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Epidemiology of HIV and selected blood-borne infections in East-Africa

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Transmission of human herpesvirus 8 by blood transfusion

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Abstract

Background: Whether human herpesvirus 8 (HHV-8) is transmissible by blood transfusion remains undetermined. We evaluated the risk of HHV-8 transmission by blood transfusion in Uganda, where HHV-8 is endemic.

Methods: We enrolled patients in Kampala, Uganda, who had received blood transfusions between December 2000 and October 2001. Pretransfusion and multiple post-transfusion blood specimens from up to nine visits over a 6-month period were tested for HHV-8 antibody. We calculated the excess risk of seroconversion over time among recipients of HHV-8-seropositive blood as compared with recipients of seronegative blood.

Results: Of the 1811 transfusion recipients enrolled, 991 were HHV-8-seronegative before transfusion and completed the requisite follow-up, 43% of whom received HHV-8-seropositive blood and 57% of whom received seronegative blood. HHV-8 seroconversion occurred in 41 of the 991 recipients. The risk of seroconversion was significantly higher among recipients of HHV-8-seropositive blood than among recipients of seronegative blood (excess risk, 2.8%; $P < 0.05$), and the increase in risk was seen mainly among patients in whom seroconversion occurred 3 to 10 weeks after transfusion (excess risk, 2.7%; $P = 0.005$), a result consistent with the transmission of the virus by transfusion. Blood units stored for up to 4 days were more often associated with seroconversion than those stored for more than 4 days (excess risk, 4.2%; $P < 0.05$).

Conclusions: This study provides strong evidence that HHV-8 is transmitted by blood transfusion. The risk may be diminished as the period of blood storage increases.

Kaposi's sarcoma is the most common cancer associated with the acquired immunodeficiency syndrome (AIDS) worldwide, and human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma-associated herpes-virus, was identified a decade ago as the causative agent of Kaposi's sarcoma.¹ The burden of Kaposi's sarcoma in Africa is high; in Uganda, Kaposi's sarcoma accounts for half of all reported cancers.² In industrialized countries, the seroprevalence of HHV-8 is relatively low (2 to 8%),³ whereas in sub-Saharan Africa, the seroprevalence of HHV-8 can exceed 50%. The modes of transmission of HHV-8 in Africa remain poorly understood. Studies indicate that the seroprevalence increases throughout childhood and reaches a plateau by adolescence, suggesting that transmission occurs mainly in the community, probably through saliva or other nonsexual routes.³

Whether HHV-8 is transmitted by blood transfusion remains controversial.⁴ Transmissibility of the virus by this route may be limited by the cell-associated nature of the virus and the low frequency of circulating virus in asymptomatic seropositive persons.⁵ Previous studies that did not find evidence of transfusion-transmitted infection enrolled small numbers of patients, most of whom received leukocyte-reduced or acellular blood components.⁶⁻⁸

The potential for blood-borne transmission of HHV-8 has been supported by the results of a number of studies. The transmission of HHV-8 has been associated with the use of injection drugs^{9,10} and transplantation of infected organs.^{11,12} HHV-8 infection has been seen among U.S. patients undergoing cardiac surgery who received multiple units of non-leukocyte-reduced blood.¹³ Several case reports of Kaposi's sarcoma have described an association with blood transfusions.¹⁴⁻¹⁷ Infectious HHV-8 has been recovered from a U.S. blood donor,¹⁸ and viral DNA has been detected in blood donors in Africa.¹⁹ The seroprevalence of HHV-8 has increased with increasing numbers of blood transfusions among patients with sickle cell anemia in Uganda.²⁰

To evaluate the risk of the transmission of HHV-8 by blood transfusion, we conducted a prospective observational cohort study of transfusion recipients in Uganda, where the seroprevalence among blood donors was 40%,²¹ leukocyte reduction was not used, and blood storage time was usually short. If transmission of HHV-8 by transfusion occurs, it is likely to be detected in such a setting.

Methods

Blood Donations

All volunteers who donated blood to the national blood-transfusion service in central Uganda between November 2000 and September 2001 were invited to participate in the study. A sample of blood from each consenting donor was stored for HHV-8 serologic testing. The samples were screened at the Nakasero Blood Bank in Kampala, Uganda, for human immunodeficiency virus (HIV), hepatitis B surface antigen, and *Treponema pallidum* and stored at 4° to 8°C according to routine procedures. Blood units were transfused as whole blood or separated into packed red cells and plasma. Some units were split into pediatric blood packs for use in young children. Leukocyte-reduction filters were not used; the buffy coat was partially removed in packed-cell units.

Transfusion Recipients

Enrollment and follow-up of transfusion recipients took place between December 2000 and October 2001 at Mulago Hospital, Kampala. Transfusion recipients were eligible for enrollment if their pretransfusion specimen (left over from blood typing and cross-matching) was available and their transfusion could be linked to an identified blood unit. Patients who had received transfusions within the previous 6 months were not eligible. Follow-up visits were scheduled 1, 2, and 4 weeks after transfusion and monthly thereafter for up to 6 months; unscheduled visits also occurred. At enrollment and at each follow-up visit, blood was drawn,

demographic data were recorded, and information was obtained about any repeated transfusions.

Transfusion recipients were included in the analysis if their pretransfusion specimen was seronegative for HHV-8 and they completed at least 2 months of follow-up. Patients who received more than one transfusion during the first 7 days of enrollment remained in the analysis, and their transfusion date was considered to be the midpoint between the first and last transfusions. The follow-up period for analysis began on day 10 after transfusion to exclude the earliest seroconversions, which were probably the result of community-acquired infections. Follow-up ended at the time of the last visit, death, seroconversion, or receipt of an additional transfusion that was either HHV-8-seropositive or had equivocal results (more than 2 months after transfusion). Transfusions that were repeatedly HHV-8-seronegative were allowed throughout follow-up and did not lead to censoring of data.

Laboratory Procedures

Specimens were transported daily from Mulago Hospital to the Centers for Disease Control and Prevention (CDC) laboratory at the Uganda Virus Research Institute in Entebbe. The recipient's pretransfusion plasma was tested for antibodies against HIV, and reactivity was confirmed by polymerase-chain-reaction assay for recipients who were 24 months of age or younger.

Testing for HHV-8 antibody was performed at the CDC in Atlanta. Three serologic assays were used: two peptide enzyme immunoassays based on epitopes in the open reading frames 65 and K8.1^{22,23} and an immunofluorescence assay based on lytic HHV-8 antigens.²⁴ The immunofluorescence assay was performed as described previously,²⁴ except that plasma was diluted to 1:40 for screening and 1:80 for confirmation. Specimens that showed reactivity in two or more tests (with the immunofluorescence assays performed at two different dilutions counted as separate tests) were categorized as positive. Results were categorized as

equivocal when more than one of the individual assays showed equivocal reactivity or when the test results were conflicting or incomplete because of depletion of the specimen. For all recipients, the pretransfusion specimen and the linked specimen from the blood donor were tested for antibodies against HHV-8. For recipients who were HHV-8–seronegative before transfusion, the last two follow-up specimens were tested, and if either was positive, all follow-up specimens were tested. The laboratory staff was unaware of the recipient–donor linkages.

For the purpose of analysis, patients who had received a transfusion of any HHV-8–seropositive blood products were categorized as exposed, regardless of the serologic status of additional units. Patients who had received transfusions of HHV-8–seronegative blood alone were categorized as unexposed. Patients who had received blood with equivocal serologic status or a combination of seronegative blood and blood with equivocal serologic status were excluded from the analysis.

Statistical Analysis

The data were double-entered with the use of Epi Info software (version 6.04) and analyzed with the use of Stata software (version 8.0) and SAS software. The primary data analysis evaluated whether the risk of HHV-8 seroconversion was higher among recipients of HHV-8–seropositive blood than among those who received seronegative blood. To allow sufficient time for HHV-8 antibodies to develop in the event of an infection and for any passive HHV-8 antibodies from the donor to be cleared, seroconversion was defined as two or more consecutive HHV-8–seropositive results obtained at least 25 days after transfusion. The date of seroconversion was defined as the midpoint between the last seronegative and the first seropositive visit.

For each recipient, we analyzed the variables of sex, number of children in the household, HIV status, hemoglobin concentration, admission diagnosis, number of transfusions,

volume and component (whole blood, packed cells, or plasma) of blood transfused, and duration of blood storage, according to the recipient's exposure status and risk of seroconversion. Continuous variables with a normal distribution were analyzed by Student's t-test, and those with a non-normal distribution were analyzed by the Wilcoxon rank-sum test. Categorical variables were analyzed by Fisher's exact test.

Using survival analysis, we compared the risk of HHV-8 seroconversion over time in the exposed and unexposed groups. We calculated the excess risk of seroconversion as the difference between the Kaplan–Meier survival functions for time to seroconversion in exposed and unexposed recipients, both for the full follow-up period and for the 3-to-10-week period after transfusion that is most likely to be associated with transfusion-transmitted infection. We used Greenwood's formula (SAS software) to calculate the variance of the excess risk as the sum of the variance of the Kaplan–Meier estimates. Confidence intervals were calculated by using a normal approximation. We evaluated recipients' age, the number of blood units transfused, and the duration of blood storage for confounding and an interaction with exposure status. All comparisons were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance.

The study was approved by the Uganda National Council for Science and Technology and the institutional review board of the CDC and the Uganda Virus Research Institute. Written informed consent was obtained from all adults and from the parents of children less than 18 years old.

Results

Study Population

A total of 6533 patients had pretransfusion specimens and were evaluated for enrollment (Fig. 7.1). Of these, 72.3% were not enrolled because they did not receive a transfusion, were too ill, declined participation, lived too far away, died, or were discharged before enrollment. The remaining 1811 recipients were enrolled and followed for an average of 4.6 months. The seroprevalence of HHV-8 among the 1761 linked blood donations was 36.2%. The seroprevalence of HHV-8 was 14.5% overall among the enrolled patients before transfusion and increased with age; the seroprevalence was 11.4% among those 2 years of age, 14.9% among those 5 years of age, 21.2% among those 10 years of age, 27.8% among those 20 years of age, and 32.4% among those 30 years of age or older.

Of the 1811 transfusion recipients who were enrolled, 820 were excluded from seroconversion analysis: 266 were seropositive for HHV-8 before transfusion, 17 had equivocal serologic results before transfusion, 101 had received blood from unlinked donors, 362 had insufficient follow-up, 62 had an additional transfusion with a positive or equivocal HHV-8 test result 8 days to 2 months after the first transfusion, and 12 had other reasons for exclusion (Fig. 7.1). The characteristics of the 991 recipients included in the seroconversion analysis are summarized in Table 7.1. The recipients tended to be young (median age, 1.5 years; interquartile range, 0.1 to 4.6), and most had received one transfusion (range, one to eight). The majority (79.2%) had received packed red cells, 14.6% had received whole blood, 0.2% had received plasma, and 6.0% had received units of undetermined type. On the average, a recipient had 7 follow-up visits (range, 3 to 12) and was observed for 144 days (Table 7.1).

HHV-8 transmission in transfusion recipients

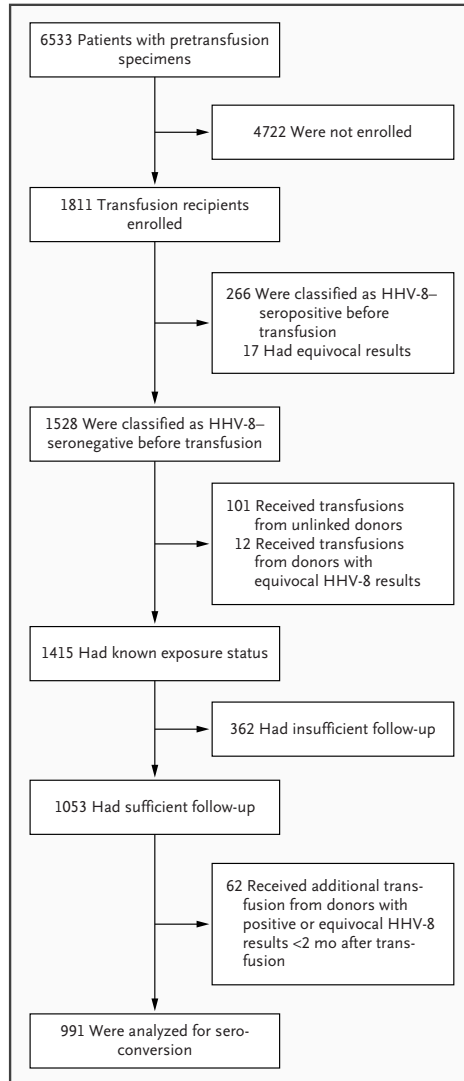


Figure 7.1 Enrollment and Outcomes.

HHV-8 Seroconversion

Of the 991 patients included in the analysis, 425 (42.9%) received HHV-8–seropositive units and 566 (57.1%) received only HHV-8–seronegative units. Forty-one recipients (4.1%) met the case definition for HHV-8 seroconversion. The excess risk of seroconversion after transfusion with HHV-8–seropositive blood during the 24-week follow-up period was 2.8% (Table 7.2), suggesting that an estimated 12 of the 425 patients who received HHV-8–seropositive blood were infected by transfusion. The seroconversion risks for various periods after transfusion are presented in Table 7.2. At week 3, there was no significant difference in risk between exposed recipients and unexposed recipients; however, by week 10, the excess risk of seroconversion for exposed recipients rose to 2.3% ($P=0.04$). The excess risk among exposed recipients was 2.8% ($P<0.05$) through week 24 and 2.7% for the period from week 3 to week 10 ($P = 0.005$) (Table 7.2 and Figure 7.2). Figure 7.3A shows the time to seroconversion after transfusion for the 41 recipients with conversion and highlights the proportionately greater number of seroconversions among exposed recipients 3 to 10 weeks after transfusion. Figure 7.3B shows the numbers of exposed and unexposed transfusion recipients according to age group.

The relation between the duration of blood storage and seroconversion was also evaluated for the recipients of HHV-8–seropositive blood. An excess risk of 4.2% was observed among patients who received blood stored for up to 4 days, as compared with those who received blood stored for more than 4 days (Table 7.2). The risk of seroconversion was not associated with the number of HHV-8–seropositive units transfused, the volume of blood transfused, the type of blood component, the sex or HIV status of the recipient, or the number of children in the recipient's household.

Table 7.1 Characteristics of the Study Patients According to Whether They Were Exposed to HHV-8–Seropositive

Characteristic	All Patients (N = 991)	Exposed Patients (N = 425)	Unexposed Patients (N = 566)	Odds Ratio†	P Value
Female sex — no. (%)	515 (52.0)	234 (55.1)	281 (49.6)	1.24	0.09
Median age — yr	1.5	1.6	1.5	—	0.14
Age ≥2 yr — no. (%)	400 (40.4)	188 (44.2)	212 (37.5)	1.32	0.03
HIV-infected — no./total no. (%)	76/758 (10.0)	28/319 (8.8)	48/439 (10.9)	0.78	0.33
Reason for transfusion — no./total no. (%)					
Malaria	828/988 (83.8)	344/423 (81.3)	484/565 (85.7)	0.73	0.07
Obstetrical or gynecologic procedure	46/988 (4.7)	19/423 (4.5)	27/565 (4.8)	0.94	0.83
Sickle cell anemia	48/988 (4.9)	21/423 (5.0)	27/565 (4.8)	1.04	0.89
Hemorrhage	20/988 (2.0)	11/423 (2.6)	9/565 (1.6)	1.65	0.27
Cancer	4/988 (0.4)	1/423 (0.2)	3/565 (0.5)	0.44	0.47
Unknown	42/988 (4.3)	27/423 (6.4)	15/565 (2.7)	2.50	0.004
Median duration of blood storage — days	5.0	5.0	5.0	—	0.73
Median observation time — days	144	144	144	—	0.92
Mean no. of follow-up visits	7.3	7.1	7.3	—	0.17
Mean no. of transfusions per recipient	1.3	1.4	1.2	—	0.001

* Patients who had received a transfusion of any HHV-8–seropositive blood products were categorized as exposed, regardless of the serologic status of additional units. Patients who had received transfusions of HHV-8–seronegative blood alone were categorized as unexposed.

† Odds ratios are for seroconversion in the exposed patients as compared with the unexposed patients.

Table 7.2 Kaplan–Meier Estimates of Cumulative Risk of HHV-8 Seroconversion after Blood Transfusion.*

Observation Period	Study Population		Patients with Seroconversion		Risk of Seroconversion		Excess Risk (95% CI)†	P Value
	Exposed Patients	Unexposed Patients	Exposed Patients	Unexposed Patients	Exposed Patients	Unexposed Patients		
Wk 1–3	425	566	4	7	0.9	1.2	–0.3 (–1.6 to 1.0)	0.69
Wk 1–10	425	566	18	11	4.2	1.9	2.3 (0.1 to 4.6)	0.04
Wk 1–24	425	566	24	17	5.9	3.1	2.8 (0.1 to 5.5)	<0.05
Wk 3–10	421	559	14	4	3.4	0.7	2.7 (0.8 to 4.6)	0.005
Blood storage‡								
≤4 days	156	—	9	—	5.9	—	4.2 (0.1 to 8.3)	<0.05
>4 days	240	—	4	—	1.7	—	—	—

* Patients who had received a transfusion of any HHV-8–seropositive blood products were categorized as exposed, regardless of the serologic status of additional units. Patients who had received transfusions of HHV-8–seronegative blood alone were categorized as unexposed.

† Confidence intervals (CIs) that do not cross zero indicate statistical significance. ‡ For the analysis of the effect of the duration of blood storage, the total number of exposed recipients was reduced to 396, because recipients who had multiple storage records or conflicting or missing data were not included.

All 41 recipients with seroconversion had been found to be seronegative for HHV-8 when examined on visits before seroconversion. Reversion to seronegative status was not observed, although one patient had equivocal reactivity at the last follow-up visit after having had four visits with seropositive results. Seroconversion did not occur in 12 patients who received seropositive units from donations linked to persons with seroconversion (split donations); however, on follow-up visits, some of them had seroreactivity on one test or were seropositive at one visit and therefore did not meet the criteria for seropositivity or seroconversion.

Discussion

We conducted a prospective cohort study assessing the risk of transfusion-associated HHV-8 infection in a large population of linked blood donors and transfusion recipients. Patients who received HHV-8-seropositive blood were significantly more likely to become infected than were recipients of seronegative blood. The increased risk associated with receiving HHV-8-seropositive blood was most striking among recipients in whom seroconversion occurred 3 to 10 weeks after transfusion, an interval that is similar to the timing of the immune response for other transfusion-transmitted herpesviruses.²⁵ The risk of seroconversion was also higher among recipients of seropositive units that had been stored with shorter storage times than among recipients of blood that had been stored for more than 4 days (excess risk, 4.2%), as has been found with other herpesviruses.²⁵ Together, these results provide compelling evidence of the transmission of HHV-8 by blood transfusion.

Previous studies have not detected transfusion-associated HHV-8 infection,^{6-8,26} probably because of small samples, low seroprevalence of HHV-8 in the donor pool, low²⁷⁻²⁹ or intermittent³⁰ viremia among antibody-positive donors, and deferral of donors at risk for infectious diseases. The design and setting of our study —

with a large study population, high seroprevalence of HHV-8 in the community, short duration of blood storage before transfusion, and absence of leukocyte reduction — optimized our ability to detect transfusion-associated transmission of HHV-8 even in the context of a high rate of incident infection, especially in our young study population, who had early and relatively rapid acquisition of HHV-8 (with a seroprevalence of 15% by the age of 5 years).

To account for the fact that HHV-8 serologic assays are not standardized, we used stringent criteria for seropositivity and seroconversion, which provided greater specificity but probably lowered our testing sensitivity and estimates of risk. In this setting, we estimated that 2.8 infections occurred for every 100 seronegative recipients of HHV-8–seropositive blood. A retrospective, cross-sectional study of children with sickle cell disease in the same hospital^{20,31} estimated a similar risk of infection. The Nakasero Blood Bank released 52,512 blood units for use in 2001. By extrapolating the findings of our study (and adjusting the seroprevalence of HHV-8 in the patient population to 21% according to age), we estimated that these transfusions may have resulted in approximately 300 HHV-8 infections in 2001.

The policy implications of our findings warrant careful consideration. High-throughput serologic assays suitable for blood-bank screening do not yet exist for HHV-8. Nucleic acid testing would not be effective, since most seropositive blood donors tested to date have had very low or undetectable HHV-8 viral loads. Having enough blood available for transfusion is an ongoing public health challenge throughout sub-Saharan Africa; availability would be jeopardized by efforts to eliminate donations from HHV-8–positive donors in high-prevalence areas. Further studies are needed to determine whether leukocyte reduction, longer storage time, or other techniques could reduce the risk of transmission of HHV-8. However, the cost and logistics of leukocyte reduction would probably be substantial barriers in most African countries, and longer storage times might increase the risk of bacterial infection and other adverse events.³²

HHV-8 transmission in transfusion recipients

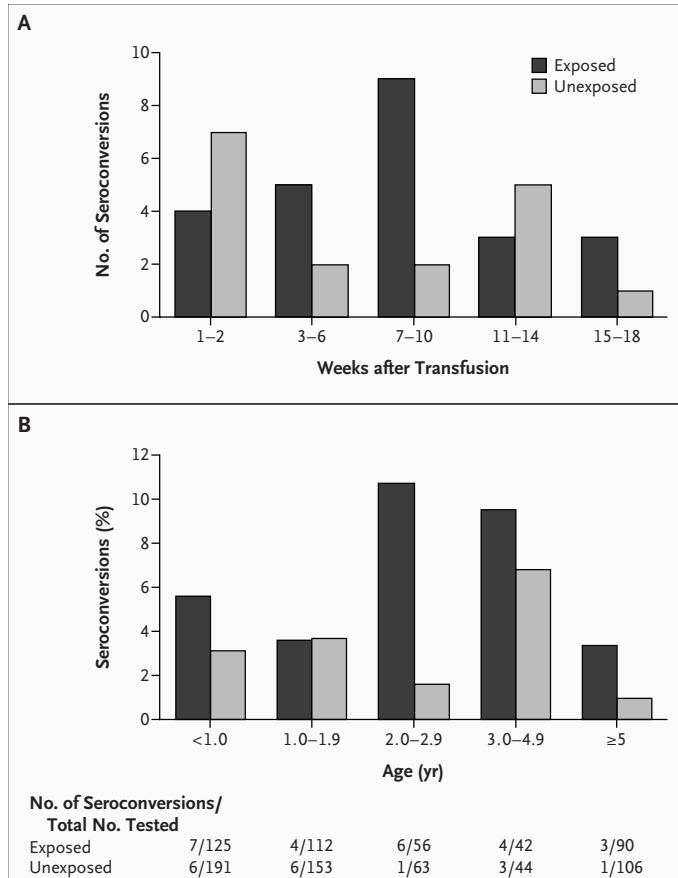


Figure 7.3 Seroconversion among Patients Who Received HHV-8–Seronegative Blood and Those Who Received HHV-8–Seropositive Blood, According to the Interval between Transfusion and Seroconversion (Panel A) and the Recipient’s Age (Panel B).

Patients who had received a transfusion of any HHV-8–seropositive blood products were categorized as exposed, regardless of the serologic status of additional units. Patients who had received transfusions of HHV-8–seronegative blood alone were categorized as unexposed. In Panel A, from 3 to 10 weeks after transfusion, seroconversion was proportionately more common among exposed recipients than among unexposed recipients.

The relevance of our findings with respect to the U.S. blood supply may be different from that in Uganda, since the seroprevalence of HHV-8 among blood donors in the United States is low (3.5%).⁵ Most blood products in the United States are leukocyte reduced, but the efficacy of this technique for reducing the risk of HHV-8 infection has not been evaluated. The risk of transfusion-associated Kaposi's sarcoma would be highest among HIV-infected and other immunocompromised recipients. Selective screening of blood products for immunocompromised populations may be warranted if this approach is found to be effective.

Acknowledgments

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Chapter 7

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