

Mother-to-Child Transmission of GB Virus C in a Cohort of Women Coinfected with GB Virus C and HIV in Bangkok, Thailand

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Background. GB virus C (GBV-C) is an apathogenic virus that inhibits human immunodeficiency virus (HIV) replication *in vitro*. Mother-to-child transmission (MTCT) of GBV-C has been observed in multiple small studies. Our study examined the rate and correlates of MTCT of GBV-C in a large cohort of GBV-C–HIV-coinfected pregnant women in Thailand.

Methods. Maternal delivery plasma specimens from 245 GBV-C–HIV-infected women and specimens from their infants at 4 or 6 months of age were tested for GBV-C RNA. Associations with MTCT of GBV-C were examined using logistic regression.

Results. One hundred one (41%) of 245 infants acquired GBV-C infection. MTCT of GBV-C was independently associated with maternal antiretroviral therapy (adjusted odds ratio [AOR], 5.21 [95% confidence interval {CI}, 2.12–12.81]), infant HIV infection (AOR, 0.05 [95% CI, 0.01–0.26]), maternal GBV-C load (≥ 8.0 log₁₀ copies/mL: AOR, 86.77 [95% CI, 15.27–481.70]; 7.0–7.9 log₁₀ copies/mL: AOR, 45.62 [95% CI, 8.41–247.51]; 5.0–6.9 log₁₀ copies/mL: AOR, 9.07 [95% CI, 1.85–44.33]; reference, <5 log₁₀ viral copies/mL), and caesarean delivery (AOR, 0.26 [95% CI, 0.12–0.59]).

Conclusions. Associations with maternal GBV-C load and mode of delivery suggest transmission during pregnancy and delivery. Despite mode of delivery being a common risk factor for virus transmission, GBV-C and HIV were rarely cotransmitted. The mechanisms by which maternal receipt of antiretroviral therapy might increase MTCT of GBV-C are unknown.

GB virus C (GBV-C) is a flavivirus that was discovered in 1995 and that is closely related to hepatitis C virus

but does not appear to cause disease in humans. The prevalence of GBV-C infection in the general population is higher than that of other bloodborne viruses, such as human immunodeficiency virus (HIV) and hepatitis C virus in western industrialized countries and varies globally, as does GBV-C genotype. Among antenatal populations, the prevalence of GBV-C RNA varies from 1%–2% in East Asia [1, 2] to 5%–7% in Europe, Australia, and Southeast Asia [3–6] and 10%–13% in Africa [7, 8]. GBV-C infection is also more prevalent in HIV-infected persons and others with risk factors for bloodborne infections [9] and can be transmitted parenterally, sexually, and vertically [10]. Mother-to-child transmission (MTCT) of GBV-C has been hypothesized as one possible mechanism for the relatively high prevalence of GBV-C infection in the general population [4, 11, 12].

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Although GBV-C infection alone appears to have no clinical significance, MTCT of GBV-C may be important for several reasons. First, GBV-C infection has been associated with slower progression and prolonged survival in HIV-infected adults in some but not all studies [13–21] and has been observed to inhibit HIV replication in vitro [17]. It is therefore possible that GBV-C coinfection may also improve survival among HIV-infected infants. Second and potentially more importantly, MTCT of GBV-C was found to be associated with reduced MTCT of HIV in our larger related analysis [22], although the biologic mechanism for this association remains unknown.

Wide variations in rates of MTCT of GBV-C (range, 13%–100%) were reported in 19 published studies that we identified [1, 2, 4, 11, 12, 23–36]. A limitation of all of these studies is their sample size, varying from 1 to 34 GBV-C-infected women. Despite small sample sizes, 3 studies identified high maternal GBV-C load, and 2 of these studies found that vaginal or emergency caesarean delivery was a risk factor for MTCT of GBV-C [1, 2, 11]. To better delineate transmission rates and risk factors for transmission, we combined data from several studies of perinatal HIV transmission in Thailand, where 20% of HIV-infected pregnant women were coinfecting with GBV-C [22]. Our cohort of 245 GBV-C–HIV-coinfecting pregnant women and their infants is the largest cohort to examine correlates of MTCT of GBV-C to date.

METHODS

The source population for this study consisted of 1498 non-breast-feeding participants (enrolled before 31 March 2004) of 3 perinatal HIV transmission studies conducted jointly by the Thailand Ministry of Public Health and the US Centers for Disease Control and Prevention at 2 large Bangkok hospitals. Study 1 (1992–1994; $n = 342$) was a natural history study conducted before the advent of antiretroviral prophylaxis (ART) for the prevention of MTCT of HIV [37]. Study 2 (1996–1998; $n = 397$) was a randomized placebo-controlled trial assessing the efficacy of short-course zidovudine prophylaxis [38]. Study 3 (1999–2004; $n = 759$) was an observational study assessing the implementation of programs to prevent MTCT of HIV [39]. Eighty-three percent of women enrolled in study 3 received zidovudine prenatally and/or at delivery, and 220 women and their infants also received nevirapine. All infants in study 3 received either zidovudine treatment or combination treatment with zidovudine and nevirapine.

Delivery blood specimens from 1440 women were available and tested for GBV-C RNA, antibody, and if the specimen was GBV-C RNA positive, genotype. Plasma specimens from the GBV-C RNA-positive women's infants at 4 or 6 months of age were tested for GBV-C RNA. For a few infants for whom 4- or 6-month specimens were not available, 2- and 12-month plasma specimens were requested. Plasma samples from 21

GBV-C RNA-positive infants from study 1 were also tested for GBV-C RNA at all other available collection times (from birth to 37 months) to assess the time of detection and clearance of GBV-C RNA in infants. Newborns had blood samples obtained directly and not from cord blood.

In the original 3 studies, specimens were collected and tested for the presence of HIV. HIV load and CD4⁺ and CD8⁺ cell counts were measured as described elsewhere [37, 38]. Laboratory staff were blinded to patient data.

GBV-C RNA was extracted from 200 μ L of plasma with use of the QIAamp MinElute Virus Vacuum kit (Qiagen) and was quantified using the Quantitect Probe reverse-transcriptase polymerase chain reaction (RT-PCR) kit (Qiagen), according to the manufacturer's instructions. The lower limit of reliable detection of this quantitative RT-PCR test is 1000 viral copies per reaction. Positive maternal samples, including 39 with 1–999 viral copies per reaction, were confirmed by genotype analysis, as described elsewhere [40, 41].

GBV-C RNA-positive women (defined as women with a GBV-C load ≥ 1000 viral copies per reaction or 1–999 viral copies per reaction and who had specimens could be genotyped) and their infants, were included in the present study. Infants were classified into 1 of 3 mutually exclusive categories: (1) GBV-C RNA positive (GBV-C load, ≥ 1000 viral copies per reaction; detected at any age), (2) GBV-C RNA negative (GBV-C load, 0 viral copies per reaction detected in the infant specimens from 4 months of age [study 3] or 6 months of age [studies 1 and 2] or 0 viral copies per reaction found in both the 2- and 12-month infant plasma specimens), and (3) GBV-C RNA indeterminate (GBV-C load, 0–999 viral copies per reaction detected at any age or at >1 time and no specimen with a GBV-C load ≥ 1000 viral copies per reaction).

Analyses were performed using SAS (version 8.2; SAS Institute). The statistical significance of associations of maternal and infant characteristics with MTCT of GBV-C within each study was assessed with 2-sided P values from χ^2 or Fisher's exact tests, using tests for trend for ordered categorical variables. Odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for participants from study 1, 2, or 3 were calculated using the Cochran Mantel-Haenszel procedure for categorical variables. Homogeneity of ORs across studies was assessed with the Breslow-Day test, and the 3 studies were combined for the multivariable analysis, with a variable indicating the perinatal study included to adjust for any unmeasured confounding between studies. Variables associated with MTCT of GBV-C in the analysis adjusted for study that had a P value of $<.20$ were included in the analysis adjusted for study and covariates and were retained in the final model if their P value was $<.05$. HIV and GBV-C loads were transformed to their \log_{10} values. If a linear relationship was not observed, continuous variables were categorized at generally used cutoff points or at levels defined by

Table 1. Characteristics of 245 women coinfected with GB virus V (GBV-C) and human immunodeficiency virus (HIV) and their infants, by original perinatal study, Bangkok, Thailand.

Variable	Study			
	1 (n = 81)	2 (n = 54)	3 (n = 110)	All (n = 245)
Perinatal GBV-C transmission rate	21 (26)	29 (54)	51 (46)	101 (41)
Perinatal HIV transmission rate	16 (20)	10 (19)	5 (4.6)	31 (13)
ART regimen				
None	81 (100)	23 (43)		104 (42)
Maternal or maternal and infant zidovudine	...	31 (57)	53 (48)	84 (34)
Infant zidovudine	24 (22)	24 (9.8)
Mother and infant zidovudine and nevirapine	33 (30)	33 (13)
Maternal characteristic				
GBV-C load, log ₁₀ copies/mL	5.4 (4.1–6.7)	8.0 (7.5–8.5)	8.0 (6.9–8.3)	7.5 (5.9–8.1)
GBV-C genotype				
2A	44 (54)	22 (41)	30 (29)	96 (40)
2B	0 (0)	1 (1.9)	3 (2.9)	4 (1.7)
3	22 (27)	18 (33)	46 (44)	86 (36)
4	7 (8.6)	11 (20)	21 (20)	39 (16)
Multiple	8 (9.8)	2 (3.7)	5 (4.8)	15 (6.3)
HIV load at delivery, log ₁₀ copies/mL	4.3 (3.8–4.9)	4.2 (3.8–4.7)	4.0 (3.2–4.7)	4.2 (3.6–4.8)
CD4 ⁺ cell count at delivery, cells/mm ³	450 (320–590)	363 (226–510)	359 (242–523)	390 (260–550)
Age, years	22 (20–25)	24 (22–29)	25 (22–28)	24 (21–27)
Gravidity	1 (1–2)	2 (1–2)	2 (1–3)	2 (1–2)
Education: primary or less	52 (64)	30 (56)	59 (54)	141 (58)
Commercial sex worker	10 (12.4)	7 (13)	10 (9.1)	27 (11)
IDU	1 (1.2)	0 (0)	7 (6.3)	8 (3.3)
Partner of IDU	5/76 (6.6)	6 (13)	17 (18)	28 (13)
Delivery characteristic				
Caesarean delivery	10 (12)	12 (22)	36 (33)	58 (24)
Duration of labor, h	6 (4–10)	9 (5–14)	7 (5–12)	7 (5–11)
Duration of membrane rupture, h	1.0 (1.0–4.0)	1.8 (0.4–6.2)	0.6 (0.05–3.0)	1 (0.2– 4.0)
Infant characteristic				
Prematurity (<37 weeks)	5 (6.2)	0 (0)	9 (8.2)	14 (5.7)
Birth weight <2500 g	9 (11)	1 (1.9)	15 (14)	25 (10)

NOTE. Data are no. (%) of participants or median value (interquartile range). Study 1 was performed during 1992–1994, study 2 was performed during 1996–1997, and study 3 was performed during 1999–2004. ART, antiretroviral therapy; IDU, injection drug user.

the relationship observed with MTCT of GBV-C. Logistic regression was used to calculate ORs and 95% Wald CIs adjusted for multiple covariates. Biologically plausible interactions were assessed by adding an interaction term to the multivariable model.

This study was approved by the Research Ethics Board, University of Toronto, Canada; the Institutional Review Board, Centers for Disease Control and Prevention, Atlanta; and the Ethical Review Committees for Research in Human Subjects at the Thailand Ministry of Public Health and Siriraj Hospital, Bangkok, Thailand.

RESULTS

We were able to determine GBV-C infection status for 1387 (96%) of 1440 HIV-infected pregnant women for whom de-

livery blood specimens were available; of these women, 274 (20%) tested positive for GBV-C RNA. Of these women, 249 had infant specimens available for testing. One hundred one (41%) of 249 infants were classified as GBV-C RNA positive, 144 (58%) of 249 were classified as GBV-C RNA negative, and 4 (2%) of 249 were classified as GBV-C RNA indeterminate. GBV-C–HIV-coinfected women and their infants with known infant GBV-C status were included in the present analysis. The 4 GBV-C RNA–indeterminate infants, one of whom was HIV infected, were not included in further analysis.

The characteristics of these 245 GBV-C–HIV-coinfected women and their infants are summarized in table 1. The overall rate of MTCT of GBV-C was 41% (95% CI, 35%–48%) but was significantly different among studies ($P = .002$). The rate of MTCT of GBV-C was 26% in study 1, 54% in study 2, and

Table 2. Correlates of GB virus C (GBV-C) infection in 245 infants, Bangkok, Thailand.

Variable	Proportion (%) of GBV-C-infected infants (n = 245)	Adjusted for study only		Final multivariate model ^a	
		AOR (95% CI)	P	AOR (95% CI)	P
Maternal GBV-C load ^b		2.63 (1.92–3.63)	<.001		
≥8.0 log ₁₀ copies/mL	54/81 (67)	58.14 (4.42–765.25)	<.001	85.77 (15.27–481.70)	.001
7.0– 7.9 log ₁₀ copies/mL	31/65 (48)	33.15 (4.39–250.17)	<.001	45.62 (8.41–247.51)	<.001
5.0– 6.9 log ₁₀ copies/mL	14/57 (25)	9.82 (1.92–50.16)	.002	9.07 (1.85–44.33)	.01
<5 log ₁₀ copies/mL	2/42 (4.8)	1.0		1.0	
Infant HIV status					
Infected	2/31 (6.5)	0.08 (0.016–0.34)	<.001	0.05 (0.01–0.26)	<.001
Uninfected	99/214 (46)	1.0		...	
Maternal HIV load ^c		0.65 (0.48–0.89)	.007	...	
5.0–5.9 log ₁₀ copies/mL	8/38 (21)	0.19 (0.06–0.66)	.007	...	
4.0–4.9 log ₁₀ copies/mL	46/109 (42)	0.74 (0.32–1.71)	.48	...	
3.0– 3.9 log ₁₀ copies/mL	30/66 (45)	0.63 (0.25–1.60)	.34	...	
2 .0–2.9 log ₁₀ copies/mL	17/32 (53)	1.0		...	
Maternal ART					
Yes	68/117 (58)	4.85 (2.18–10.75)	<.001	5.21 (2.12–12.81)	<.001
No	33/128 (26)	1.0		...	
Maternal CD4 ⁺ cell count at delivery ^d					
<200	7/25 (28)	0.36 (0.14–0.92)	.03	...	
≥200	92/217 (45)	1.0		...	
Caesarean delivery					
Yes	16/58 (28)	0.35 (0.18–0.69)	.002	0.26 (0.12–0.59)	.001
No	85/187 (46)	1.0		...	
Duration of membrane rupture >4 h					
Yes	30/58 (52)	1.66 (0.90–3.06)	.10	...	
No	69/183 (38)	1.0		...	
Prematurity					
Yes	2/14 (14)	0.21 (0.04–1.05)	.045	...	
No	99/231 (43)	1.0		...	
Sex of baby					
Female	45/128 (35)	0.62 (0.37–1.06)	.08	...	
Male	56/117 (48)	1.0		...	
Maternal CD8 ⁺ cell percentage at delivery ^d					
≥40%	38/99 (38)	0.70 (0.41–1.21)	.20	...	
<40%	61/143 (43)	1.0		...	
Maternal CD4/CD8 ratio ^e					
≥0.5	51/105 (49)	1.87 (1.09–3.22)	.02	...	
<0.5	48/134 (36)	1.0		...	
Duration of labor, h					
≥4	80/177 (45)	1.81 (0.88–3.71)	.09	...	
<4	12/42 (29)	1.0		...	
Study 2		0.24 (0.07–0.84)	.03
Study 3		0.12 (0.04–0.42)	<.001

NOTE. AOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval.

^a The final multivariate model included maternal GBV-C load, maternal receipt of ART, caesarean delivery, infant HIV status, and the original study in which the mother participated.

^b Shown are trend AORs per log₁₀ increase. Cochran-Armitage test for trend, *P* < .001.

^c Shown are trend AORs per log₁₀ increase. Cochran Armitage test for trend, *P* = .009.

^d Data are for 242 infants.

^e Data are for 239 infants.

46% in study 3. In study 1, we also observed significantly lower maternal GBV-C titers than in study 2 or 3 ($P < .001$).

The correlates of MTCT of GBV-C are presented in table 2. Mothers receiving ART were significantly more likely than mothers not receiving ART to transmit GBV-C to their infants (adjusted OR, 5.21 [95% CI, 2.12–12.81]; adjusted for study and covariates). The effect of maternal receipt of ART on MTCT of GBV-C was independent of GBV-C load, HIV load, and CD4⁺ cell count (adjusted OR 4.81 [95% CI, 1.97–11.72]). Table 3 presents rates of MTCT of GBV-C, MTCT of HIV, and maternal GBV-C and HIV load by ART regimen and study. When women did not receive ART, the rates of MTCT of GBV-C and HIV were very similar, whereas when women received ART, the rate of MTCT of HIV decreased (relative risk, 0.16; $P < .001$) and the rate of MTCT of GBV-C increased (relative risk, 2.25; $P < .001$); the ratio of MTCT of GBV-C to MTCT of HIV changed from 1.2 to 17.1. The rate of MTCT of GBV-C did not vary with the addition of nevirapine to zidovudine therapy ($P = .36$), and infant ART, compared with no ART, was not associated with increased MTCT of GBV-C ($P = .54$).

GBV-C and HIV were rarely cotransmitted, and only 2 of 245 infants acquired both viruses. The rate of MTCT of GBV-C was significantly lower among HIV-infected infants than among HIV-uninfected infants (6.5% [2 of 31 infants] vs. 46% [99 of 214]; $P < .001$; adjusted for study and covariates). The inverse association between MTCT of HIV and MTCT of GBV-C was independent of maternal receipt of ART, maternal HIV load, maternal GBV-C load, and maternal CD4⁺ cell count (adjusted OR, 0.06 [95% CI, 0.01–0.32]).

High maternal GBV-C load significantly increased the likelihood of MTCT of GBV-C in a dose-response relationship. There were no instances of MTCT of GBV-C detected among women with a GBV-C load $< 4.0 \log_{10}$ copies/mL; however, among women with a GBV-C load $\geq 8.0 \log_{10}$ copies/mL, the rate of MTCT of GBV-C was 67%. We observed no evidence

of a difference in MTCT rate according to GBV-C genotypes (2, 3, or 4) in this study.

Infants born by caesarean delivery were significantly less likely to be GBV-C infected than were infants delivered vaginally ($P < .001$; adjusted for study and covariates). There was no statistically significant difference between rates of MTCT of GBV-C among infants delivered by elective (20% [5 of 25 infants]) and emergency caesarean delivery (33% [11 of 33]; $P = .43$). No infant acquired GBV-C from mothers who had vaginal deliveries and GBV-C loads $< 4 \log_{10}$ copies/mL, from mothers who had emergency cesarean deliveries and GBV-C loads $< 6 \log_{10}$ copies/mL, or from mothers who had elective cesarean deliveries and GBV-C loads $< 7 \log_{10}$ copies/mL.

Premature newborns were significantly less likely to acquire GBV-C than were full-term newborns (2 [14%] of 14 vs. 99 [43%] of 231; $P = .045$; adjusted for study), but the association was not statistically significant in analysis adjusted for covariates in the final multivariate model. Other factors associated with an increased likelihood of MTCT of GBV-C in analysis adjusted for study but not other covariates included low maternal HIV load, high maternal CD4⁺ cell count, and a high CD4⁺/CD8⁺ ratio at delivery. Male infants were slightly more likely to become GBV-C infected than were female infants in all 3 perinatal studies (48% vs. 35%; $P = .08$; adjusted for study), but the difference was of borderline significance.

Although the crude rate of MTCT of GBV-C was higher in studies 2 and 3 than in study 1, after adjusting for maternal receipt of ART, the risk of MTCT of GBV-C was not significantly different between studies (adjusted OR for study 1 vs. study 2, 1.35 [95% CI, 0.56–3.27]; adjusted OR for study 1 vs. study 3, 0.68 [95% CI, 0.27–1.73]). However, after adjusting for maternal GBV-C load and ART, women in studies 2 and 3 had a significantly lower risk of transmitting GBV-C to their infants than did women in study 1 (adjusted OR for study 1 vs. study 2, 0.22 [95% CI, 0.07–0.65]; adjusted OR for study

Table 3. Mother-to-child transmission (MTCT) of GB virus C (GBV-C) and human immunodeficiency virus (HIV) and maternal viral load, by antiretroviral therapy (ART) regimen and study, for 245 GBV-C–HIV-coinfected mothers, Bangkok, Thailand.

Study, ART regimen	Rate of MTCT of GBV-C, % (proportion)	Rate of MTCT of HIV, % (proportion)	Maternal GBV-C load at delivery, median copies/mL (IQR)	Maternal HIV load at delivery, median copies/mL (IQR)
1: no ART	26 (21/81)	20 (16/81)	5.4 (4.1–6.7)	4.3 (3.8–4.9)
2				
Placebo	30 (7/23)	30 (7/23)	7.9 (7.2–8.4)	4.7 (4.1–4.9)
Maternal AZT	71 (22/31)	10 (3/31)	8.1 (7.8–8.5)	4.1 (3.6–4.3)
3				
Infant AZT	21 (5/24)	17 (4/24)	8.0 (6.9–8.2)	4.7 (4.2–5.1)
Maternal and infant AZT	55 (29/53)	2 (1/53)	8.0 (6.7–8.3)	3.9 (3.2–4.4)
Maternal and infant AZT and NVP	52 (17/33)	0 (0/33)	8.0 (7.2–8.4)	3.6 (2.3–4.3)

NOTE. AZT, zidovudine; IQR, interquartile range; NVP, nevirapine.

creased rate of MTCT of GBV-C was independent of both maternal HIV and GBV-C load. Therefore, the biologic pathway for an effect of ART on MTCT of GBV-C remains unknown.

ART has been associated with a reduced rate of MTCT of HIV independent of its effect on reducing HIV load [44]. Our results may suggest another potential mechanism by which maternal receipt of ART prevents MTCT of HIV, because GBV-C infection may protect against HIV infection. In support of this, HIV infection of the infant was associated with a lower rate of MTCT of GBV-C, and coinfection in the infants occurred less frequently than would be predicted if they were independent events. In the combined study, only 2 (0.8%) of 245 infants of HIV–GBV-C–coinfected mothers acquired both GBV-C and HIV at birth, whereas with perinatal transmission rates of 13% for HIV and 41% for GBV-C in our study, we might have expected 13 (5%) of 245 infants to be coinfecting. Two other studies also observed a low prevalence of GBV-C infection among HIV-infected children [45, 46]; however, we identified 3 studies of MTCT of GBV-C in HIV-infected women, and none of these studies observed a difference in cotransmission of HIV or GBV-C [23, 25, 26]. Possible reasons for the lack of association observed in these studies include small sample sizes ranging from 2 to 9 GBV-C–infected infants and different study populations. A mechanism for the strong inverse association between infant GBV-C and HIV infection that we observed remains unknown. Because both HIV and GBV-C infection appear to be vertically acquired by infants at approximately the same time [22], it is possible that either virus may inhibit the other or that a third factor (e.g., placental inflammation, which has been associated in some studies with reduced MTCT of HIV [47–49]) or the infant’s cytokine milieu prevents coinfection with both viruses. However, because GBV-C appears to reduce replication of HIV *in vitro*, most strongly when the cell is infected with GBV-C first, but also when the cell is infected simultaneously with HIV and GBV-C [17], there is a biologically plausible basis for the reduction of MTCT of HIV through infant GBV-C infection.

We confirmed observations from previous studies [1, 2, 11] that, not surprisingly, high GBV-C load and vaginal mode of delivery are associated with increased MTCT of GBV-C. Because the rate of MTCT of GBV-C was 67% at a GBV-C load of $\geq 8 \log_{10}$ copies/mL, there may not be a threshold over which transmission is 100%. However, both of the mothers with a GBV-C load of $9 \log_{10}$ viral copies/mL at delivery transmitted GBV-C to their infants (both also delivered vaginally). Although not significant, our data are consistent with elective caesarean deliveries having the lowest rate of MTCT of GBV-C, compared with other forms of delivery, as was reported in 2 other studies [1, 2].

Risk factors associated with increased viral exposure, such

as high maternal viral load and a vaginal delivery, were similar for MTCT of HIV and MTCT of GBV-C. However, risk factors commonly associated with increased MTCT of HIV (no maternal receipt of ART, high maternal HIV load, low maternal CD4⁺ cell count, prematurity, and female sex of the infant) were reversed for MTCT of GBV-C. Mechanisms for this dichotomy are unknown.

The timing of GBV-C transmission is unknown, but because 21% of newborn samples available for testing were positive for GBV-C RNA, *in utero* transmission is likely for at least some infants. The remainder were likely infected either *in utero* or at delivery, given that 16 (94%) of 17 tested positive at 2 months and that mode of delivery was significantly associated with MTCT of GBV-C. Our study, in which all GBV-C RNA was of genotype 2, 3, or 4, supports evidence of vertical transmission of GBV-C; however, some studies from Africa, where genotypes 1 and 5 are most prevalent [50], have also reported evidence of horizontal transmission [24, 35].

Our study had several limitations. Because all study participants were HIV-infected Thai women, the generalizability of our findings may be limited to certain populations or GBV-C genotypes. A limitation of studies on GBV-C in general is the lack of a gold standard test for the detection of GBV-C RNA. Although reasons for the significantly lower maternal GBV-C titers in study 1 are unknown, possible explanations may include duration of specimen storage or changes in the population or epidemiology of GBV-C over the study periods. Studies of hepatitis C virus, the closest known relative to GBV-C are suggestive of viral deterioration with long-term storage; however, the effect of duration of storage on the stability of the GBV-C has not been established. Among women who did not receive ART, the rate of MTCT of GBV-C was similar in all 3 perinatal studies (table 3). Because viral load is a major determinant of MTCT of HIV, this might indicate that the true maternal GBV-C load in study 1 was similar to that observed in studies 2 and 3. Differences in maternal GBV-C load appear to have confounded our estimate of study differences in the rate of MTCT of GBV-C. Although positive samples from infants were not confirmed with genotype testing, only 4 indeterminate samples from infants were excluded from analysis, and this would not have affected our results.

In summary, in our cohort of GBV-C–HIV–coinfected women, GBV-C was frequently transmitted from mother to infant. Maternal receipt of ART was independently associated with increased rate of MTCT of GBV-C, although the mechanism remains unknown. We observed that high maternal GBV-C load and vaginal mode of delivery—both factors that increase the level of virus to which an infant is exposed—were associated with increased rate of MTCT of GBV-C. Despite mode of de-

livery being a common risk factor, GBV-C and HIV were rarely cotransmitted.

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