Published in final edited form as:

J Acquir Immune Defic Syndr. 2011 October 1; 58(2): 188–192. doi:10.1097/QAI.0b013e31822d0433.

The interrelated transmission of human immunodeficiency virus type 1 and cytomegalovirus during gestation and delivery in the offspring of HIV-infected mothers

Woottichai Khamduang, M.S.^{1,2}, Gonzague Jourdain, M.D., Ph.D.^{1,2,3}, Wasna Sirirungsri, Ph.D.¹, Prapaisri Layangool, M.D.⁴, Suparat Kanjanavanit, M.D.⁵, Pornsuda Kittigamas, M.D.⁵, Karin Pagdi, M.D.⁶, Rosalin Somsamai, M.D.⁶, Surat Sirinontakan, M.D.⁷, Tamsiri Hinjiranandana, M.D.⁸, Wanna Ardong, M.D.⁹, Suchat Hongsiwon, M.D.¹⁰, Sirisak Nanta, M.D.¹¹, Thitiporn Borkird, M.D.¹², Marc Lallemand, M.D.^{1,2,3}, Kenneth McIntosh, M.D.^{3,13}, and Nicole Ngo-Giang-Huong, Pharm.D., Ph.D.^{1,2,3} for the Program for HIV Prevention and Treatment (PHPT) study group*

¹Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand ²Institut de Recherche pour le Développement (IRD) UMI 174, Marseilles, France ³Harvard School of Public Health, Department of Immunology and Infectious Diseases, Boston, MA, USA ⁴Bhumibol Adulyadej Hospital, Bangkok, Thailand ⁵Nakornping Hospital, Maerim, Chiang Mai, Thailand ⁶Lamphun Provincial Hospital, Lamphun, Thailand ⁷Health Promotion Hospital Regional Center I, Bangkok, Thailand ⁸Somdej Pranangchao Sirikit Hospital, Chonburi, Thailand ⁹Buddhachinaraj

Corresponding Authors: Kenneth McIntosh, M.D., Division of Infectious Diseases, Children's Hospital, 300 Longwood Avenue, Boston, MA 02115; kenneth.mcintosh@childrens.harvard.edu; Telephone: 617-355-6832. Fax: 617-730-0911.

Nicole Ngo-Giang-Huong, Program for HIV Prevention and Treatment (PHPT), Department of Medical Technology, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand; Telephone: 66 53 894 431, Fax: 66 53 894 220

Name and address for reprints: Woottichai Khamduang, Program for HIV Prevention and Treatment (PHPT), Department of Medical Technology, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand; Telephone: 66 53 894 431, Fax: 66 53 894 220

*The PHPT-1 study team: McCormick Hospital: Charas Pimpilai (Dir.), Chit-ari Tangchaitrong (Obst.), Somchitt Suwansarakul (Ped.); Lamphun Hospital: Wiwat Chavengchaiyong (Dir.), Karin Pagdi (Ped.), Pornpun Wannarit (Ped.), Rosalin Somsamai (Ped.), Wanmanee Matanasarawut (Obst.); Phayao Provincial Hospital: Jittapol Hemvuttiphan (Obst.), Sorakij Bhakeechep (Ped.), Suraphan Sangsawang (Obst.), Guttiga Halue (Intern.); Chiangrai Prachanukroh Hospital: Pongsatorn Wattapanorn (Obst.), Renu Srismith (Dir.), Jullapong Achalapong (Obst.), Raviwan Hansudewechakul (Ped.); Chiang Kham Hospital: Sanit Charkrit (Dir.), Sirichai Limsuwan (Ped.), Chaiwat Putiyanun (Obst.); Phan Hospital: Pisak Lersruangpanya (Dir.), Tikamporn Changchit (Dir.), Sivaporn Jungpichanvanich (Obst.), Mae Sai Hospital: Patsun Chinda-abhirakul (Obst.), Sura Kunkongkapan (Dir.), Mae Chan Hospital: Surachai Piyaworawong (Dir.), Sudanee Buranabanjasatean (Intern.); Prapokklao Hospital: Saluey Phongpanich (Obst.), Chaiwat Ngampiyaskul (Ped.), Prapap Yuthavisuthi (Obst.); Chiang Khong Royal Crown Prince: Suchan Parinya (Dir.), Chanya Taiyaitiang (Obst.); Banglamung Hospital: Jirapan Ithisuknanth (Obst.), Kamol Boonrod (Intern.); Chonburi Hospital: Preecha Kittikoon (Dir.), Nantasak Chotivanich (Obst.), Suchat Hongsiwon (Ped.), Chureeratana Bowonwatanuwong (Intern.); Rayong Hospital: Supawadee Lorenz (Obst.), Warit Karnchanamayul (Ped.), Surabhon Ariyadej (Obst.); Banchang Hospital: Garnchit Kunawudhi (Dir.), Saravudh Tragangool (Obst.), Sombat Chutimanukul (Ped.); Klaeng Hospital: Anchana Palasudhi (Dir.), Somnuek Techapalokul (Obst.), Somboon Hotrawarikarn (Ped.); Chachoengsao Hospital: Annap Kanjanasing (Obst.), Rachada Kaewsonthi (Ped.), Chai Jirawison (Dir.); Nakornping Hospital: Sampant Kahintapongs (Dir.), Kemarassami Kunsuikmengrai (Dir.), Pisut Leelanitkul (Obst.), Vorapin Gomuthbutra (Obst.), Suparat Kanjanavanit (Ped.); Bamrasnaradura Hospital: Achara Chaovavanich (Dir.), Preecha Tunthanathip (Obst.), Siriwan Sirikwin (Ped.); Somdej Prapinklao Hospital: Niptatt Kalwantawanich (Dir.), Narida Tawornpanit (Ped.), Sunee Maitrisathit (Obst.), Surachet Suphanich (Obst.); Nopparat Rajathane Hospital: Prasart Hotrapavanond (Dir.), Nantasak Thamanavat (Obst.), Somchai Ruangsirinorn (Ped.), Truengta Chanpoo (Obst.); Bhumibol Adulyadej Hospital: Veera Suraseranivong (Obst.), Sinart Prommas (Obst.), Prapaisri Layangool (Ped.); Health Promotion Hospital Region I: Surat Sirinontakan (Ped.), Worapapa Laphikanont (Obst.); Somdej Pranangchao Sirikit Hospital: Witaya Pornkitprasarn (Obst.), Tamsiri Hinjiranandana (Ped.), Pranangkla Hospital: Samruay Mookmakkul (Obst.), Sinchai Wanwaisart (Ped.), Surachai Pipatnakulchai (Obst.), Seri Hongyok (Dir.); Buddhachinaraj Hospital: Charan Chaipat (Dir.), Piriya Thanomrat (Obst.), Wanna Ardong (Ped.), Wiroj Wannapira (Obst.); Hat Yai Hospital: Boonyarat Warachit (Ped.), Kamol Veerapradist (Dir.), Surachai Lamlertkittikul (Obst.), Phayamengrai Hospital: Thara Onchomchan (Dir.).

The data included in this report were partially presented at the 18th Conference on Retroviruses and Opportunistic Infections, Boston, Feb-Mar, 2011.

Conflict of Interest Declaration: None of the authors has any commercial or other association that might pose a conflict of interest.

Hospital, Pitsanuloke, Thailand ¹⁰Chonburi Regional Hospital, Chonburi, Thailand ¹¹Mae Sai Hospital, Mae Sai, Chiang Rai, Thailand ¹²Hat Yai Hospital, Hat Yai, Songkla, Thailand ¹³Children's Hospital, Division of Infectious Diseases, Boston, MA, USA

Abstract

Our objective was to analyze, in formula-fed infants, correlates of HIV mother-to-child transmission, including cytomegalovirus (CMV) infection.

HIV-infected infants were matched with HIV-uninfected by maternal HIV RNA in a case-control design. Infant CMV infection was determined by CMV-IgG at 18 months and timed by earlier CMV-IgM or -DNA. Correlations were assessed using logistic regression.

In utero HIV infection was independently associated with congenital CMV infection ($P=0.01$), intrapartum HIV infection with congenital-plus-intrapartum/neonatal CMV infection ($P=0.01$), and overall HIV with overall CMV infection ($P=0.001$), as well as prematurity ($P=0.004$).

Congenital and acquired CMV infections are strong independent correlates of mother-to-child HIV transmission.

Introduction

The correlates of human immunodeficiency virus type 1 (HIV) transmission from mother to child have been extensively analyzed. Maternal viral load is widely accepted as the most important of these,¹ although many other maternal, obstetric, and infant independent risk factors have been described.² Cytomegalovirus (CMV) infection of the infant, despite the fact that it has been examined often in the context of HIV infection of mothers and infants, has never been subject to multivariate analysis.

In non-HIV-infected populations, *in utero* CMV infection affects 0.1 to 2.0% of live births,³ and intrapartum CMV infection occurs in 5-10%.⁴⁻⁶ Among HIV-infected infants, rates of intrauterine CMV infection between 0 and 26% have been recorded,⁷⁻¹³ and several studies in non-breast-feeding infants have shown high overall CMV infection rates in HIV-infected infants.^{9, 12, 14}

We conducted a retrospective case-control study to examine correlates, including infant CMV infection, of both intrauterine and intrapartum HIV transmission, using data and frozen specimens from a non-breast-feeding Thai clinical trial cohort.¹⁵ To eliminate the strongest known risk factor for mother-to-child HIV transmission,¹ HIV-transmitting mother-infant pairs were matched on maternal viral load. The study tested the primary hypothesis that CMV infection, congenital or intrapartum/neonatal, was independently associated with mother-to-child HIV infection.

Methods

This study was conducted according to the principles in the Declaration of Helsinki of 1975 (2000 revision), and was approved by the ethics committees of the Thai Ministry of Public Health, Chiang Mai University, and the Harvard School of Public Health. Informed consent was obtained.

The study population was derived from participants in a clinical trial investigating long and short durations of zidovudine for prevention of mother-to-child HIV transmission conducted from 1997-2001 in Thailand (ClinicalTrials.gov NCT00386230).¹⁵ The original study

contained 1409 live-born infants, 97 of whom were HIV-infected. All HIV-infected and a 2:1 sample of HIV-uninfected children were included, matched on baseline maternal plasma HIV RNA level. One HIV-infected infant had an uninfected twin, and one matched mother had two HIV-uninfected offspring, leading to 194 control mothers and 196 control HIV-uninfected infants.

Mothers were not tested for CMV serology since previous studies among Thai pregnant women reported almost 100% seroprevalence.¹⁶⁻¹⁹ Babies were formula-fed from birth. Maternal blood samples were collected as scheduled for the clinical trial and infant blood samples at birth, 6 weeks, and 4, 6, 12 and 18 months of age.

All infants were screened by testing 18-month plasma or serum for CMV-IgG antibody (Vironostika® anti CMV II, BioMerieux, France). Those testing negative were classified as CMV-uninfected. In others all available samples collected within the first 12 months of life were tested to time the onset of CMV infection. Plasma or serum was tested for CMV-IgM antibodies (Vironostika® anti CMV-IgM II, BioMerieux, France with 88% sensitivity and 99% specificity), and cell samples were tested for CMV-DNA using one microgram of DNA per reaction and a real-time CMV-DNA-PCR.²⁰

A child was considered to have: 1) No CMV infection if tests for CMV-IgG antibody were negative at or after 18 months of age; 2) Congenital CMV infection if cord (for CMV-IgM) or neonatal (that is, obtained before 10 days of age) peripheral blood (for CMV-DNA) tested positive; 3) No congenital CMV infection if cord or neonatal peripheral blood tested negative; 4) Intrapartum/neonatal CMV infection if cord or neonatal peripheral blood tested negative, and CMV-DNA and/or -IgM antibody was found at 6 weeks of age; 5) No intrapartum/neonatal CMV infection if cord/neonatal and 6-week samples were available and tested negative; 6) Acquired CMV infection if cord or neonatal peripheral blood tested negative, and plasma or serum tested positive at 18 months of age, and/or CMV-DNA and/or CMV-IgM antibody was found at any time before 18 months of age; 7) CMV infection at undefined time if samples tested positive for CMV-IgG at 18 months of age and/or CMV-DNA or CMV-IgM antibody at any time before 12 months of age, but no sample was available to rule out congenital CMV infection; and 8) Indeterminate CMV status either if no sample was available at or before 18 months of age for CMV antibody or CMV-DNA testing, or if plasma obtained at 18 months yielded an indeterminate CMV antibody test result, and all prior samples tested CMV-IgM or CMV-DNA negative. Five infants who died before 18 months of age satisfied criteria for indeterminate CMV status, but two, who died in the neonatal period soon after the last negative CMV test, were considered CMV-congenitally-uninfected. Indeterminates were otherwise omitted from all calculations except those with negative cord/neonatal CMV tests or 6-week CMV tests who were included in the denominator for calculation of rates of congenital and intrapartum/neonatal infection, respectively.

The HIV status of children was determined by HIV DNA PCR testing (Amplicor HIV DNA, v 1.5, Roche Molecular systems, Alameda, USA) as previously described¹⁵ at 1, 45, 120, and 180 days of age, or by anti-HIV IgG antibody serology at 18 months. Maternal plasma HIV RNA was measured using the COBAS Amplicor HIV-1 Monitor Version 1.5 test (Roche Diagnostic Systems, Branchburg, USA).

Continuous variables were categorized using common cut-off values or the median. Maternal baseline CD4+ T-cell counts, length of zidovudine prophylaxis, delivery mode, and infant sex, prematurity, and birth weight were tested for association with HIV transmission. If p-values were <0.2, their independent roles were studied using multivariate

exact conditional logistic regression with stepwise forward variable selection (STATA™ 10.1).

Results

The median duration of zidovudine prophylaxis was significantly lower (5.4 weeks) in HIV-1 transmitting mothers than in the HIV-1 non-transmitting mothers (6.8 weeks, $P=0.04$). Median baseline maternal CD4+ T-cell counts were similar in the two groups. Both prematurity and low birth weight were significantly more frequent in HIV-infected than HIV-uninfected infants. All other mother/infant characteristics were similar in transmitting and non-transmitting mother-infant pairs (see Table S1 in Supplementary Material).

Among the 97 HIV-infected children, 11 had indeterminate CMV status, 72 were co-infected by CMV and 14 were CMV-uninfected. Among the 196 HIV-uninfected infants, 118 were CMV-infected and 70 were uninfected (See Figure S1 in Supplementary Material). Congenital and overall CMV infections were more common in HIV-infected than HIV-uninfected infants (14% vs. 3%; 84% vs. 63%) (See Table S2 in Supplementary Material).

Among the 97 HIV-infected infants, 84 had samples available to time the infection: 35 (42%) were infected *in utero*, while 49 (58%) were infected during delivery²¹. Univariate correlates of *in utero*, intrapartum, and overall HIV infection, with prior matching on maternal baseline RNA level in plasma, are shown in Table 1a. Interestingly, neither duration of zidovudine administration (dichotomized at the median duration) nor CD4<200 cells/mm³, was significantly associated with HIV transmission, whereas both low birth weight and prematurity were ($P=0.02$ and 0.003 , respectively). Maternal syphilis, other sexually transmitted disease at delivery, and infant gender were also examined and showed no correlations (data not shown). Congenital (OR 4.9, $P=0.009$) and overall CMV (OR 3.0, $P<0.001$) infection were strongly correlated with overall HIV infection. Timing of the two infections also appeared important: congenital CMV infection was associated with both *in utero* HIV infection (OR 8.1, $P=0.01$) and intrapartum HIV infection ($P=0.03$, Fisher exact test), whereas perinatal CMV infection was not associated with *in utero* HIV infection (OR 0.9, $P=1.00$) but was significantly correlated with intrapartum HIV infection (OR 2.5, $P=0.04$).

Multivariate analysis, adjusting for prematurity (low birth weight, closely associated with prematurity, was omitted from this analysis) is shown in Table 1b. The results show the same associations as above.

Discussion

This analysis of multiple risk factors for mother-to-child transmission of HIV reports, in a formula-fed population receiving zidovudine monotherapy as HIV prophylaxis, significant independent correlations of congenital, intrapartum/neonatal, and overall CMV infection with infant HIV infection. In addition, we found, as others have,^{7-9, 11, 12, 14} a very high rate (14%) of congenital CMV infection in HIV-infected infants.

In the design of our case-control study we matched HIV-uninfected control infants on the strongest and most consistent risk factor for mother-to-child HIV transmission, namely maternal viral load. Perhaps as a consequence, prematurity was the only other significant correlation with HIV transmission, and not maternal immune status nor length of maternal zidovudine. In addition, CMV and HIV infection remained strongly correlated in multivariate analysis. While it is possible that these two viral infections are themselves correlated to some unmeasured parameter, it seems likely that these two viral infections are themselves interrelated, one virus predisposing to infection with the other. Further, when the

timing of CMV infection was clear, it appeared possible that prior or proximate CMV infection may have been important: *in utero* CMV infection correlated with both *in utero* and intrapartum HIV infection ($P=0.01$ and 0.03 , respectively), whereas intrapartum/neonatal CMV infection correlated with intrapartum HIV infection but not *in utero* HIV infection ($P=0.04$ and 1.0 , respectively). This ordering of correlations implies that fetal or infant CMV infection predisposes to HIV infection rather than the other way around, but this is not proven, and confounding by some unmeasured, possibly immunologic, factor may have occurred. Interestingly, facilitation of HIV infection by CMV *in vitro* has also been described.²²⁻²⁴

Published rates of congenital CMV infection in HIV-infected infants have varied widely, from 0%¹³ to as high as 26%,⁸ the two largest studies showing 10% transmission.^{11, 25} Several groups have described high rates of congenital CMV infection in babies with specifically *in utero* HIV infection: 4/14 (29%) in Kenyan infants and 6/49 (12%) in a French cohort.^{11, 25} High rates of early postnatally acquired and overall CMV infection among HIV-infected, formula-fed children with no or single-drug HIV prophylaxis have also been reported.^{9, 12, 14}

Guibert also reported, as we did, rates of HIV intrauterine infection in congenitally CMV-infected infants, and found that intrauterine HIV infection was more common (67% of all HIV-infected infants) in CMV-infected newborns than in those not CMV-infected (42%).¹¹ These percentages are almost identical to those we report (70% and 36%, Table 1a).

We used a combination of methods for the detection of CMV infection in this study. Because of limited availability of freezer samples, CMV-IgM and CMV-DNA assays were not both done at all time points (see Supplementary Figure 2). At birth, all CMV-IgM tests were done on cord samples, and all CMV-DNA-PCR tests were done on peripheral blood cells. An analysis of congenital CMV vs. HIV infection using only CMV-IgM data showed very similar rates of CMV infection (6/51, or 12%, congenital CMV in HIV-infected infants; 3/100, or 3% in HIV-uninfected infants), but the correlations with HIV-infection, while similar, lost significance presumably because of smaller numbers (data not shown).

Acquired CMV infection was common in all infants of this study, but was significantly more common when accompanied by infant HIV infection ($P=0.027$, Table S2). The excess in the co-infected group was largely accounted for by intrapartum/neonatal infection, detected by measuring CMV-IgM antibody or DNA in blood at 6 weeks of age and presumably transmitted from cervical shedding or horizontal transmission. Intrapartum/neonatal infection rates we found were higher than those previously reported in offspring of non-HIV-infected mothers⁶ and may have reflected higher cervical shedding in HIV-infected mothers.²⁶

It is also possible that HIV-infected infants have impaired immunologic surveillance that cannot abort incipient CMV infections, leading to greater susceptibility to horizontally acquired infection. In our study, 85% of HIV-infected children were co-infected with CMV by 18 months of age. Studies conducted in the USA in non-breast-feeding infants have shown a lower CMV prevalence, but with a consistent excess in the HIV-infected group.^{9, 12}

In conclusion, our case-control study showed that, in the offspring of HIV-infected mothers, both *in utero* and intrapartum infant HIV infections were significantly more frequent in the presence of proximate or prior infant CMV infection. HIV-infected children matched on their mothers' HIV viral loads were at much greater risk of being co-infected by CMV than those without HIV infection. This risk was particularly high for congenital CMV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Dr. Marianne Leruez-Ville (CHU Necker-Enfants Malades, France) for kindly providing of CMV recombinant plasmid, Mr. Sanupong Chailert (IRD-UMI174/PHPT) for providing patient's clinical data, and Dr. Patrinee Traisathit and Mr. Baptiste Leurent for their excellent statistical advice. We are also grateful to the women and children who participated in this study and the medical teams involved for their active and faithful commitment.

Financial support: Mr. Khamduang received a scholarship from the Faculty of Associated Medical Sciences, Chiang Mai University, and was supported by a Fogarty International Research Collaboration Award from the National Institutes of Health (R03 TW 01346-01). Also supported by grants from the National Institutes of Health (5 R01 HD 33326), the Thai Ministry of Public Health, Institut de Recherche pour le Développement, and the Thai Department of Technical and Economic Cooperation.

References

1. Mayaux MJ, Dussaix E, Isopet J, et al. Maternal virus load during pregnancy and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohort studies. SEROGEST Cohort Group. *J Infect Dis*. 1997; 175:172–175. [PubMed: 8985214]
2. Bryson YJ. Perinatal HIV-1 transmission: recent advances and therapeutic interventions. *AIDS*. 1996; 10 3:S33–42. [PubMed: 8970710]
3. Fowler KB, Stagno S, Pass RF. Maternal age and congenital cytomegalovirus infection: screening of two diverse newborn populations, 1980-1990. *J Infect Dis*. 1993; 168:552–556. [PubMed: 8394857]
4. Numazaki Y, Yano N, Morizuka T, Takai S, Ishida N. Primary infection with human cytomegalovirus: virus isolation from healthy infants and pregnant women. *Am J Epidemiol*. 1970; 91:410–417. [PubMed: 4316198]
5. Montgomery R, Youngblood L, Medearis DN Jr. Recovery of cytomegalovirus from the cervix in pregnancy. *Pediatrics*. 1972; 49:524–531. [PubMed: 4335205]
6. Reynolds DW, Stagno S, Hosty TS, Tiller M, Alford CA Jr. Maternal cytomegalovirus excretion and perinatal infection. *N Engl J Med*. 1973; 289:1–5. [PubMed: 4350775]
7. Doyle M, Atkins JT, Rivera-Matos IR. Congenital cytomegalovirus infection in infants infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J*. 1996; 15:1102–1106. [PubMed: 8970220]
8. Marin Gabriel MA, Fernandez Ibieta M, Gonzalez Tome MI, et al. Congenital cytomegalovirus infection in the infants of HIV-infected mothers. *An Pediatr (Barc)*. 2005; 62:38–42. [PubMed: 15642240]
9. Chandwani S, Kaul A, Bebenroth D, et al. Cytomegalovirus infection in human immunodeficiency virus type 1-infected children. *Pediatr Infect Dis J*. 1996; 15:310–314. [PubMed: 8866799]
10. Duryea EL, Sanchez PJ, Sheffield JS, et al. Maternal human immunodeficiency virus infection and congenital transmission of cytomegalovirus. *Pediatr Infect Dis J*. 2010; 29:915–918. [PubMed: 20431424]
11. Guibert G, Warszawski J, Le Chenadec J, et al. Decreased risk of congenital cytomegalovirus infection in children born to HIV-1-infected mothers in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2009; 48:1516–1525. [PubMed: 19388872]
12. Kovacs A, Schluchter M, Easley K, et al. Cytomegalovirus infection and HIV-1 disease progression in infants born to HIV-1-infected women. Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection Study Group. *N Engl J Med*. 1999; 341:77–84. [PubMed: 10395631]
13. Mussi-Pinhata MM, Yamamoto AY, Figueiredo LT, Cervi MC, Duarte G. Congenital and perinatal cytomegalovirus infection in infants born to mothers infected with human immunodeficiency virus. *J Pediatr*. 1998; 132:285–290. [PubMed: 9506642]

14. Cooper ER, Schwartz T, Brena A, Regan AM, Pelton SI. Cytomegalovirus as a cofactor in transmission and progression of perinatal HIV infection. *Pediatr AIDS and HIV Infect: Fetus to Adolesc.* 1992; 3:302–307.
15. Lallemand M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. *Perinatal HIV Prevention Trial (Thailand) Investigators. N Engl J Med.* 2000; 343:982–991. [PubMed: 11018164]
16. Tantivanich S, Auwanich W, Tharavanij S. Infection rates of Cytomegalovirus among Thai pregnant women. *Southeast Asian J Trop Med Public Health.* 1982; 13:596–600. [PubMed: 6302921]
17. Taechowisan T, Sutthent R, Louisirirothanakul S, Puthavathana P, Wasi C. Immune status in congenital infections by TORCH agents in pregnant Thais. *Asian Pac J Allergy Immunol.* 1997; 15:93–97. [PubMed: 9346273]
18. Tantivanich S, Suphadtanaphongs V, Siripanth C, et al. Prevalence of cytomegalovirus antibodies among various age groups of Thai population. *Southeast Asian J Trop Med Public Health.* 1999; 30:265–268. [PubMed: 10774691]
19. Tantivanich S, Amarapal P, Suphadtanaphongs W, Siripanth C, Sawatmongkonkun W. Prevalence of congenital cytomegalovirus and Toxoplasma antibodies in Thailand. *Southeast Asian J Trop Med Public Health.* 2001; 32:466–469. [PubMed: 11944699]
20. Leruez-Ville M, Ouachee M, Delarue R, et al. Monitoring cytomegalovirus infection in adult and pediatric bone marrow transplant recipients by a real-time PCR assay performed with blood plasma. *J Clin Microbiol.* 2003; 41:2040–2046. [PubMed: 12734246]
21. Bryson YJ, Luzuriaga K, Sullivan JL, Wara DW. Proposed definitions for in utero versus intrapartum transmission of HIV-1. *N Engl J Med.* 1992; 327:1246–1247. [PubMed: 1406816]
22. Skolnik PR, Kosloff BR, Hirsch MS. Bidirectional interactions between human immunodeficiency virus type 1 and cytomegalovirus. *J Infect Dis.* 1988; 157:508–514. [PubMed: 2830343]
23. Ho WZ, Harouse JM, Rando RF, et al. Reciprocal enhancement of gene expression and viral replication between human cytomegalovirus and human immunodeficiency virus type 1. *J Gen Virol.* 1990; 71(Pt 1):97–103. [PubMed: 2154540]
24. McKeating JA, Griffiths PD, Weiss RA. HIV susceptibility conferred to human fibroblasts by cytomegalovirus-induced Fc receptor. *Nature.* 1990; 343:659–661. [PubMed: 2154697]
25. Slyker JA, Lohman-Payne BL, John-Stewart GC, et al. Acute cytomegalovirus infection in Kenyan HIV-infected infants. *AIDS.* 2009; 23:2173–2181. [PubMed: 19617812]
26. Mostad SB, Kreiss JK, Ryncarz AJ, et al. Cervical shedding of cytomegalovirus in human immunodeficiency virus type 1-infected women. *J Med Virol.* 1999; 59:469–473. [PubMed: 10534728]

Table 1
Table 1A. Risk factors for in utero, intrapartum, and overall HIV infection (Univariate analysis)

Analyzed factors	In utero HIV infection			Intrapartum HIV infection			Overall HIV infection		
	Case n/N ^a (%)	Controls n/N ^a (%)	OR(95%CI) ^b	p-value ^c	Case n/N ^a (%)	Controls n/N ^a (%)	OR(95%CI) ^b	p-value ^c	Case n/N ^a (%)
Maternal factors									
CD4 < 200 cell/μL	6/33 (18)	19/70 (27)	0.6 (0.2-1.8)	0.44	12/46 (26)	22/95 (23)	1.2 (0.5-2.9)	0.85	23/91 (25)
ZDV duration <6.14 weeks	24/35 (69)	41/71 (58)	1.6 (0.6-4.1)	0.40	22/46 (48)	45/99 (45)	1.1 (0.5-2.4)	0.91	54/94 (57)
Short ZDV arm	25/35 (71)	45/71 (63)	1.4 (0.6-3.9)	0.55	22/49 (45)	46/99 (46)	0.9 (0.4-2.0)	1.00	55/97 (57)
Infant factors									
Vaginal delivery	28/35(80)	55/71 (77)	1.2 (0.4-3.7)	0.97	40/49 (82)	76/99 (77)	1.3 (0.5-3.7)	0.66	80/97(82)
Low birth weight	9/35 (26)	9/71 (13)	2.3 (0.7-7.4)	0.17	10/49 (20)	12/99 (12)	1.9 (0.7-5.3)	0.27	23/97 (24)
Prematurity	5/35 (14)	5/71 (7)	2.2 (0.5-10.0)	0.40	8/49 (16)	5/99 (5)	3.7 (1.0-15.3)	0.05	18/97 (19)
Congenital CMV infection	7/27 (26)	3/58 (5)	8.1 (1.5-63.7)	0.01	3/38 (8)	0/81 (0)	-	0.03	10/71 (14)
Intrapartum/neonatal CMV infection	4/18 (22)	12/55 (22)	0.9 (0.2-3.8)	1.00	18/34 (53)	24/78 (31)	2.5 (1.0-6.4)	0.04	24/58 (41)
Congenital plus intrapartum/ neonatal CMV infection	11/25(44)	15/58 (26)	2.2(0.7-6.7)	0.16	21/37 (57)	24/78 (31)	3.0 (1.2-7.4)	0.01	34/68 (50)
Overall CMV infection	26/32(81)	41/68 (60)	2.9 (1.0-10.0)	0.06	37/43 (86)	61/95 (64)	3.5 (1.3-11.3)	0.01	72/86 (84)
									118/188 (63)
									3.0 (1.6-6.3)
									<0.001

^a n/N: number of transmissions / number at risk

^b Odds ratio (95% confidence interval)

^c P-values derived from exact conditional logistic regression except for intrapartum HIV infection/congenital CMV where P-value was derived from Fisher's exact test because the number of transmissions among controls was 0. Significant values (<0.05) are bolded.

Table 1B. Risk factors for in utero, intrapartum, and overall HIV infection (multivariate analysis using exact conditional logistic regression)

Variables	In utero HIV infection		Intrapartum HIV infection		Overall HIV infection ^b	
	OR(95%CI) ^a	p-value	OR(95%CI) ^a	p-value	OR(95%CI) ^a	p-value
Congenital CMV infection	8.1 (1.5-63.7)	0.012	- ^c	- ^c		
Congenital plus intrapartum/neonatal CMV infection			3.0 (1.2-7.4)	0.01		
Overall CMV infection					2.9 (1.5-6.0)	0.001

Table 1B. Risk factors for in utero, intrapartum, and overall HIV infection (multivariate analysis using exact conditional logistic regression)

Variables	In utero HIV infection	Intrapartum HIV infection	Overall HIV infection ^b
Prematurity	<i>d</i>	<i>d</i>	3.6 (1.5-9.1) 0.004

^a Odds ratio (95% confidence interval)

^b Adjusting for prematurity, the only factor remaining associated ($P<0.05$) with HIV overall infection in addition to CMV transmission at different time points

^c Not estimable because none of the controls matched to intrapartum HIV infected infants were congenitally CMV infected.

^d Not selected in the model