death in infants of narcotic-dependent mothers.* Early Hum Dev, 1978. **2**(3): p. 219-25.
35. Kandall SR, et al., *Relationship of maternal substance abuse to subsequent sudden infant death syndrome in offspring.* J Pediatr, 1993. **123**(1): p. 120-6.
36. Bertolli JM, et al., *Breastfeeding among HIV-Infected Women, Los Angeles and Massachusetts, 1988-1993*, in *XI International Conference on AIDS*. 1996: Vancouver, Canada. p. 158.
37. Whitmore SK, et al., *Characteristics of Breastfeeding and Non-Breastfeeding HIV-Infected Women delivering Live Infants, Enhanced Perinatal Surveillance, 26 Areas, 1999-2008*, in *National HIV Prevention Conference*. 2009: Atlanta, GA.
38. Volmink J, et al., *Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection (Review).* The Cochrane Database of Systematic Reviews, 2009.
39. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*, D.o.H.a.H. Services, Editor. 2010: Washington D.C.

CHAPTER 5: PUBLIC HEALTH IMPLICATIONS

Explanation of Results:

While the rate of SIDS among HIV-exposed infants in this cohort was approximately 3.5 times higher than the national average in 1985, by 2004 this rate had dropped to 0.4 per 1,000 infants, about the same as the rate observed in the general U.S. population at that time [43]. Though the data limited the analysis to largely univariate associations, it appears that a lack of prenatal care, low birth weight, and maternal drug use were also significantly associated with an increased risk of SIDS.

Interestingly, among infants dying from all causes during the first year of life, HIV infection was a significant risk factor for SIDS, after controlling for age at death. In fact, after controlling for age at death, HIV infection increased the risk of SIDS more than 11 times. This study could not determine the reason for an increased risk of SIDS among infants infected with HIV, though it seems plausible that HIV infection could cause delays in intra-uterine growth and development that may increase an infant's risk of SIDS. Prenatal HIV-exposure is also associated with low birth weight and premature birth, which both increased an infant's risk of SIDS.

Maternal drug use during pregnancy was also common among mothers in this cohort, where 42% of pediatric records revealed some kind of prenatal maternal drug dependency. Though the annual proportion of pregnant women using illicit substances decreased from approximately 78% in 1988 to less than 11% in 2004 ($p<0.001$), drug use remained an issue among mothers in the cohort. Maternal drug use during pregnancy increases the risk of SIDS by as much as 5.5 times in some studies [76], a risk that is

supported by the results of this study where maternal drug use increased the risk of SIDS by more than 4 (OR: 4.18; 95% CI: 1.35, 12.97). In fact, in-utero exposure to drugs accounted for 57.1% of SIDS cases in this cohort, and 76.1% of SIDS cases among infants prenatally exposed to drugs. Drug prevention efforts and counseling pregnant women may decrease the risk of SIDS for HIV-exposed infants.

Not receiving prenatal care was also a significant risk factor for SIDS in this cohort. Though this association is likely confounded by other factors, including maternal health, socio-economic factors, race, and healthcare reimbursement status, ensuring the timely receipt of prenatal care for HIV-infected women may not only reduce the risk of mother-to-child HIV transmission, it may also reduce an infant's risk of SIDS.

Unfortunately this study could not determine the relationship between perinatal HIV-exposure and/or HIV-infection with the most significant risk factors for SIDS, including infant sleep position, infant sleep environment, and maternal smoking status. Additional research could examine the importance of HIV infection among HIV-exposed infants relative to these other known risk factors. Due to limitations in the data, this study was unable to control for potential confounders while evaluating the relationship between perinatal HIV infection and SIDS. Further research could also model the effects of HIV-infection while controlling for a number of other risk factors, including premature birth, low birth weight, maternal drug use, maternal age, prenatal care, race, gender, and breastfeeding.

Effects of Recommending Breastfeeding:

Questions have arisen recently about the need for HIV-infected mothers to avoid breastfeeding if their viral loads are stable and undetectable due to effective HAART treatment. The positive health effects associated with breastfeeding, specifically in reducing the risk of SIDS by approximately 50%, have prompted further speculation. However, even effective HAART treatment cannot fully eliminate the risk of sexual or perinatal HIV transmission. Studies from Africa have found an MTC risk of approximately 1% among infants born to mothers on highly active antiretroviral therapy (HAART) who were HIV-uninfected at birth, and who were exclusively breastfed for six months [15-17].

If the HIV-infected women in this cohort had all breastfed their infants the crude rate of SIDS in the cohort would have been reduced from 1.30 per 1000 infants to 0.65 per 1000 infants, assuming a 50% reduction in the risk of SIDS among breastfed infants [38]. Assuming a 15% HIV transmission rate among infants breastfed for 6 months in the absence of ARV therapy [1], approximately 400 additional infants would have been infected before the introduction of antiretroviral prophylaxis in 1994. Assuming that all women received ARV treatment after 1994 and a conservative breastfeeding transmission rate of 1% for woman and/or infants on ARV therapy [15-17], approximately 89 additional HIV transmissions would have likely occurred through breastfeeding. During the entire study period, the number of perinatally infected infants would have increased from 1512 to 2001. (**Appendix: Figure 1**). In fact, for every case of SIDS prevented, nearly 58 infants would have been postnatally infected

with HIV through breastfeeding. During the ARV period this number decreased significantly, given the lower risk of late-postnatal HIV transmission as a result of effective antiretroviral treatment. From 1995-2004, for every case of SIDS prevented, approximately 8 additional cases of perinatal HIV transmission would have resulted from breastfeeding.

Because a SIDS death is not easily comparable to a perinatal HIV infection—which many view more as a chronic disease now that HIV treatments have improved and lengthened the lives of those infected—using a measure of comparison may be helpful. One such measure of health impact is known as the disability-adjusted life year (DALY), which is a measure developed by the World Health Organization (WHO) of the number of years lost due to an illness, a disability, or premature death. According to the WHO, the DALY measure "extends the concept of potential years of life lost due to premature death…to include equivalent years of 'healthy' life lost by virtue of being in states of poor health or disability" [77]. The measure combines mortality and morbidity into a common measure that can compare the impacts of different diseases. By calculating DALYs for SIDS and perinatal HIV, the effects of each disease can be more easily compared.

Future research could calculate DALYs for U.S. infants with SIDS and with perinatal HIV to better compare the effects of breastfeeding on this population. This approach could also consider the effects of breastfeeding on diseases/conditions beyond SIDS, including otitis media, childhood leukemia, overweight/obesity, and respiratory infections.

An additional option would be to compare the cost-effectiveness of preventing perinatal HIV transmission versus preventing deaths from SIDS. The burden (in 2007 U.S. Dollars) of an infant death from SIDS was estimated to be approximately $10,560,000 per case in one recent study [10]. The cost in terms of treatment, disability, and premature death as a result of perinatal HIV could then be compared to this to better evaluate the effects of breastfeeding among a population of HIV-exposed infants.

Conclusions:

The results of this study indicate that the current recommendations against breastfeeding by HIV-infected mothers should not be rescinded based on reducing the risk of SIDS. Interventions such as infant sleep position, a safe infant sleep surface/environment, maternal receipt of prenatal care, maternal avoidance of smoking and the use of illicit drugs, and perinatal HIV prevention would likely have substantial impact on the prevention of SIDS among HIV-exposed infants.

Though breastfeeding provides important health benefits for both mothers and infants, in regions such as the United States, where breastfeeding alternatives are acceptable, feasible, affordable, sustainable, and safe (AFASS), the risk of breastfeeding in the context of maternal HIV infection likely still outweighs the benefits. This remains true for women on HAART with stably suppressed viral loads, as the risk of late post-natal HIV transmission cannot be completely eliminated.

CHAPTER 6: RESOURCES

1. Connor EM, et al., *Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group.* N Eng J Med, 1994. **331**(18): p. 1173-80.
2. Taylor A and et al. *Estimated Number of Perinatal HIV Infections in the United States*. in *National HIV Prevention Conference*. 2009. Atlanta, GA.
3. Burgard M, et al., *Mother-to-child transmission of HIV-1 infection from 1986 to 2007 in the ANRS French Perinatal Cohort EPF-CO1.* Clin Infect Dis, 2010. **51**(7): p. 833-43.
4. Warszawski J, et al., *Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort.* AIDS, 2008. **22**(2): p. 289-99.
5. Peters V, et al., *Missed opportunities for perinatal HIV prevention among HIV-exposed infants born 1996-2000, pediatric spectrum of HIV disease cohort.* Pediatrics, 2003. **111**(5 Part 2): p. 1186-91.
6. Whitmore SK, et al., *Missed opportunities to prevent perinatal human immunodeficiency virus transmission in 15 jurisdictions in the United States during 2005-2008.* Women Health, 2010. **50**(5): p. 414-25.
7. Centers for Disease Control and Prevention, *Recommendations for assisting in the prevention of perinatal transmission of human T-lymphotrophic virus type III/lymphophadenopathy-associated virus and acquired immunodeficiency syndrome.* MMWR Morb Mortal Wkly Rep, 1985. **34**: p. 721-726, 731-732.
8. WHO, *Guidelines on HIV and infant feeding 2010*. 2010, WHO: Geneva, Switzerland.
9. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*, D.o.H.a.H. Services, Editor. 2010: Washington D.C.
10. Bartick M, R.A., *The Burden of Suboptimal Breastfeeding in the United States: A Pediatric Cost Analysis.* Pediatrics, 2010. **125**(5): p. e1048-e1056.
11. Vernazza P, Hirschel B, and Bernasconi E, *HIV-infected persons on effective antiretroviral therapy (and free of other STDs) are sexually non-infectious.* Bulletin des medecins suisses, 2008. **89**(5): p. 1-10.
12. Volmink J, et al., *Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection (Review).* The Cochrane Database of Systematic Reviews, 2009.
13. Garcia-Tejedor A, et al., *Influence of highly active antiretroviral treatment (HAART) on risk factors for vertical HIV transmission.* Acta Ostet Gynecol Scand, 2009. **88**(8): p. 882-7.
14. Kesho Bora Study Group and de Vincenzi I, *Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomized controlled trial* Lancent Infect Dis, 2011. **11**(3): p. 171-180.
15. Taha TE, et al., *Post-Exposure Prophylaxis of Breastfeeding HIV-Exposed Infants with Antiretroviral Drugs to Age 14 Weeks: Updated Efficacy Results of the PEPI-Malawi Trial.* J Acquir Immune Def Syndr, 2011: p. e-pub.
16. Thomas TK, et al., *Triple-Antiretroviral Prophylaxis to Prevent Mother-To-Child HIV Transmission through Breastfeeding-The Kisumu Breastfeeding Study, Kenya: A Clinical Trial.* J Acquir Immune Def Syndr, 2011. **8**(3): p. e1000-e1015.

17. Kilewo C, et al., *Prevention of Mother-to-Child Transmission of HIV-1 Through Breastfeeding by Treating Mothers with Triple Antiretroviral Therapy in Dar es Salaam, Tanzania: The Mitra Plus Study.* J Acquir Immune Defic Syndr, 2009. **52**(3): p. 406-416.
18. Krous HF, et al., *Sudden Infant Death Syndrome and Unclassified Sudden Infant Deaths: A Definitional and Diagnostic Approach.* Pediatrics, 2004. **114**(1): p. 234-238.
19. Matthews TJ and Macdorman MF, *Infant mortality from 2004 period linked birth/death data set.* Natl Vital Stat Rep, 2007. **55**(14): p. 1-32.
20. Mathews TJ and MacDorman MF, *Infant mortality statistics from the 2006 period linked birth/infant death data set.* Natl Vital Stat Rep, 2010. **58**(17): p. 1-31.
21. Moon RY, Horne RSC, and Hauck FR, *Sudden infant death syndrome.* Lancet, 2007. **370**: p. 1578-87.
22. US Department of Health and Human Services, *Breastfeeding and Maternal and Infant Health Outcomes*. 2007, Agency for Healthcare Research and Quality: Rockville, MD. p. 93-97.
23. Vennemann MM, et al., *Does Breastfeeding Reduce the Risk of Sudden Infant Death Syndrome?* Pediatrics, 2009. **123**(3): p. e406-e410.
24. Association, A.D., *Position of the American Dietetic Association: Promoting and Supporting Breastfeeding.* Journal of the American Dietetic Association, 2009. **109**(11): p. 1926-1942.
25. McVea KLSP, Turner PD, and Peppler DK, *The Role of Breastfeeding in Sudden Infant Death Syndrome.* J Hum Lact, 2000. **16**(1): p. 13-20.
26. Ip S, et al., *Breastfeeding and maternal and infant health outcomes in developed countries.* Evid Rep Technol Assess (Full Rep), 2007. **153**: p. 1-186.
27. Hauck FR, et al., *Sleep environment and the risk of sudden infant death syndrome in a an urban population: the Chicago Infant Mortality Study.* Pediatrics, 2003. **111**: p. 1207-1214.
28. Brooke H, G.A., D, T., & H, B,, *Case-control study of sudden infant death syndrome in Scotland.* BMJ, 1997. **314**: p. 1516-1520.
29. Gilbert RE, et al., *Bottle feeding and the sudden infant death syndrome.* BMJ, 1995. **310**: p. 88-90.
30. Women Children and HIV. *Glossary of HIV/AIDS Terms*. 2011 [cited 2011 March 1]; Available from: http://www.womenchildrenhiv.org/wchiv?page=gl-h.
31. Bulterys M, et al., *Sudden Infant Death Among Children Born to Women With Human Immunodeficiency Virus Type 1 Infection.* The Pediatric Infectious Disease Journal, 1993. **12**(2): p. 172.
32. European Collaborative Study, *Children born to women with HIV-1 infection: natural history and risk of transmission.* Lancet, 1991. **337**(8736): p. 253-260.
33. Mayaux MU, et al., *Maternal factors associated with perinatal HIV-1 transmission: the French Cohort Study: 7 years of follow-up observation.* J Acquir Immune Def Syndr, 1995. **8**(2): p. 188-94.
34. Kind C, et al., *Epidemiology of vertically transmitted HIV-1 infection in Switzerland: results of a nationwide prespective study.* Eur J Pediatr, 1992. **151**(6): p. 442-8.
35. Kahlert C, Rudin C, and Kind C, *Sudden infant death syndrome in infants born to HIV-infected and opiate-using mothers.* Arch Dis Child, 2007. **92**: p. 1005-1008.
36. The Perinatal Safety Review Working Group, *Nucleoside Exposure in the Children of HIV-Infected Women Receiving Antiretroviral Drugs: Absence of Clear Evidence for Mitochondrial Disease in Children Who Died Before 5 Years of Ae in Five United States Cohorts.* JAIDS, 2000. **25**: p. 261-268.

37. Whitmore SK, et al., *Characteristics of Breastfeeding and Non-Breastfeeding HIV-Infected Women delivering Live Infants, Enhanced Perinatal Surveillance, 26 Areas, 1999-2008*, in *National HIV Prevention Conference*. 2009: Atlanta, GA.
38. Vennemann MM, et al., *Does Breastfeeding Reduce the Risk of Sudden Infant Death Syndrome?* Pediatrics, 2009. **123**(3): p. e406-e410.
39. Unger B, et al., *Racial Disparity and Modifiable Risk Factors Among Infants Dying Suddenly and Unexpectedly.* Pediatrics, 2003. **111**(2): p. e127-e131.
40. Task Force on Sudden Infant Death Syndrome, *The Changing Concept of Sudden Infant Death Syndrome: Diagnostic Coding Shifts, Controversies Regarding the Sleeping Environment, and New Variables to Consider in Reducing Risk.* Pediatrics, 2005. **116**(5): p. 1245-1255.
41. Schlaud M, et al., *The German case-control scene investigation study on SIDS: epidemiological approach and main results.* Int J Legal Med, 2010. **124**: p. 19-26.
42. Kraus JF, Greenland S, and Bulterys M, *Risk factors for sudden infant death syndrome in the US Collaborative Perinatal Project.* Int J Epidemiol, 1989. **18**: p. 113-120.
43. Colson ER, et al., *Trends and Factors Associated With Infant Sleeping Position.* Arch Pediatr Adolesc Med, 2009. **163**(12): p. 1122-1128.
44. *Back to Sleep Public Education Campaign*. Eunice Kennedy Shriver National Institute of Child Health and Human Development 2010 [cited 2011 January 15, 2011]; Available from: http://www.nichd.nih.gov/sids/.
45. Wedgwood RJ, *Review of USA Experience*, in *Sudden and Unexpected Deaths in Infancy (Cot Deaths)*, Camps FE and Carpenter RG, Editors. 1972, Wright: Bristol, England.
46. Filiano JJ and Kinney HC, *A perspective on neuropathologic findings in victims of the sudden infant death syndrome: a triple-risk model.* Biol Neonate, 1994. **65**: p. 194-197.
47. Guntheroth WG and Spiers PS, *The Triple Risk Hypothesis in Sudden Infant Death Syndrome.* Pediatrics, 2002. **110**(5): p. e64.
48. Fleming P and Blair PS, *Sudden Infant Death Syndrome and parental smoking.* Early Hum Dev, 2007. **83**(11): p. 721-5.
49. Fleming PJ, et al., *Environment of infants during sleep and risk of the suddent infant death syndrome: results of 1993-5 case-control study for confidential inquiry into stillbirths and deaths in infancy.* BMJ, 1996. **313**: p. 191-5.
50. Gunn AJ, Gunn TR, and Mitchell EA, *Is changing the sleep environment enough? Current recommendations for SIDS.* Sleep Medicine Reviews, 2000. **4**(5): p. 453-469.
51. Mage DT and Donner M, *A Unifying Theory for SIDS.* Int J Pediatr, 2009. **2009**: p. 1-10.
52. Samuels M, *Viruses and sudden infant death.* Paediatric Respiratory Reviews, 2003. **4**: p. 178-183.
53. Alroomi LG, D.J., Evans TJ, Galea P, & Howat R,, *Maternal narcotic abuse and the newborn.* Arch Dis Child, 1988. **63**: p. 81-83.
54. Chavez CJ, et al., *Sudden infant death syndrome among infants of drug-dependent mothers.* J Pediatr, 1979. **95**(3): p. 407-9.
55. Harper RG, Concepcion GS, and Blenman S, *Observations on the sudden death of infants born to addicted mothers*, in *Proceedings of Fifth National Conference on Methadone Treatment*. 1973, National Association for the Prevention to Narcotics: New York. p. 1122-1127.
56. Kandall SR, et al., *Relationship of maternal substance abuse to subsequent sudden infant death syndrome in offspring.* J Pediatr, 1993. **123**(1): p. 120-6.
57. Peterson DR, *SIDS in infants of drug-dependent mothers.* J Pediatr, 1980. **96**(4): p. 784-5.

58. Rajegowda BK, Kandall SR, and Falciglia H, *Sudden unexpected death in infants of narcotic-dependent mothers.* Early Hum Dev, 1978. **2**(3): p. 219-25.
59. Klonoff-Cohen H and Lam-Kruglick P, *Maternal and Paternal Recreational Drug Use and Sudden Infant Death Syndrome.* Arch Pediatr Adolesc Med, 2001. **155**: p. 765-770.
60. Bulterys MG, Greenland S, and Kraus JF, *Chronic Fetal Hypoxia and Sudden Infant Death Syndrome: Interaction Between Maternal Smoking and Low Hematocrit During Pregnancy.* Pediatrics, 1990. **86**(4): p. 535-540.
61. Richardson HL, Walker AM, and Horne RS, *Maternal smoking impairs arousal patterns in sleeping infants.* Sleep 2009. **32**(4): p. 515-21.
62. Dietz PM, et al., *Infant morbidity and mortality attributable to prenatal smoking in the U.S.* Am J Prev Med, 2010. **1**: p. 45-52.
63. Carpenter RG, et al., *Sudden unexplained infant death in 20 regions in Europe: case control study.* Lancet, 2004. **363**(9404): p. 185-91.
64. Kahn A, et al., *Sudden infant deaths: from epidemiology to physiology.* Forensic Science International, 2002. **130S**: p. S8-S20.
65. Vennemann MM, et al., *Sleep environment risk factors for sudden infant death syndrome: the German Sudden Infant Death Syndrome Study.* Pediatrics, 2009. **123**(4): p. 1162-70.
66. Fu LY, Moon RY, and Hauck FR, *Bed sharing among black infants and sudden infant death syndrome: interactions with other known risk factors.* Acad Pediatr, 2010. **10**(6): p. 376-82.
67. Vennemann MM, et al., *Modifiable risk factors for SIDS in Germany: results of GeSID.* Acta Paediatr, 2005. **94**(6): p. 655-60.
68. Bertolli JM, H.H., Frederick T, Caldwell B, Nieburg P, Simonds RJ, et al,. *Breastfeeding among HIV-infected women, Los Angeles and Massachusetts, 1988-1993*. in *International Conference on AIDS*. 1996. Vancouver, Canada.
69. World Health Organization, *HIV transmission through breastfeeding: a review of available evidence*. 2007: Geneva, Switzerland.
70. World Health Organization, *HIV and Infant Feeding 2010: Principles and recommendations for infant feeding in the context of HIV and a summary of evidence*. 2010: Geneva, Switzerland. p. 1-58.
71. Fawzi W, et al., *Transmission of HIV-1 Through Breastfeeding Among Women in Dar es Salaam, Tanzania.* JAIDS, 2002. **31**: p. 331-338.
72. Fowler MG and Newell ML, *Breast-Feeding and HIV-1 Transmission in Resource-Limited Settings.* JAIDS, 2002. **30**: p. 230-239.
73. Kourtis A, et al., *Prevention of human immunodeficiency virus-1 transmission to the infant through breastfeeding: New developments.* American Journal of Obstetrics and Gynecology, 2007. **197**(3 Suppl): p. S113-S122.
74. Horvath T, et al., *Interventions for preventing late postnatal mother-to-child transmission of HIV (Review).* The Cochrane Database of Systematic Reviews, 2010(1): p. 1-36.
75. Sturt AS, Dokubo EK, and Sint TT, *Antiretroviral therapy (ART) for treating HIV infection in ART-eligible pregnant women.* Cochrane Database Syst Rev, 2010(3): p. 1-100.
76. Ostrea EM Jr, Ostrea AR, and Simpson PM, *Mortality Within the First 2 Years in Infants Exposed to Cocaine, Opiate, or Cannabinoid during Gestation.* Pediatrics, 1996. **100**(1): p. 79-83.

77. World Health Organization. *Metrics: Disability-Adjusted Life Year (DALY)*. Health statistics and health information systems 2011 [cited 2011 March 1]; Available from: http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/.

CHAPTER 7: APPENDIX

Table 1: Studies of Infant Risk Factors for Sudden Infant Death Syndrome

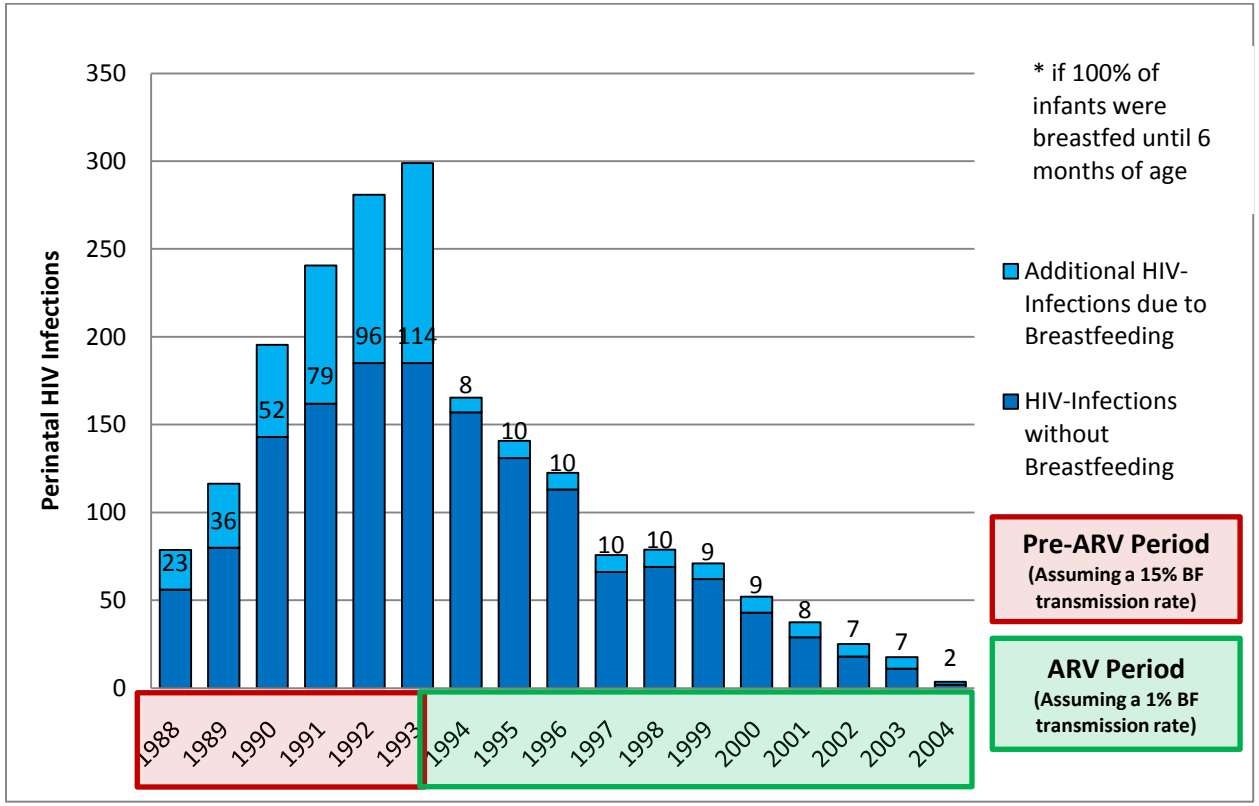
Risk Factor	Ratio Measure	Measure of Association	95% CI	# of Cases/# of Infants	Author	Year	Location
Infant Sleep Environment							
Prone Sleep Position	aOR	6.96	(1.51, 31.97)	201/477	Brooke	1997	Scotland
Prone Sleep Position	aOR	9.00	(2.84, 28.47)	195/975	Fleming	1996	England
Side Sleep Position	aOR	1.84	(1.02, 3.31)	195/975	Fleming	1996	England
Pillow Use	aOR	4.3	(1.6, 11.6)	52/206	Schlaud	2010	Germany
Use of a Heavy Duvet	aOR	4.4	(1.5, 13.3)	52/206	Schlaud	2010	Germany
Use of a Soft Underlay	aOR	3.0	(1.1, 8.7)	52/206	Schlaud	2010	Germany
Face Covered by Bedding	aOR	15.8	(2.5, 102.1)	52/206	Schlaud	2010	Germany
Sleeping in Living Room (and Not Parents' Bedroom)	aOR	2.41	(1.06, 5.51)	333/1331	Vennemann	2009	Germany
Sleeping in Bedroom at Friends' House (and Not Parents' Bedroom)	aOR	38.67	(3.89, 384.05)	333/1331	Vennemann	2009	Germany
Bed Sharing (With No Maternal Smoking)	OR	2.4	(1.2, 4.6)	745/2411	Carpenter	2004	Europe

Risk Factor	Ratio Measure	Measure of Association	95% CI	# of Cases/# of Infants	Author	Year	Location
Pacifier Use							
Pacifier Use	**Pooled aOR**	**0.39**	**(0.31, 0.50)**	**7 studies**	**Task Force on SIDS**	**2005**	**United States**
Pacifier Use	**aOR**	**0.39**	**(0.25, 0.59)**	**333/1331**	**Vennemann**	**2005**	**Germany**
No Pacifier Use	**aOR**	**2.7**	**(1.1, 7.0)**	**195/390**	**Fu**	**2010**	**United States**
Pacifier Use	**Pooled aOR**	**0.39**	**(0.31, 0.50)**	**7 studies**	**Task Force on SIDS**	**2005**	**United States**
Pacifier Use	**aOR**	**0.39**	**(0.25, 0.59)**	**333/1331**	**Vennemann**	**2005**	**Germany**
Breastfeeding							
Breastfeeding	Pooled aOR	0.64	(0.51, 0.81)	6 studies	AHRQ	2007	United States
Bottle-Feeding	Pooled OR	2.11	(1.66, 2.68)	23 studies	McVea	2000	United States
<2 Weeks of Breastfeeding	aOR	1.71	(1.06, 2.77)	333/1331	Vennemann	2005	Germany
Any Breastfeeding at 2 Weeks of Age	aOR	0.43	(0.27, 0.69)	333/1331	Vennemann	2009	Germany

Risk Factor	Ratio Measure	Measure of Association	95% CI	# of Cases/# of Infants	Author	Year	Location
Exclusive Breastfeeding at 1 Month of Age	aOR	0.48	(0.28, 0.82)	333/1331	Vennemann	2009	Germany
Exclusive Breastfeeding in the Month Before Death/Interview	aOR	0.27	(0.13, 0.56)	333/1331	Vennemann	2009	Germany
HIV Exposure							
Perinatal HIV Exposure	OR	18	(9, 38)	7/466	Kahlert	2007	Switzerland
Intrauterine HIV and Opioid Exposure	OR	69	(33, 141)	7/466	Kahlert	2007	Switzerland
Drug Exposure							
In utero Methadone or Heroin Exposure	Adjusted RR	3.2	(1.2, 8.6)	1760/ 1,209,534	Kandall	1993	New York, NY
In Utero Cocaine Exposure	Adjusted RR	1.6	(1.2, 2.2)	1760/ 1,209,534	Kandall	1993	New York, NY
Smoke Exposure							
Parental Smoking (both)	aOR	5.19	(2.26, 11.91)	201/477	Brooke	1997	Scotland

Risk Factor	Ratio Measure	Measure of Association	95% CI	# of Cases/# of Infants	Author	Year	Location
Maternal Smoking	aOR	2.7	(2.4, 3.0)	1926/ 3,352,756	Dietz	2010	United States
Maternal Smoking with Bed Sharing	OR	27	(13.3, 54.9)	745/2411	Carpenter	2004	Europe

Figure 1: Predicted Additional HIV-Infections Caused by Breastfeeding in the PSD Cohort, 1988-2004*



Attachment 1: Signature Form for Non-Research Projects

HUBERT DEPARTMENT OF GLOBAL HEALTH

Signature form for Non-Research Projects

This form is to be used for students who have chosen to write a Literature Review or Special Project and are not required to apply for IRB approval.

Attach a one to two page description of the project including general subject, hypothesis to be tested or question(s) to be answered, and lay summary.

I have read the attached information and verify that this project is not research and therefore does not need to be submitted to the Emory University Institutional Review Board.

_____ _____

Signature of Thesis Advisor **Date**

_____ _____

Signature of Thesis Advisor **Date**

Concept Sheet

In the absence of any interventions, breastfeeding accounts for approximately 40% of total mother to child HIV transmissions [1]. To prevent mother-to-child transmission (MTCT) of HIV in resource-limited settings, the World Health Organization (WHO) currently recommends that HIV-infected mothers exclusively breastfeed their infants for the first six months of life, during which the mother and/or infant continue to receive antiretroviral (ARV) therapy [2]. Since 1985 in the United States—where safe and affordable alternatives to breastfeeding are available—HIV-infected women have been advised to utilize replacement feeding options in order to reduce the risk of transmitting the virus to their infants [3]. Avoidance of breastfeeding and advances in treatment options have resulted in MCT rates in the U.S. of about 2.8% [4].

Developments in HIV treatments, including the advent of Highly Active Antiretroviral Therapy (HAART), have also resulted in improvements in maternal health. Many HIV-infected women receiving HAART now have undetectable viral loads (<50 copies/ml). Recent studies demonstrating significantly reduced rates of sexual and perinatal transmissions among individuals with stably suppressed viral loads [5-8] have led to questions about the need for all HIV-infected women to universally avoid breastfeeding. In the future, the numbers of HIV-infected pregnant women who have undetectable viral loads will likely increase and the question of breastfeeding will only become more important.

Breastfeeding is associated with a myriad of health benefits for both mothers and their infants. A meta-analysis by Agency for Healthcare Research and Quality (AHRQ) on SIDS found that any breastfeeding was associated with an adjusted odds ratio (OR) of 0.64. Other studies have found the reduction in risk to be as high as 71% [9]. However, despite considerable rate reduction, SIDS remains the leading cause of death in the post-neonatal period for infants in the U.S. [10]. Breastfeeding significantly reduces this risk.

This paper seeks to explore the potential effects of allowing HIV-infected women on HAART to breastfeed their infants. While several studies have reported an increased rate of SIDS among HIV-exposed infants [11-14] as well as the relationship between SIDS and breastfeeding [15, 16], no other studies have examined the potential effects of breastfeeding on SIDS in HIV-exposed infants. To explore this issue, I will analyze data from approximately 13,000 perinatally-exposed infants from the Pediatric Spectrum of HIV Disease (PSD) cohort who were born between 1988 and 2004. The PSD study was a chart review at sites across the country. The analysis will be limited to infants who were followed from birth, as the risk of SIDS (by definition) extends only through the first year of life.

I will calculate the yearly rates of SIDS in the cohort (#/1000 infants). Due to the small number of cases per year, changes in the annual rates of SIDS over time will be smoothed using locally weighted regression. Mean rates for treatment eras (i.e. pre- or post-HAART) will also be compared between the cohort and the general population using t-tests. Data permitting, logistic regression analysis will be used to determine the associations between SIDS and known risk factors, including previous live births, gestational age, birth weight, receipt of prenatal care, race, gender, HIV-infection, and maternal drug use. In order to model potential effects of allowing breastfeeding in this population, projected SIDS rates will be calculated using measures of effect determined in a 2007 report by AHRQ [9]. A range of MCT rates during breastfeeding

will also be obtained from the existing literature and used to calculate excess transmission were breastfeeding by HIV-infected mothers allowed.

This project does not require IRB approval.

References

1. Kourtis AP, et al., *Mother-to-child transmission of HIV-1: timing and implications for prevention.* Lancet Infect Dis, 2006. **6**: p. 726-732.
2. WHO, *Guidelines on HIV and infant feeding 2010*. 2010, World Health Organization: Geneva, Switzerland. p. 1-58.
3. CDC, *Current Trends Recommendations for Assisting in the Prevention of Perinatal Transmission of Human T-Lymphotropic Virus Type III/Lymphadenopathy-Associated Virus and Acquired Immunodeficiency Syndrome.* MMWR, 1985. **34**(48): p. 721-726, 731-732.
4. Zhang X, et al., *Estimated number of perinatal HIV infections in the United States, 2005*, in *National HIV Prevention Conference*. 2009: Atlanta, GA.
5. Attia S, et al., *Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis.* AIDS, 2009. **23**(11): p. 1397-1404.
6. Vernazza P, Hirschel B, and Bernasconi E, *HIV-infected persons on effective antiretroviral therapy (and free of other STDs) are sexually non-infectious.* Bulletin des medecins suisses, 2008. **89**(5): p. 1-10.
7. Shapiro RL, et al., *Antiretroviral regimens in pregnancy and breast-feeding in Botswana.* N Engl J Med, 2010. **362**(24): p. 2282-2294.
8. European Collaborative Study, *Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy.* Clin Infect Dis, 2005. **40**(3): p. 458-65.
9. Ip S, et al., *Breastfeeding and Maternal and Infant Health Outcomes in Developed Countries*. 2007, Agency for Healthcare Research and Quality: Rockville, MD.
10. Colson ER, et al., *Trends and Factors Associated With Infant Sleeping Position.* Arch Pediatr Adolesc Med, 2009. **163**(12): p. 1122-1128.
11. Starc TJ, et al., *Unexpected Non-HIV Causes of Death in Children Born to HIV-Infected Mothers.* Pediatrics 1999. **104**(1): p. 1-4.
12. European Collaborative Study, *Children born to women with HIV-1 infection: natural history and risk of transmission.* The Lancet, 1991. **337**(8736): p. 253-260
13. Mayaux MJ, et al., *Maternal Factors Associated with Perinatal HIV-1 Transmission: The French Cohort Study: 7 Years of Follow-Up Observation.* Journal of Aquired Immune Deficiency Syndromes and Human Retrovirology, 1995. **8**(2): p. 188-194.
14. Kind C, et al., *Epidemiology of vertically transmitted HIV-1 infection in Switzerland: results of a nationwide prospective study.* Eur J Pediatr, 1992. **151**: p. 442-448.
15. Vennemann MM, et al., *Does Breastfeeding Reduce the Risk of Sudden Infant Death Syndrome?* Pediatrics 2009. **123**(3): p. e406-e410.
16. McVea KLSP, Turner PD, and Peppler DK, *The Role of Breastfeeding in Sudden Infant Death Syndrome.* Journal of Human Lactation, 2000. **16**(1): p. 13-20.