Safety and Efficacy of HIV Hyperimmune Globulin for Prevention of Mother-to-Child HIV Transmission in HIV-1–Infected Pregnant Women and Their Infants in Kampala, Uganda (HIVIGLOB/NVP STUDY)

Carolyne Onyango-Makumbi, MBChB, MS, Saad B. Omer, MBBS, MPH, PhD,† Michael Mubiru, BSc, Dip Med Stat,* Lawrence H. Moulton, PhD,‡ Clemensia Nakabiito, MBChB, MMed,*§ Philippa Musoke, MBChB, FAAP,*|| Francis Mmiro, MBChB, FRCOG,*[1] Sheryl Zwerski, RN, MSN, CRNP,¶ Hans Wigzell, MD,# Lars Falksveden, MD,** Britta Wahren, MD,** Gretchen Antelman, ScD,†† Mary Glenn Fowler, MD, MPH,‡‡ Laura Guay, MD,§§|||| and J. Brooks Jackson, MD‡‡*

Background: This phase III, randomized, clinical trial compared single-dose nevirapine (sdNVP) plus HIV hyperimmune globulin (HIVIGLOB) with sdNVP alone for preventing maternal-to-child transmission of HIV. Primary objectives were to determine rates of HIV infection among infants and to assess the safety of HIVIGLOB in combination with sdNVP in HIV-infected Ugandan pregnant women and their infants.

Methods: Mother–infant pairs were randomized to receive 200 mg of nevirapine to women in labor and 2 mg/kg NVP to newborns within 72 hours after birth (sdNVP arm) or to receive sdNVP plus a single intravenous 240-mL dose of HIVIGLOB given to women at 36- to 38-week gestation and a single intravenous 24-mL dose to newborns within 18 hours of birth (HIVIGLOB/sdNVP arm). Risk of HIV infection was determined using Kaplan–Meier and risk ratio estimates at birth, 2, 6, 14 weeks, 6, and 12 months of age.

Results: Intent-to-treat analysis included 198 HIVIGLOB/sdNVP and 294 sdNVP mother–infant pairs. At 6 months of age, the primary endpoint, there was no statistically significant difference in HIV transmission in the HIVIGLOB/sdNVP arm vs. the sdNVP arm [18.7% vs. 15.0%; risk ratio = 1.240 (95% confidence interval: 0.833 to 1.846); $P = 0.290$]. Similarly, the proportion of serious adverse events in the HIVIGLOB/sdNVP and sdNVP arms, respectively, for mothers (18.9% vs. 19.3%; $P = 0.91$) and infants (62.6% vs. 59.5%; $P = 0.51$) was not significantly different.

Conclusions: Giving mother–infant pairs an infusion of peripartum HIV hyperimmune globulin in addition to sdNVP for preventing maternal-to-child transmission was as safe as sdNVP alone but was no more effective than sdNVP alone in preventing HIV transmission.

Key Words: HIV, HIVIGLOB, sdNVP, breastfeeding, PMTCT, Uganda

(*J Acquir Immune Defic Syndr* 2011;58:399–407)

INTRODUCTION

The majority of pediatric HIV-1 infections are due to maternal-to-child transmission (MTCT). Globally, about 370,000 children became HIV infected in 2009 with more than 90% living in sub-Saharan Africa.[1] Vertical transmission may occur in utero, during parturition or via breastfeeding. Without intervention, rates of MTCT of HIV are estimated to

Received for publication March 25, 2011; accepted July 19, 2011.

From the *Makerere University, Johns Hopkins University Research Collaboration/MU-JHU CARE LTD, Kampala, Uganda; †Rollins School of Public Health, Emory University, Atlanta, GA; ‡Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD; §Mulago National Referral Hospital, Kampala, Uganda; ||Department of Pediatrics, Makerere University College of Health Sciences, Kampala, Uganda; ¶Division of AIDS, NIAID, NIH, Rockville, MD; #Karolinska Institute, Stockholm, Sweden; **Swedish Institute for Infectious Disease Control, Stockholm, Sweden; ††International Center for AIDS Care and Treatment Programs, Mailman School of Public Health, Columbia University, New York, NY; ‡‡Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, MD; §§George Washington University, School of Public Health and Health Services, Washington, DC; and ||||Elizabeth Glaser Pediatrics AIDS Foundation, Washington, DC.

[1]Deceased.

Supported by National Institute of Allergy and Infectious Diseases, NIH, USA, and the Ugandan Ministry of Health (clinicaltrials.gov number: NCT00639938). The HIVIGLOB/NVP study was sponsored by NIAID/NIH (RO1-AI34235, UO1 AI038576 S, and UO1 AI69350-01).

Presented at the XVII International AIDS Conference, August 3–8, 2008, Mexico City.

J. Brooks Jackson as Principal Investigator for the trial has full access to all the data and has final responsibility for the decision to submit for publication. None of the authors have any conflicts of interest related to the conduct or reporting of this study.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the US National Institutes of Health.

Authors Contributions: C. Onyango-Makumbi coordinated the HIVIGLOB/NVP trial, contributed to the data analysis, and wrote the article. S. B. Omer, M. Mubiru and L. H. Moulton provided data management and statistical support for analysis and writing of the article. C. Nakabiito contributed to acquisition of data, monitoring of adverse events, and writing of the article. H. Wigzell, L. Falksveden, and B. Wahren contributed to the study design and HIVIGLOB product development. S. L. Zwerski, P. Musoke, F. Mmiro (Principal Investigator), G. Antelman, M. G. Fowler, L. A. Guay, and J. B. Jackson (Principal Investigator) contributed to protocol development, conduct of the trial including monitoring of adverse events and also with analyses, and writing of the article.

Correspondence to: Dr. Carolyne Onyango-akumbi, MBChB, MS, Makerere University, Johns Hopkins University Research Collaboration/MU-HU CARE LTD, PO Box 23491, Kampala, Uganda (eail: carolonyango@mujhu.org).

range from 25% to 48% in resource-poor settings where breastfeeding is common.[2]

The majority of breast milk transmission occurs during the first 6 weeks of life with an estimated absolute cumulative risk of 14%–16%, with 63% occurring by 6 weeks and 75% occurring by 6 months, based on trial data from Kenya.[3] Analyses from the South African Intrapartum Nevirapine Trial study in South Africa showed high rates of early transmission at age 8 weeks for formula-fed vs. breastfed infants.[4] Data from Malawi show a monthly hazard rate of 0.7% from 1 to 5 months postpartum, 0.6% from 6 to 11 months postpartum, and 0.3% from 12 to 17 months postpartum.[5] These data indicate an increased rate of early transmission, followed by a lower but ongoing risk of transmission associated with prolonged breastfeeding.

Given the protective effects of breastfeeding on overall infant survival, it is critical to test interventions that can target both early and later breast milk transmission. Extensive trials of short course antiretroviral (ARV) therapy to prevent MTCT of HIV have been shown to reduce in utero and intrapartum transmission of HIV-1 in resource-limited settings.[4,6–9] Although the ARV regimens were effective in reducing HIV transmission, these benefits diminished over time with continued breastfeeding and showed the need to supplement short-course regimens to prevent MTCT of HIV.[7,10,11]

Several studies, both observational and clinical trials, suggest that use of either maternal triple ARV prophylaxis[12–17] during the breastfeeding period or extended infant prophylaxis[18–22] is a promising public health intervention that decrease the risk of HIV transmission among HIV-infected breastfeeding women who do not yet require treatment for their own health. The World Health Organization now recommends use of either one of the 2 approaches[23]; however, the benefits and relative risks of these 2 strategies have not been directly compared.

A combined approach using both perinatal ARVs and immune globulin interventions has also been proposed.[24] This approach would take advantage of host immunity and potent drugs that attack the HIV life cycle during the high-risk period shortly after delivery. In Uganda, a passive immunoprophylaxis perinatal phase I/II trial was conducted to assess the safety, tolerance, pharmacokinetics, and virologic and immunologic changes associated with the use of Ugandan HIV hyperimmune globulin (HIVIGLOB) in HIV-infected pregnant Ugandan women and their infants.[25] The product was prepared by collecting whole blood units from asymptomatic Ugandan HIV-1 antibody–positive blood donors with CD4 cell counts greater than 500 cells per microliter. Plasma was separated and shipped frozen to the Swedish Institute for Infectious Disease Control in Stockholm, Sweden, for fractionation into intravenous (IV) HIV-1 hyperimmune globulin rendered noninfectious for HIV-1. The product was found to have a 10- to 35-fold reduction in infectivity against a number of different primary subtype isolates, including 3 subtype B, 1 C, 1 E, and 2 Ugandan A isolates.[25]

This phase III randomized trial was undertaken to assess whether the same HIVIGLOB product plus single-dose nevirapine (sdNVP) (HIVIGLOB/sdNVP) given to mothers and infants would provide additional benefit over sdNVP alone for prevention of peripartum HIV transmission. The second objective of the study was to assess the safety and tolerance of HIVIGLOB/sdNVP compared with sdNVP alone.

METHODS

Study Population

HIV-seropositive pregnant women who presented for antenatal care were recruited from Mulago National Referral Hospital's preventing maternal-to-child transmission (PMTCT) program in Kampala, Uganda, from July 2004 to May 2006. These women were offered the local standard of care for PMTCT of HIV (primarily sdNVP) and provided infant feeding counseling consistent with Uganda's Ministry of Health Guidelines at the time of the study.[26,27] Women who chose to breastfeed were offered study participation if they met other eligibility criteria.

Eligibility Criteria

Inclusion criteria included documentation of HIV-1 infection by Western blot, pregnancy of 32- to 36-week gestation, age $\geq$18 years, intention to breastfeed, hemoglobin $\geq$7.5 g/dL, creatinine $<$1.5 mg/dL, serum glutamic pyruvic transaminase $<$5 times upper limit of normal, and provision of informed consent. All liveborn infants of enrolled women were eligible for inclusion in the trial.

Study Design

The HIVIGLOB/NVP study was a phase III, randomized, 3-arm, partially blinded, clinical trial that compared the efficacy of either HIVIGLOB/sdNVP or extended daily infant nevirapine (NVP) dosing until 6 weeks of age with the sdNVP regimen alone (ie, maternal sdNVP at labor onset, newborn sdNVP within 72 hours of birth followed by 6 weeks of daily multivitamins as study drug placebo) for the prevention of perinatal and breast milk–associated HIV transmission. Only results from the analysis of the efficacy of the addition of HIVIGLOB to the sdNVP regimen given to HIV-infected pregnant women and their infants compared with the sdNVP regimen alone are presented here. Details of the evaluation of the efficacy of the extended infant NVP regimen including merged results from similar trials in India and Ethiopia are reported elsewhere.[20,21]

Randomization

At enrollment, participants were given a study-specific identification number that was linked to a preassigned randomization arm known only by the study pharmacist. A computer-generated block randomization scheme created the treatment allocation for the trial. As part of the larger phase III trial, the original design was to enroll 300 mother–infant pairs into the sdNVP arm, 300 pairs into the extended daily infant NVP arm, and 200 pairs into the HIVIGLOB/sdNVP arm allowing for a 3:3:2 ratio. Changes to the enrollment numbers were subsequently made after a recommendation by the data and safety monitoring board to merge data from Uganda,

Ethiopia, and India to allow for rapid accrual to answer the question on efficacy of extended infant NVP. The remaining participants in the Uganda trial were re-randomized into a ratio of 5:4:1 to allow for complete and timely enrollment into all arms and to ensure sufficient numbers of participants randomized to the sdNVP and HIVIGLOB/sdNVP arms.

Study Drug Regimens

All women in the HIVIGLOB/sdNVP arm and the sdNVP-only arm were given 200 mg of NVP to take at the onset of labor; and all newborns were given NVP syrup (2mg/kg) within 7 days of birth. In the HIVIGLOB/sdNVP arm, women also received a single IV infusion of 240 mL (approximately 200 mg/kg) of HIVIGLOB at 36- to 38-week gestation. Infants born to these mothers received a single IV infusion of 24 mL (approximately 400 mg/kg) of HIVIGLOB preferably within 18 hours of birth but could receive the dose up to 6 weeks of age if the baby was not well enough to receive the infusion earlier, if delivered outside Mulago Hospital, or for any other delay in availability of the infant. The infant infusion was given via peripheral vein using an autosyringe in the Mulago Hospital special care unit with continuous monitoring. The 200 mg/kg dosage for the mothers was based on the dosage chosen for a US perinatal trial [Pediatric AIDS Clinical Trials Group (PACTG 185)], and the 400 mg/kg dosage for the infants was based on findings from the phase I/II study.[24,25]

Study Follow-up and Procedures

Medical history, physical examination, and routine laboratory tests were done for women at 36 weeks of gestation, labor, and delivery and 2 and 6 weeks postpartum. For infants, evaluations were conducted at birth, weekly for the first 6 weeks, then at weeks 10 and 14, and at 6, 12, and 18 months. The HIVIGLOB/NVP trial was originally designed to follow-up infants through 18 months of age, but funding constraints necessitated early closure with follow-up reduced to 12 months of age for approximately 100 children who had not yet completed their 18-month final visit. Counseling on infant feeding was conducted at every scheduled visit. All infants received co-trimoxazole prophylaxis against *Pneumocystis jirovecii* pneumonia from 6 weeks of age until they were determined to be HIV uninfected after breastfeeding cessation. Children identified as being HIV infected continued with co-trimoxazole prophylaxis. All women and any infants with confirmed HIV infection were referred to HIV clinics for care and treatment.

Study Endpoints

The primary endpoint was HIV infection status at 6 months of age among liveborn infants but also included the rate of infection at birth, 2 weeks, 6 weeks, 14 weeks, 6 months, 12 months, and 18 months of age, regardless of HIV infection status at birth. Infant HIV infection status was determined using the Roche Amplicor Version 1.5 qualitative DNA polymerase chain reaction (PCR) assay or quantitative HIV-1 RNA PCR assay (Roche Diagnostics Corporation, IN). A positive diagnosis was based on 2 independent positive PCR tests at different time points or if one test was positive, and there was no subsequent sample available. HIV RNA PCR tests were considered positive if viral load (VL) was over 5000 copies per milliliter based on a modification of the PACTG definition for infant HIV diagnosis, generally requiring at least 10,000 HIV RNA copies per milliliter to be deemed positive.[28] Infants who died or were lost to follow-up after only 1 positive PCR or antibody test were classified as infected. Secondary endpoints included death and HIV transmission or death at 2, 6, and 14 weeks and at 6, 12, and 18 months. Safety was assessed by evaluation and grading of adverse events (AEs) according to the Division of AIDS Toxicity Tables for Grading Severity of Adverse Experiences, April 1994. AEs in mothers were documented from enrollment to 8 weeks postpartum; among infants, AEs were collected from birth through 14 weeks of age, and thereafter, only serious adverse events (SAEs) were documented.

Statistical Analysis

Only the HIVIGLOB/sdNVP efficacy component of this trial with follow-up to 12 months is presented. Intent-to-treat analysis (primary analysis) included all liveborn infants with an evaluable infection status at 6 months. Risk of HIV infection and/or death was determined using Kaplan–Meier and risk ratio (RR) estimates, and the z test was used to compute P values for the RRs. In the analysis of HIV transmission, infants were censored at the time of study termination, last HIV determination, or death. A similar approach was used for the endpoints involving death and HIV transmission or death (complement of infection-free survival). The secondary modified intent-to-treat analysis excluded infants HIV positive at birth (infants with unknown birth status were included in the modified intent-to-treat analysis). AEs were compared across the 2 arms using an exact test. Statistical analyses were performed using Stata 10,[29] and statistical significance of comparisons and associations was evaluated at $\alpha = 0.05$. The data and safety monitoring board provided ongoing and interval review of efficacy and safety data from this study.

Ethical Considerations

The study was approved by the National AIDS Research Committee in Kampala, Uganda, and Western Institutional Review Board in Olympia, Washington.

RESULTS

Seven hundred twenty-two women were enrolled into the HIVIGLOB/NVP trial of which 228 were assigned to the 6-week extended NVP arm.[20] Of the remaining 494 women, 204 were randomly assigned to the HIVIGLOB/sdNVP arm and 290 were assigned to the sdNVP arm (Fig. 1). Of the 204 women randomized to the HIVIGLOB/sdNVP arm, only 173 (85%) women received the HIVIGLOB infusion. Twenty-six

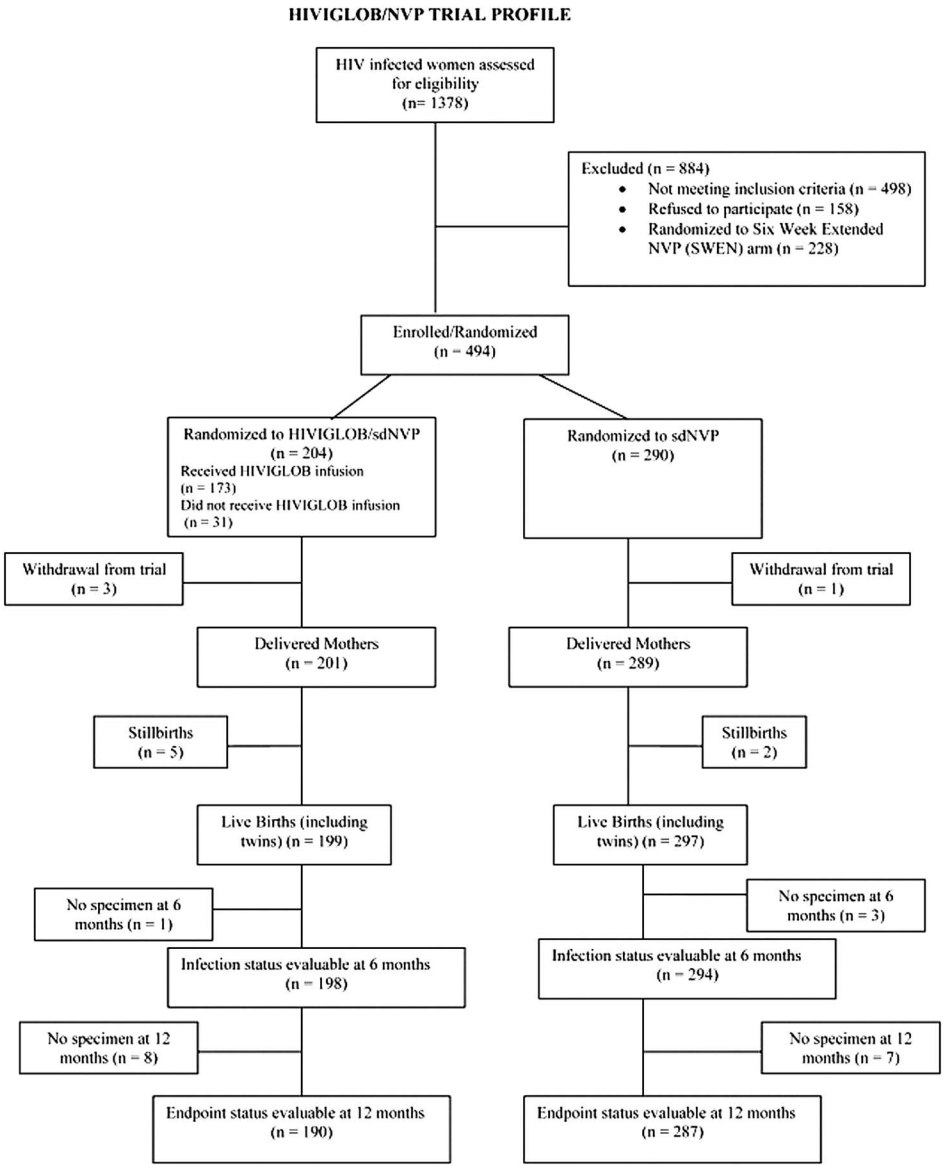

FIGURE 1. HIVIGLOB/NVP Trial Profile.

women delivered before or missed their HIVIGLOB infusion date; 3 withdrew from the study before infusion; 1 had an intrauterine fetal death diagnosed at her infusion appointment; and 1 was diagnosed with severe malaria, preventing infusion. One participant assigned to the sdNVP arm withdrew from participation before delivery.

There were 199 live births (including twins) and 5 stillbirths in the HIVIGLOB/sdNVP arm, whereas 297 live births (including twins) and 2 stillbirths were delivered to women randomized to the sdNVP arm. Four infants did not receive their HIVIGLOB infusion; 2 early neonatal deaths and 2 maternal refusals. Analysis included 198 infants in the HIVIGLOB/sdNVP arm and 294 infants in the sdNVP arm who had an evaluable infection status at 6 months.

Maternal characteristics including age, proportion of cesarean section deliveries, proportion that received sdNVP at onset of labor, maternal CD4 cell counts, and VL were similar in the 2 groups (Table 1). Infant characteristics including sex, proportion receiving sdNVP at birth, and proportion breastfeeding at given time points did not differ significantly between the 2 study groups (Table 1).

Frequency of Breastfeeding

Reported breastfeeding was 100% at 1 week and 63%–65% at 14 weeks in both study groups (Table 1). There was a substantial reduction in breastfeeding after 14 weeks, with proportions of any breastfeeding at 6 months of 33.1% in the HIVIGLOB/sdNVP arm and 31% in the sdNVP arm ($P = 0.64$). Rates of exclusive breastfeeding among those still breastfeeding at 6 months were 41.7% in the HIVIGLOB/sdNVP arm and 37.2% in the sdNVP arm ($P = 0.59$). By 12 months, the proportion of babies receiving any breast milk was 13.1% in the HIVIGLOB/sdNVP arm and 9.9% in the sdNVP arm.

TABLE 1. Comparison of Maternal and Infant Characteristics by Study Regimen

Study Arm Maternal characteristics	HIVIGLOB/sdNVP (n = 198)	sdNVP (n = 294)	*P*
Maternal age [y: median (percentile 25, percentile 75)]	25 (22, 29)	25 (22, 29)	0.27
Cesarean section, n (%)	35 (17.7)	49 (16.7)	0.77
Received NVP dose, n (%)	193 (97.5)	284 (96.6)	0.58
CD4 count at enrollment (cells/mm^3), n (%)			
≤200	27 (13.7)	56 (19.2)	—
201–350	38 (19.3)	63 (21.6)	0.17
>350	132 (67.0)	173 (59.3)	—
VL at enrollment [copies/mL: median (percentile 25, percentile 75)]	34362 (9381, 106938)	41937 (10622, 117888)	0.20
Infant characteristics			
Sex [male, n (%)]	87 (43.9)	151 (51.4)	0.11
Received postpartum NVP dose, n (%)	194 (98.0)	280 (95.2)	0.11
Any breastfeeding, n (%)			
Week 1	189 (100)	272 (100)	NA
Week 6	170 (91.4)	262 (93.9)	0.30
Week 14	119 (63.3)	184 (65.9)	0.56
Month 6	60 (33.1)	86 (31)	0.64
Month 12	23 (13.1)	27 (9.9)	0.30
Exclusive breastfeeding, n (%)*			
Week 1	184 (97.4)	258 (94.9)	0.18
Week 6	152 (89.4)	223 (85.1)	0.20
Week 14	90 (75.6)	137 (74.5)	0.82
Month 6	25 (41.7)	32 (37.2)	0.59
Month 12	0 (0)	0 (0)	NA

Analysis for both maternal and infant characteristics based on number of liveborn infants; therefore, mothers of twins counted twice.

*Exclusive breastfeeding status was assessed on a subset of infants whose mothers reported any breastfeeding at the specified study visits. The calculation of exclusive breastfeeding status at a certain visit/age accounted for status at all previous visits.

Risk of HIV Transmission

There was a significant difference in the proportion of children with HIV infection detected at birth in the HIVIGLOB/sdNVP arm (9.1%, 18 infections) compared with the low rate found in the sdNVP control arm (4.1%, 12 infections) [RR = 2.3, 95% confidence interval (CI): 1.100 to 4.500, $P = 0.030$] (Fig. 2, Table 2). The difference persisted throughout the study period; however, it was no longer statistically significant by the 6-week time point. The difference in the proportion of children with HIV infection at 6 months, the primary endpoint, was not statistically significant between the HIVIGLOB/sdNVP arm and the sdNVP arm (18.7% vs. 15.0%, RR = 1.240, 95% CI: 0.833 to 1.846, $P = 0.290$). Secondary analyses in the modified intent-to-treat population (infants uninfected at birth) showed that there were no statistically significant differences in the proportion of children with HIV infection between the 2 arms at any of the study time points (Table 2).

After adjusting for study arm, maternal baseline VL of >100,000 copies per milliliter led to more than a 5-fold overall increase in risk of transmission [hazard ratio (HR) = 5.360, 95% CI: 2.606 to 11.024, $P = 0.000$], whereas maternal baseline VL of 10,001–100,000 copies per milliliter led to more than a 2-fold overall increase in risk of transmission (HR = 2.451, 95% CI: 1.170 to 5.136, $P = 0.018$) when compared with maternal baseline VL of ≤10,000 copies per milliliter.

Risk of Death

Two mothers died during the 8-week study participation period. One death in the HIVIGLOB/sdNVP arm was due to advanced HIV disease associated with wasting, puerperal sepsis, and gastroenteritis and the other death in the sdNVP arm was due to cryptococcal meningitis.

There were 28 infant deaths during the 12-month follow-up period: 14 in the HIVIGLOB/sdNVP arm and 14 in the sdNVP arm (Table 2). Risk of infant mortality in the HIVIGLOB/sdNVP arm was statistically similar to that in the sdNVP arm at all time points (Fig. 2, Table 2). At 6 months, risk of mortality was 5.6% (HIVIGLOB/sdNVP arm) vs. 3.4% (sdNVP arm) (RR = 1.630, 95% CI: 0.706 to 3.767, $P = 0.253$). Reasons for death included respiratory conditions (10), gastroenteritis (6), other infections (3), malnutrition (2), sudden infant death syndrome (2), anemia (2), and others (3). These conditions were responsible for a similar proportion of deaths in both arms (data not shown). There was a significantly reduced overall risk of infant mortality among women with CD4 cell counts >350 cells per cubic millimeter compared to those with CD4 cell counts <200 cells per cubic millimeter (HR = 0.405, 95%

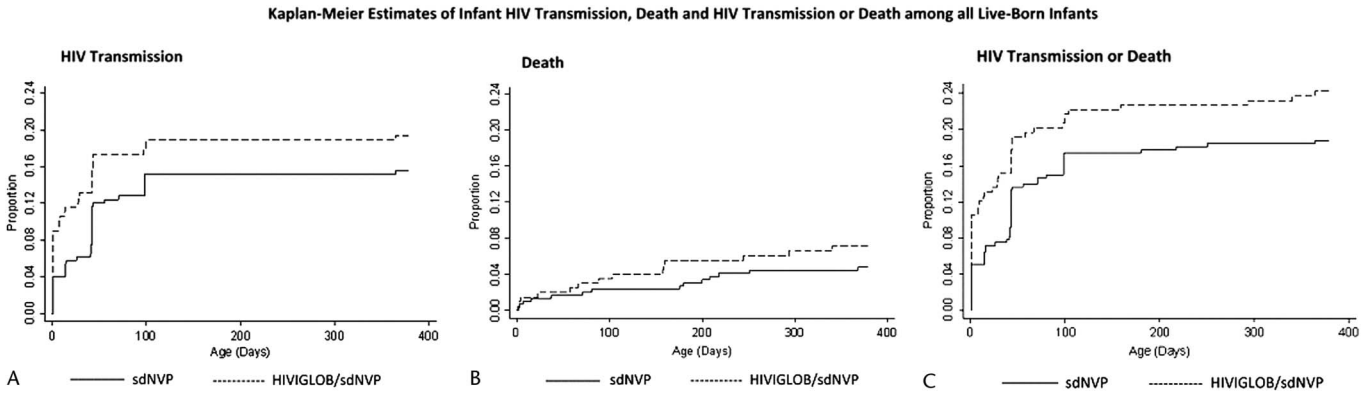

FIGURE 2. Kaplan-Meier Estimates of Infant HIV Transmission, Death and HIV Transmission or Death Among all Live-born Infants.

CI: 0.167 to 0.981, $P = 0.045$). Overall risk of infant death was not different in women with CD4 cell counts 201–350 cells per cubic millimeter compared with women who had lower CD4 cell counts (HR = 0.682, 95% CI: 0.247 to 1.884, $P = 0.461$). Overall risk of infant death adjusted for study arm was not associated with maternal baseline VL.

Secondary modified intent-to-treat population showed that there were no statistically significant differences in the proportion of children who died at any of the study time points (Table 2).

Risk of HIV Transmission or Death

The cumulative risk of infant HIV transmission or death was significantly lower in the sdNVP arm (9.9%) than in the HIVIGLOB/sdNVP arm (17.2%) at 2 weeks (RR = 1.834, 95% CI: 1.061 to 3.169, $P = 0.030$) (Table 2). A similar trend was observed at all the other time points (6 and 14 weeks, 6 and 12 months); however, the difference in risk at these time points was not significant (Fig. 2). Secondary analyses for transmission or death showed no significant difference in risk at all time points (Table 2).

Safety

The number of women experiencing SAEs (ie, grades 3 and 4 AEs) was balanced between the 2 groups with at least 1 grade 3 or 4 AEs reported in 38 (19.3%) women in the HIVIGLOB/sdNVP arm and 54 (18.9%) women in the sdNVP arm ($P = 0.91$). Complications of pregnancy and

TABLE 2. Risk of HIV Transmission, Death, and HIV Transmission or Death Among All LiveBorn Infants and Infants Uninfected at Birth by Study Regimen

	All LiveBorn Infants				Infants Uninfected at Birth			
	KM Estimate of Risk, n (%)				KM Estimate of risk, n (%)			
Age	HIVIGLOB/sdNVP	sdNVP	RR (95% CI)	*P*	HIVIGLOB/sdNVP	sdNVP	RR (95% CI)	*P*
HIV transmission								
Birth	18 (9.1)	12 (4.1)	2.300 (0.030 to 4.500)	0.030	—	—	—	—
2 wks	23 (11.6)	17 (5.8)	2.007 (0.023 to 3.662)	0.023	5 (2.8)	5 (1.8)	1.558 (0.457 to 5.314)	0.479
6 wks	34 (17.2)	35 (11.9)	1.434 (0.106 to 2.220)	0.106	16 (8.9)	23 (8.2)	1.087 (0.591 to 2.000)	0.787
14 wks	37 (18.7)	44 (15.0)	1.240 (0.290 to 1.846)	0.290	19 (10.6)	32 (11.3)	0.928 (0.543 to 1.585)	0.784
6 mo	37 (18.7)	44 (15.0)	1.240 (0.290 to 1.846)	0.290	19 (10.6)	32 (11.3)	0.928 (0.543 to 1.585)	0.784
12 mo	38 (19.2)	45 (15.3)	1.247 (0.271 to 1.846)	0.271	20 (11.1)	33 (11.7)	0.948 (0.563 to 1.598)	0.842
Death								
2 wks	3 (1.5)	4 (1.4)	1.118 (0.884 to 4.957)	0.884	3 (1.7)	4 (1.4)	1.176 (0.269 to 5.142)	0.829
6 wks	4 (2.0)	5 (1.7)	1.188 (0.795 to 4.359)	0.795	4 (2.2)	5 (1.8)	1.254 (0.339 to 4.635)	0.734
14 wks	8 (4.0)	7 (2.4)	1.690 (0.302 to 4.581)	0.302	7 (3.9)	7 (2.5)	1.562 (0.557 to 4.379)	0.396
6 mo	11 (5.6)	10 (3.4)	1.630 (0.253 to 3.767)	0.253	9 (5.0)	10 (3.5)	1.407 (0.582 to 3.404)	0.448
12 mo	14 (7.1)	14 (4.8)	1.485 (0.281 to 3.051)	0.281	11 (6.1)	14 (5.0)	1.230 (0.572 to 2.648)	0.596
HIV transmission or death								
2 wks	34 (17.2)	29 (9.9)	1.834 (1.061 to 3.169)	0.030	16 (8.9)	17 (6.0)	1.383 (0.543 to 3.521)	0.496
6 wks	45 (22.7)	46 (15.6)	1.404 (0.935 to 2.107)	0.102	27 (15.0)	34 (12.1)	1.112 (0.647 to 1.912)	0.701
14 wks	47 (23.7)	54 (18.4)	1.274 (0.888 to 1.827)	0.188	29 (16.1)	42 (14.9)	1.037 (0.655 to 1.643)	0.876
6 mo	47 (23.7)	54 (18.4)	1.278 (0.895 to 1.826)	0.177	29 (16.1)	42 (14.9)	1.050 (0.669 to 1.648)	0.831
12 mo	48 (24.2)	55 (18.7)	1.290 (0.916 to 1.818)	0.450	30 (16.7)	43 (15.2)	1.087 (0.710 to 1.666)	0.701

childbirth were the most frequent cause of maternal SAEs in both groups, followed by laboratory abnormalities. Fifty-six mothers had at least 1 AE considered related to the HIVIGLOB infusion, and all involved vital sign changes common with immunoglobulin infusions, such as changes in blood pressure, heart rates, and respiratory rates. One woman had a grade 3 AE that was considered definitely related to HIVIGLOB that necessitated permanent discontinuation of the infusion. All other women who experienced an infusion-related AE completed the infusion. All infusion-related events resolved with no complications.

There were no differences in the number of infants experiencing at least 1 grade 3 or 4 SAE between the 2 arms, 124 (62.6%) in the HIVIGLOB/sdNVP arm, and 175 (59.5%) in the sdNVP arm, $P = 0.51$. The majority involved common illnesses in the study population such as malaria, pneumonia, gastroenteritis, and laboratory abnormalities. Fifteen infants had grade 3 events considered definitely or probably related to the HIVIGLOB infusion; 6 infusions were permanently discontinued, 4 were temporarily held then restarted, 4 were continued, and 1 event occurred after completion of the infusion. All these events resolved without complications. Fourteen infants had SAEs considered possibly related to the HIVIGLOB infusion. Eight events occurred during the infusion (1 permanent discontinuation, 2 temporarily held, and 5 no change in infusion), and the remaining 6 occurred after the infusion was completed.

DISCUSSION

This study assessed the relative safety and efficacy of an HIV hyperimmune globulin product combined with peripartum ARVs compared with a peripartum ARV strategy alone in HIV-infected pregnant women and their breastfeeding infants for the prevention of peripartum transmission of HIV-1 infection. The proportions of breastfeeding infants were similar between the 2 arms throughout the duration of the study. The low rates of breastfeeding that were observed at 12 months reflect the recommendations from the Ugandan Ministry of Health PMTCT Guidelines at the time which recommended that HIV-infected women breastfeed for 3–6 months after delivery. This is reflected in the results that show that the proportion of breastfeeding infants was high at and before 14 weeks of age when the efficacy of the HIVIGLOB infusion was most likely to be effective.

The study demonstrated that there was no significant difference in HIV transmission rates at 6 months (primary endpoint) and 12 months of age in Ugandan mother, infant pairs who each received a single infusion of HIVIGLOB in addition to the standard sdNVP regimen for PMTCT compared with the standard sdNVP regimen alone. Although there was no demonstrable difference in treatment efficacy, the study also showed that that there were no significant differences in mortality or serious AEs between the 2 arms. The majority of the infant deaths were due to infections common in children in Uganda and were unrelated to the receipt of the HIVIGLOB infusion.

Our trial findings do not support a role for use of HIVIGLOB to help reduce peripartum or early breast milk transmission of HIV-1 among breastfed HIV-1–exposed infants. These results are similar to those of the PACTG 185 trial of a hyperimmune product, HIVIG, to reduce peripartum transmission in a non–breastfeeding population in the United States, which failed to demonstrate efficacy due to the overall low rate of transmission in both study arms.[24] However, there was a trend toward decreased transmission in women with low CD4 count in the US study, which was not found in this study. It had been hypothesized that the addition of HIVIGLOB to sdNVP would be a promising intervention strategy for various reasons. The presence of antibodies to specific HIV-1 V3 loop peptides has been negatively correlated with vertical transmission in some earlier studies.[30,31] Likewise, the presence of neutralizing antibodies in the serum of HIV-1–infected women appears to correlate with delivery of uninfected children.[32] It was hoped that preparation of HIVIGLOB from the plasma of multiple asymptomatic HIV-1–infected Ugandan blood donors would have the potential to provide both group-specific and type-specific neutralizing antibodies, gp120/CD4 blocking antibodies, and V3 loop antibodies to the diverse strains of HIV-1 found in Uganda.[33]

Although there are no data at present to show what viral subtypes the women in the study had, it is possible that the HIVIGLOB product did not demonstrate broadly neutralizing antibody activity against Ugandan subtype isolates, particularly subtype D, which is the second most common subtype in the Ugandan population. Antibody responses are often very specific to the individual viral strain with which one is infected and may not have activity against other strains of viruses. It is also possible that the antibodies in the HIVIGLOB solution were able to neutralize the strains used in the laboratory but may have had less neutralizing activity against individual strains found in the mothers participating in the trial. It is also possible that the concentration of the HIVIGLOB antibodies present in cord blood, vaginal fluids, or breast milk was not sufficient to inhibit virus at different time points for viral transmission to infants. Giving the maternal dose of HIVIGLOB several weeks before delivery may have allowed selection of viral escape mutants such that subsequent administration of HIVIGLOB to the baby did not confer protection against maternal virus at delivery and during the early breastfeeding period. Passive immunization with a broadly reactive monoclonal antibody cocktail just to the infant may possibly be a better option in preventing early HIV transmission after birth.

Interpretation of the comparative efficacy of the HIVIGLOB product is complicated by the unanticipated low rate of HIV infection at birth in the sdNVP control arm in this study. At 4.1%, the sdNVP birth infection rate was significantly lower than the HIVIGLOB/sdNVP arm (9.1%) and the birth transmission rates seen with the same sdNVP regimen in the third arm of this trial (9.6%) and the HIV Network for Prevention Trials 012 study at the same trial site (8.1%).[6,20] There were no identifiable differences in the characteristics of the mothers or infants across the study arms to account for this unbalanced infection rate at birth. Kaplan–Meier estimates excluding infants infected at birth showed no significant difference in HIV infection risk between the arms at any other time point including the primary endpoint

at 6 months. Although there is a theoretical risk of early enhanced transmission due to high-dose HIV antibody via immune complexes, we believe it is unlikely that the addition of the HIVIGLOB product led to an increased risk of transmission compared with the sdNVP arm alone because the transmission rate in the HIVIGLOB arm was similar to the transmission rate in the sdNVP arm at 6 weeks of age.

The fact that 26 women delivered before or missed their HIVIGLOB infusion raises the possibility of selection bias. However, the 2 study groups in the final analysis were similar in terms of maternal and infant characteristics, which is reassuring in terms of the internal validity of this study.

In conclusion, the theoretical plausibility of the benefit of adding passive immunotherapy with HIV immune globulin to sdNVP for further reduction in peripartum and early HIV-1 transmission through breast milk was not evident from this trial. Further studies using novel broadly neutralizing monoclonal antibodies may yield critical information on the ultimate contribution of passive immunotherapy to the prevention of MTCT.

ACKNOWLEDGMENTS

The authors sincerely thank the mothers and children who volunteered and participated in the trial and all the staff of Makerere University–Johns Hopkins University Research Collaboration for their participation in and support of the trial.

REFERENCES

1. UNAIDS. *Global Report: UNAIDS Report on the Global AIDS Epidemic 2010*. Geneva, Switzerland; UNAIDS; 2010.
2. De Cock KM, Fowler MG, Mercier E, et al. Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. *JAMA*. 2000;283:1175–1182.
3. Nduati R, John G, Mbori-Ngacha D, et al. Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial. *JAMA*. 2000;283:1167–1174.
4. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis*. 2003;187:725–735.
5. Miotti PG, Taha TE, Kumwenda NI, et al. HIV transmission through breastfeeding: a study in Malawi. *JAMA*. 1999;282:744–749.
6. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomized trial. *Lancet*. 1999;354:795–802.
7. The Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa and Uganda [Petra Study]: a randomized, double blind, placebo-controlled trial. *Lancet*. 2002;359:1178–1186.
8. Wiktor SZ, Ekpini E, Karon JM, et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomized trial. *Lancet*. 1999;353:781–785.
9. Leroy V, Sakarovitch C, Cortina-Borja M, et al. on behalf of the Ghent Group on HIV in Women and Children. Is there a difference in the efficacy of peripartum antiretroviral regimens in reducing mother-to-child transmission of HIV in Africa? *AIDS*. 2005;19:1865–1875.
10. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet*. 2003;362:859–868.
11. Leroy V, Karon J, Alioum A, et al. Twenty-four month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa. *AIDS*. 2002;16:631–641.
12. Thomas T, Masaba R, Ndivo R, et al. PMTCT of HIV among breastfeeding mothers using HAART: the Kisumu Breastfeeding Study, Kisumu, Kenya, 2003-2007 [abstract 45aLB]. Presented at: 15th Conference on Retroviruses and Opportunistic Infections; 2008; Boston, MA.
13. Kilewo C, Karlsson K, Ngarina M, 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;52:406–416.
14. Peltier CA, Ndayisaba GF, Lepage P, et al. Breastfeeding with maternal antiretroviral therapy or formula feeding to prevent HIV postnatal mother-to-child transmission in Rwanda. *AIDS*. 2009;23:2415–2423.
15. Palombi L, Marazzi MC, Voetburg A, et al. Treatment acceleration program and the experience of the DREAM program in prevention of mother-to-child transmission of HIV. *AIDS*. 2007;4:S65–S71.
16. The Kesho Bora Study Group. 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. *Lancet Infect Dis*. 2011;11:171–180.
17. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *N Engl J Med*. 2010;362:2282–2294.
18. Vyankandondera J, Lutchers S, Hassink E, et al. Reducing risk of HIV transmission from mother to infant through breastfeeding using antiretroviral prophylaxis in infants (SIMBA). 2nd IAS Conference on HIV Pathogenesis, Treatment and Prevention; 2003; Paris, France Abstract LB7.
19. Kilewo C, Karlsson K, Massawe A, et al. Prevention of mother-to-child transmission of HIV-1 through breast-feeding by treating infants prophylactically with lamivudine in Dar es Salaam, Tanzania: The Mitra Study. *J Acquir Immune Defic Syndr*. 2008;48:315–323.
20. Six Week Extended-Dose Nevirapine (SWEN) Study Team. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet*. 2008;372:300–313.
21. Omer SB. Six Week Extended Dose Nevirapine (SWEN) Study Team. Twelve-month follow-up of Six Week Extended Dose Nevirapine randomized controlled trials: differential impact of extended-dose nevirapine on mother-to-child transmission and infant death by maternal CD4 cell count. *AIDS*. 2011;25:767–776.
22. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med*. 2008;359:119–129.
23. WHO. *Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infections in Infants. Recommendations for a Public Health Approach. 2010 Version.* Geneva, Switzerland; World Health Organization; 2010.
24. Stiehm ER, Lambert JS, Mofenson LM, et al. Efficacy of zidovudine and human immunodeficiency virus (HIV) hyperimmune immunoglobulin for reducing perinatal HIV transmission from HIV-infected women with advanced disease: results of Pediatric AIDS Clinical Trials Group protocol 185. *J Infect Dis*. 1999;179:567–575.
25. Guay L, Musoke P, Hom D, et al. Phase I/II trial of HIV-1 hyperimmune globulin (HIVIGLOB) for the prevention of HIV-1 vertical transmission in Uganda. *AIDS*. 2002;16:1391–1400.
26. WHO. *New Data on the Prevention of Mother-to-Child Transmission of HIV and Their Policy Implications. Conclusions and Recommendations. WHO Technical Consultation on Behalf of the UNFPA/UNICEF/WHO/UNAIDS Inter-Agency Task Team on Mother-to-Child Transmission of HIV*. Geneva, Switzerland: World Health Organization 2001; 2000:11–13 WHO/RHR/01.28.
27. Ministry of Health, Republic of Uganda. *Policy for Reduction of the Mother-to-Child HIV Transmission in Uganda*. Ministry of Health, Republic of Uganda; 2003.

28. Read JS. Committee on Pediatric AIDS. Diagnosis of HIV-1 infection in children younger than 18 months in the United States. *Pediatrics*. 2007; 120:1547–1562.
29. Corp Stata. *Stata Statistical Software: Release 10*. College Station, TX: StataCorp LP; 2003.
30. Rossi P, Moschese V, Broliden PA, et al. Presence of maternal antibodies to human immunodeficiency virus 1 envelope glycoprotein gp120 epitopes correlates with the uninfected status of children born to seropositive mothers. *Proc Natl Acad Sci U S A*. 1989;86: 8055–8058.
31. Devash Y, Calvelli TA, Wood DG, et al. Vertical transmission of human immunodeficiency virus is correlated with the absence of high-affinity/avidity maternal antibodies to the gp120 principal neutralizing domain. *Proc Natl Acad Sci U S A*. 1990;87:3445–3449.
32. Scarlatti G, Albert J, Rossi P, et al. Mother-to-child transmission of human immunodeficiency virus type 1: correlation with neutralizing antibodies against primary isolates. *J Infect Dis*. 1993;168:207–210.
33. Oram JD, Downing RJ, Roff M, et al. Nucleotide sequence of a Ugandan HIV-1 provirus reveals genetic diversity from other HIV-1 isolates. *AIDS Res Hum Retroviruses*. 1990;6:1073–1078.