別紙様式第2-1

No. 6

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 6. 15	該当なし	
一般的名称	人血清アルブミン		研究報告の公表状況	松林圭二, 坂田秀勝, 阿部生馬, 佐藤進一郎, 加藤俊明, 池田久實. 第57回日本輸血・細胞治療学会総会; 2009 May 28-30; 大宮.	公表国 日本	
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)					

研究報告の概要

○北海道内献血者におけるHEV感染の動向—4年間のまとめ—

【背景】北海道はHEV浸淫地区と考えられ、献血者におけるHEV感染の実態を解明するため、2005年から道内献血者のHEV RNAスクリーニング調査(HEV NAT)を実施してきた。

【方法】2005年1月から2008年11月にかけて、北海道内で献血した献血者、総数1,075,793名(男性663,155名、女性412,638名)について、20本プールによるHEV NATを行った。核酸抽出を行い、RT-PCRによりHEV RNAを検査した。また、陽性献血者について追跡調査および遡及調査を行い、喫食歴や自覚症状に関するアンケート調査、HEV抗体測定、HEV RNA定量、生化学検査、分子系統樹解析等を行なった。

【結果】HEV NAT陽性者総数は140名(男性103名、女性37名)で、2005年30名(男性17名、女性12名)、2007年31名(男性28名、女性3名)、2008年40名(男性31名、女性9名)であった。またHEV NAT陽性頻度(献血者延べ1万人当りの陽性者数)は、平均1.3人(男性1.6人、女性0.9人)、2005年1.0人(男性1.0人、女性1.1人)、2006年1.4人(男性1.6人、女性1.1人)、2007年1.2人(男性1.7人、女性0.3人)、2008年1.7人(男性2.0人、女性1.0人)であった。献血時のHEV抗体保有率は3割以下で、感染初期の献血が多かった。陽性者のHEV genotypeは3型と4型で、9割以上を3型が占めた。3型はさらに複数のクラスターに分類され、一部はブタ由来HEV株と高い相同性を示した。陽性者の約7割は献血前に動物内臓肉の喫食歴があり、また、陽性者の約半数は、その後ALT値の上昇が見られた。

【結論】北海道内の献血者集団におけるHEV RNA陽性頻度は高く、zoonotic infectionが起きていると考えられる。とくに男性におけるHEV陽性頻度は上昇傾向にあり、HEVは今後も十分な注意を要する肝炎ウイルスの一つである。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
赤十字アルブミン20%静注4g/20mL
赤十字アルブミン20%静注10g/50mL
赤十字アルブミン25%静注12.5g/50mL

血液を原料とすることに由来する感染症伝播等

報告企業の意見

北海道内の献血者集団におけるHEV RNA陽性頻度は高く、特に男性においては上昇傾向にあり、zoonotic infectionが考えられるとの報告である。
HEVは脂質膜のないRNAウイルスである。本剤の製造工程にはコーン分画および液状加熱の2つのウイルス除去・不活化工程が含まれているが、最近HEVの耐熱性を示唆する成績が発表され、液状加熱の有効性に疑念を生じている。しかし疫学的に見て、血漿分画製剤で最も長い歴史を持つアルブミンではHEVの侵淫度が遥かに高い過去においても世界的にHEV感染の報告はないことから、本剤の安全性は確保されていると考える。

今後の対応

今後もHEV感染の実態に関する情報の収集及び安全対策に努める。
なお、日本赤十字社では、北海道における輸血後HEV感染報告を受け、献血者の疫学調査や、北海道で研究的NATを実施している。

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O-051 北海道内献血者における HEV 感染の動向—4 年間のまとめ—

北海道赤十字血液センター検査部[1], 日本赤十字社血漿分画センター品質管理部 検査課[2]
松林圭二[1], 坂田秀勝[1], 佐藤進一郎[1], 加藤俊明[1], 池田久實[2]

【背景】北海道は HEV 浸淫地区と考えられ、献血者における HEV 感染の実態を解明するため、2005 年から道内献血者の HEV RNA スクリーニング調査 (HEV NAT) を実施してきた.
【方法】2005 年 1 月から 2008 年 11 月にかけて、北海道内で献血した献血者、総数 1,075,793 名 (男性 663,155 名, 女性 412,638 名)について、20 本プールによる HEV NAT を行った. Qiagen BioRobot 9604/MDx で核酸抽出を行い、TaqMan RT-PCR 法により HEV RNA を検査した. また、陽性献血者について追跡調査および遡及調査を行い、喫食歴や自覚症状に関するアンケート調査、HEV 抗体測定 (HEV Ab IgM, IgG, 特殊免疫研究所), HEV-RNA 定量, 生化学検査, 分子系統樹解析等を行なった.
【結果】HEV NAT 陽性者総数は 140 名 (男性 103 名, 女性 37 名) で、2005 年 30 名 (男性 17 名, 女性 13 名), 2006 年 39 名 (男性 27 名, 女性 12 名), 2007 年 31 名 (男性 28 名, 女性 3 名), 2008 年 40 名 (男性 31 名, 女性 9 名) であった. また HEV NAT 陽性頻度 (献血者延べ 1 万人当りの陽性者数) は、平均 1.7 人 (男性 1.6 人, 女性 0.9 人) で、2005 年 1.0 人 (男性 1.0 人, 女性 1.1 人), 2006 年 1.4 人 (男性 1.6 人, 女性 1.1 人), 2007 年 1.2 人 (男性 1.7 人, 女性 0.3 人), 2008 年 1.7 人 (男性 2.0 人, 女性 1.0 人) であった. 献血時の HEV 抗体保有率は 3 割以下で、感染初期の献血が多かった. 陽性者の HEV genotype は 3 型と 4 型で、9 割以上を 3 型が占めた. 3 型はさらに複数のクラスターに分類され、一部はブタ由来 HEV 株と高い相同性を示した. 陽性者の約 7 割は献血前に動物内臓肉の喫食歴があり、また、陽性者の約半数は、その後 ALT 値の上昇が見られた.
【結論】北海道内の献血者集団における HEV RNA 陽性頻度は高く、zoonotic infection が起きていると考えられる. とくに男性における HEV 陽性頻度は上昇傾向にあり、HEV は今後も十分な注意を要する肝炎ウイルスの一つである.

O-052 輸血前後感染症検査の実施状況と検査を契機に見出された C 型肝炎の 1 症例

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【はじめに】当院では 2005 年 3 月より、輸血前後感染症検査を実施している. 今回、2008 年 11 月までの検査状況と、検査を契機に見出された C 型肝炎の 1 症例を報告する.
【方法】1) 輸血前検査は、初回輸血または前回輸血から 3 ヵ月を経過した患者を対象とし、輸血施行を確認した時点で実施した. 2)輸血後検査は、最終輸血後 3 ヶ月を経過した時点で、輸血歴リストを提示し、主治医が必要と判断した患者について実施した.
【結果】1) 輸血前検査実施件数は 1270 件 (内科系 61.4%、外科系 38.6%)、平均年齢は 70.6 歳であった. 2) 輸血後検査実施件数は 640 件 (50.4%)、未実施件数は 630 件 (49.6%) であり、未実施の内訳は、死亡 468 件(74.3%)、ターミナル 26 件(4.1%)、退院不能 87 件(13.8%)、他院入院中 36 件(5.7%)、その他 13 件 (2.1%) であった. 3) 輸血前検査実施の際、HCV コア抗原の陽性となる症例を経験した.
【症例】87 歳女性. 1996 年、心臓カテーテル施行. 2004 年、乳癌手術. 2008 年 7 月、認知症が進行し、食欲不振・脱水にて入院. 同年 8 月、胃ろう造設術後、出血性ショックにて RCC6 単位、FFP10 単位の輸血を実施. 輸血前検査により、HCV 抗体陰性、HCV コア抗原陽性であることが判明. 輸血後、コア抗原量が上昇し、重症の肝機能異常が認められた後、HCV 抗体が陽性化したが、1 週間後には陰性化した. 免疫抑制状態・免疫寛容状態などが想定されたが、確定することはできなかった.
【まとめ】今回の症例では、輸血前検査を実施していたことで、輸血による感染ではなく、輸血前からの感染であったことを把握できた. 感染症は自覚症状がないこともあり、早期に発見し、必要な治療を開始することが重要である. その点からも輸血前感染症検査は意義があると思われた. 輸血後検査実施率が 50% に留まっている現状は、死亡率が高いことに起因し、輸血を施行する患者は高齢者が多く、予後が悪いことが考えられた.

別紙様式第2-1

No. 20

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 6. 15	該当なし	
一般的名称	人血清アルブミン		研究報告の公表状況	Cannon MJ, Operskalski EA, Mosley JW, Radford K, Dollard SC. J Infect Dis. 2009 Jun 1;199(11):1592-8.	公表国 米国	
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)					

研究報告の概要

○過去の米国の集団においてヒトヘルペスウイルス-8が輸血を介して伝播したエビデンスはない

背景:ヒトヘルペスウイルス(HHV)-8はカポジ肉腫の原因ウイルスである。最近の試験では、ヒトヘルペスウイルス-8が輸血を介して伝播する証拠が時折発見されている。しかし、これらの研究は米国外で行われており、供血者-受血者の関連が確認されていないため、米国の血液バンクの方針に反映するには限りがある。

方法:1970年代に登録されたTransfusion-Transmitted Viruses Study(TTVS)の参加者にHHV-8血清学検査を行うことにより、米国における輸血を介したHHV-8伝播を調べた。

結果:HHV-8抗体陽性率は、供血者が2.8%(29/1023)、受血者が7.1%(96/1350)、輸血を受けず手術を受けた対照患者が7.7%(46/599)、カポジ肉腫を有する対照患者が96.3%(77/80)であった。1名の受血者はセロコンバージョンしたが(0.08%[1/1259])、この患者はHHV-8血清陽性血液をまったく投与されておらず、感染が輸血関連ではなかったことが示された。輸血を受けず手術を受けた対照患者の1例がセロコンバージョンした(0.18%[1/556])。セロコンバージョン率は、受血者が1000人年あたり1.6(95%信頼区間[CI]、1000人年につき0.04-8.9)、輸血を受けず手術を受けた対照患者が1000人年あたり3.6(95%CI、1000人年につき0.09-20.1)であった。

結論:輸血群および非輸血群のHHV-8セロコンバージョン率に統計学的な差はなく、過去の集団の特徴(例、白血球除去施行前)からは、現在の輸血を介する伝播が稀であることが示される。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
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赤十字アルブミン20%静注4g/20mL
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赤十字アルブミン25%静注12.5g/50mL

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
1970年代に登録された米国のコホートにおいて、ヒトヘルペスウイルス-8が輸血を介して伝播したエビデンスはなかったとの報告である。 HHV-8は脂質膜を持つ大型DNAウイルスである。これまで、本製剤によるHHV-8感染の報告はない。本製剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれていることから、本製剤の安全性は確保されていると考える。	念のため今後も情報収集に努める。

①

Lack of Evidence for Human Herpesvirus–8 Transmission via Blood Transfusion in a Historical US Cohort

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(See the editorial commentary by Busch and Glynn, on pages 1564–6.)

Background. Recent studies have found evidence of occasional human herpesvirus (HHV)–8 transmission via blood transfusion. However, because these studies were conducted outside the United States or did not have linked donor-recipient pairs, they have a limited ability to inform US blood-banking policy.

Methods. We investigated HHV-8 transmission via blood transfusion in the United States by conducting HHV-8 serologic testing among participants of the Transfusion-Transmitted Viruses Study (TTVS), who enrolled during the 1970s.

Results. HHV-8 seroprevalence was 2.8% (29/1023) among blood donors, 7.1% (96/1350) among transfusion recipients, 7.7% (46/599) among surgical control patients who did not receive transfusions, and 96.3% (77/80) among control patients with Kaposi sarcoma. One transfusion recipient seroconverted (0.08% [1/1259]), but this patient did not receive any HHV-8–seropositive blood units, suggesting that the infection was not related to blood transfusion. One of the surgical control patients who did not receive transfusions also seroconverted (0.18% [1/556]). Rates of seroconversion were 1.6 per 1000 person-years (95% confidence interval [CI], 0.04–8.9 per 1000 person-years) for the transfusion recipients and 3.6 per 1000 person-years (95% CI, 0.09–20.1 per 1000 person-years) for the surgical control patients who did not receive transfusions ($P = .61$).

Conclusions. Rates of HHV-8 seroconversion in the transfusion and nontransfusion groups were not statistically different, and the historical nature of the cohort (e.g., before leukoreduction) suggests that any current transmission via blood transfusion is rare.

Human herpesvirus (HHV)–8 is necessary for the development of Kaposi sarcoma (KS), primary effusion lymphomas, and multicentric Castleman disease. Disease tends to occur, however, only in the presence of immunosuppression [1]. In the overall US population, HHV-8 seroprevalence is low (estimated at between 1% and 7% [2, 3]), but higher seroprevalences are found among men who have sex with men [4] and among persons with human immunodeficiency virus (HIV) infection or risk factors for HIV infection [5].

Initial studies found no evidence of HHV-8 transmission via blood transfusion [6–8]. However, these studies were limited by relatively small numbers of patients, many of whom received leukoreduced or acellular blood components. Later reports that HHV-8 infection was associated with injection drug use and, presumably, needle sharing [5, 9–12] led to larger-scale investigations of transmission via transfused blood [13–15]. These studies found evidence that HHV-8 was transmitted occasionally via blood transfusion, leading to renewed questions about the advisability of screening of blood for HHV-8 [16–19]. Nevertheless, all 3 studies had a limited ability to inform US blood-banking policy, either because they were conducted outside the United States or because they did not have linked donor-recipient pairs to prove transmission via transfusion.

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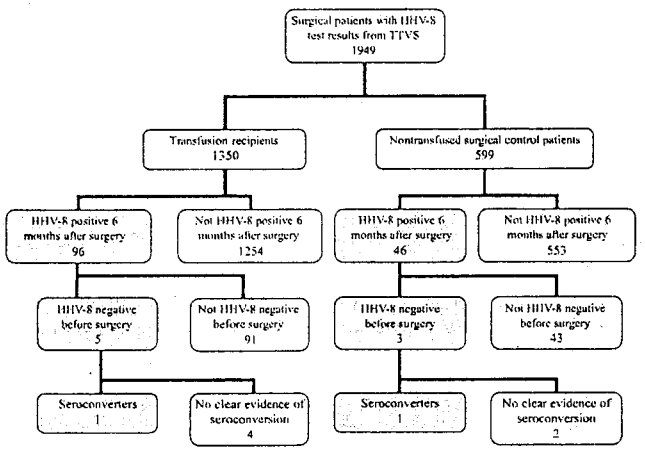

Figure 1. Testing algorithm and outcomes among the transfusion recipients and the surgical control patients who did not receive transfusions. All 4 blood donors for the 1 seroconverter who received a transfusion tested negative. HHV, human herpesvirus; TTVS, Transfusion-Transmitted Viruses Study.

To better evaluate the possibility of HHV-8 transmission via blood transfusion in the United States, we conducted HHV-8 serologic testing among participants of the Transfusion-Transmitted Viruses Study (TTVS). To our knowledge, this was the largest US study conducted with linked donor-recipient pairs and longitudinal follow-up specimens. The specimens were collected before the advent of several blood-safety improvements (such as HIV testing, more-stringent donor-deferral guidelines, transition to extended storage of blood components, and routine leukoreduction by filtration and apheresis techniques), making this study an important opportunity to detect HHV-8 transmission via blood transfusion in the United States.

METHODS

Study design and population. The TTVS was designed in the 1970s to prospectively identify cases of non-A, non-B hepatitis among a cohort of 1533 patients who had received transfusions and to create a repository for detecting the occurrence of virus transmission via blood transfusion [20]. The TTVS repository was funded by the National Heart, Lung, and Blood Institute (NHLBI) and is now housed at the NHLBI Biologic Specimen Repository. The TTVS repository has been used to demonstrate transmission of other viruses via transfusion, such as hepatitis B virus (HBV) and hepatitis C virus (HCV) [21–25]. TTVS participants consisted of blood donors, transfusion recipients (nearly all of whom underwent surgery), and surgical patients who did not receive transfusions (referred to hereafter as surgical control patients without transfusions). All transfusions occurred during the years 1974–1979. Donors could be linked to transfusion recipients, and both the transfusion recipients and the surgical control patients without transfusions had blood drawn before surgery and at multiple time points after surgery. The TTVS received institutional review board approval from the institutions at which it was performed. TTVS participants consented to future testing. The present analysis of HHV-8 was cleared by the Centers for Disease Control and Prevention (CDC) and the University of Southern California; specimens and associated data were delinked from participant identifiers so that the study did not fall under the category of human-subjects research.

For this study, we tested specimens from 1023 randomly selected TTVS blood donors (20.8% of the 4918 donors who had samples available), specimens from all transfusion recipients who had samples available 6 months after transfusion (n = 1350), and specimens from all surgical control patients without transfusions who had samples available 6 months after surgery (n = 599) (figure 1). To identify seroconverters, we tested the pretransfusion or presurgery specimens from all patients who were HHV-8 seropositive at 6 months. To determine the time of seroconversion, for all those who tested negative before surgery and positive 6 months after surgery, interim specimens were tested at monthly intervals. These serial specimens from individual patients were randomized and masked for testing. A small number of patients had specimens with repeated marginal reactivity; the specimens from these patients were grouped on the same slides and plates for retesting. We also tested any blood-donor specimens (masked to the laboratory) that were linked to seroconverters but were not part of the initial sample of tested donors. As an additional control, 80 specimens from HIV-positive patients with KS were randomly and blindly inserted among specimens from study patients. To help evaluate the performance of the HHV-8 assay, we also tested serial specimens from 7 randomly selected HHV-8–positive (i.e., positive before and 6 months after surgery) and 57 randomly selected HHV-8–negative (i.e., negative before and 6 months after surgery) surgical patients (both those who had received transfusions and those who had not). To compute seroconversion rates, person-time was measured as the time from surgery until the 6-month visit.

Serologic analysis. Specimens were tested at the CDC for antibodies against HHV-8 by an immunofluorescence assay (IFA), as described elsewhere [3, 13, 14]. Specimens were considered positive if they were reactive at a dilution of 1:80 or greater. Specimens that were equivocal or negative at a dilution of 1:80 were classified as not positive. To avoid false identification of seroconverters, we chose a conservative a priori definition of seroconversion: negative (not equivocal) at a dilution of 1:40 before surgery and positive at a dilution of 1:80 after surgery at ≥2 consecutive time points. All specimens that tested positive at a dilution of 1:80 were also tested at a dilution of 1:160.

Table 1. Human herpesvirus–8 seroprevalence in different groups in the Transfusion-Transmitted Viruses Study (TTVS).

Group	Proportion (%) positive
Control patients with KS[a]	77/80 (96.3)
Blood donors[b]	29/1023 (2.8)
Surgical control patients who did not receive transfusions	46/599 (7.7)
Transfusion recipients[c]	96/1350 (7.1)

NOTE. Data are the no. of positive specimens per the total no. tested. Specimens were considered positive if they were reactive at a dilution of 1:80 or greater by an immunofluorescence assay. KS, Kaposi sarcoma.

[a] Specimens from control patients with KS were randomly and blindly inserted among the other specimens.

[b] Donors were randomly selected from all the blood donors in the TTVS.

[c] Specimens were collected ~6 months after surgery.

RESULTS

HHV-8 seroprevalences in the 4 different study populations are described in table 1. Nearly all specimens from control patients with KS were positive (96.3%). Blood donors had the lowest seroprevalence (2.8%), and the transfusion recipients and the surgical control patients without transfusions had similar seroprevalences 6 months after surgery (7.1% and 7.7%, respectively). For the 4918 donors linked to the 1350 transfusion recipients, the type of transfused units were whole blood (61.3%), unknown (17.9%), packed cells (17.8%), plasma (2.0%), other (0.8%), washed frozen (0.1%), and platelets (0.1%). Of the 142 patients who were seropositive 6 months after surgery (figure 1), 8 were seronegative at their presurgery visits and were considered potential seroconverters.

Serial specimen testing was done for the 8 potential seroconverters, with each having a total of 8 specimens tested (1A, 1B, and 2A–2F in figure 2). Of the 8 potential seroconverters, 2 (2D and 2F in figure 2) were clearly seropositive only at their last (6-month) visit, suggesting that their 6-month postsurgery specimen may have been mislabeled or had a false-positive result or that the patient may have acquired a community HHV-8 infection near the end of the follow-up period. Another 4 patients (2A–2C and 2E in figure 2) had mixed reactivities that did not meet our definition of seroconversion. The remaining 2 potential seroconverters (1A and 1B in figure 2) had serial test results that met our a priori criteria for seroconversion (figures 1 and 2). On the basis of these 2 seroconverters, we computed the risk of seroconversion as 0.08% (1/1259) (95% confidence interval [CI], 0.0%–0.44%) for the transfusion recipients and as 0.18% (1/556) (95% CI, 0.0%–1.0%) for the surgical control patients without transfusions. Rates of seroconversion were 1.6 per 1000 person-years (95% CI, 0.04–8.9 per 1000 person-years) for the transfusion recipients and 3.6 per 1000 person-years (95% CI, 0.09–20.1 per 1000 person-years) for the surgical control patients without transfusions. The difference in rates was not statistically significant (P = .61). Rates of seroconversion determined using a more relaxed definition (i.e., negative at a dilution of 1:80 before surgery and positive at a dilution of 1:80 six months after surgery) were similar between the 2 groups (5.2% [5/96] for the transfusion recipients vs. 6.5% [3/46] for the surgical control patients without transfusions; P = .72) (figure 1).

The seroconverter who had undergone transfusion received a unit of blood from each of 4 donors (2 U of whole blood and 2 U of packed cells), none of whom was HHV-8 seropositive. Applying the HHV-8 seroprevalence of 2.8% to the 4918 donors who gave blood to the 1350 transfusion recipients, we estimate that ~138 seropositive units were transfused, 128 (92.9%) of which would have been given to HHV-8–seronegative transfusion recipients, none of whom seroconverted.

Serial testing was also done for patients whose serostatus was constant before surgery and 6 months after surgery (either positive or negative at both time points). For these 64 patients, serial HHV-8 testing results are shown in figure 2 (3A–3G and 4A–4H) and table 2. For the 7 HHV-8–positive patients, all serial specimens were positive at dilutions of 1:80 or greater at all visits. For the 57 HHV-8–negative patients, nearly all test results were negative, although a few were equivocal and 2 were positive (table 2).

DISCUSSION

In the present study—the largest US study to analyze HHV-8 infection among transfusion recipients and their linked donors—we found no evidence that HHV-8 is transmitted via

Figure 2. Human herpesvirus–8 serial test results among Transfusion-Transmitted Viruses Study surgical patients.

Table 2. Consistency of human herpesvirus–8 test results among serial specimens from patients in the Transfusion-Transmitted Viruses Study.

Group	Patients tested,[a] no.	No. of visits with specimen results that were			
		Negative	Equivocal	Positive at 1:80	Positive at ≥1:160
Positive before surgery and positive 6 months after surgery	7	0	0	1	43
Negative before surgery and negative 6 months after surgery	57	379	11	0	2

NOTE. Included are test results for specimens from the presurgery visits and from all follow-up visits through 6 months after surgery (mean no. of visits, 6.8).

[a] Patients were selected to be positive and negative control subjects for the seroconversion study.

blood transfusion. Two study patients met our a priori definition of seroconversion—they were negative by the IFA at a dilution of 1:40 before surgery and had at least 2 consecutive positive IFA results at a dilution of 1:80 after surgery. One seroconverter received only HHV-8–seronegative blood, and the other seroconverter was a surgical control patient without a transfusion.

The study design did not allow us to determine the cause of seroconversion in these 2 patients. It is conceivable that the patient who underwent transfusion received blood from an HHV-8–infected donor who was in the so-called window period—that is, not yet HHV-8 seropositive but with newly acquired HHV-8 circulating in the blood. Alternatively, the seroconverters might have experienced community-acquired infections or nosocomial infections unrelated to transfusion.

The lack of evidence in this historical cohort suggests that the current risk of HHV-8 transmission via blood transfusion is very low. Even if we assume that the one seroconverter who received a blood transfusion was infected via the transfusion, current practices make it much less likely that such transmission would occur now compared with when the TTVS specimens were collected. Since the 1970s, blood banks have stricter donor-deferral guidelines [26], and tests that screen out blood positive for HIV, HBV, and HCV may also screen out blood positive for HHV-8, given that there are shared risk factors for infection among HHV-8 and these other viruses [5, 27]. Moreover, leukoreduction, which became commonplace in the mid-1990s, is likely to reduce the risk of HHV-8 transmission via transfusion, because HHV-8 is highly cell associated [7, 16, 28]. Similarly, the current increased use of red blood cell components, which are stored for up to 42 days at 4°C, is likely to reduce HHV-8 transmission because such storage conditions are known to decrease the infectivity of transfusion-transmissible herpesviruses, such as cytomegalovirus. However, it is worth noting that the seroprevalence of HHV-8 among TTVS blood donors is very similar to more recent estimates [3], suggesting that HHV-8 is endemic at low levels in the United States.

Our results are consistent with those from previous studies of HHV-8 transmission via blood transfusion in the United States—the risk to current transfusion recipients is very low, but rare transmission cannot be ruled out [6–8, 13]. For example, Pellett et al. [3] found that HHV-8 seroprevalence among blood donors was low (~3.5%), and HHV-8 DNA was not detected in the blood of seropositive donors. Although in another historical cohort we identified 2 possible transfusion-related HHV-8 seroconversions, that study was not able to show a linkage to seropositive donor blood [13]. Given the safety improvements created by current blood donation and transfusion practices, a cohort containing thousands of linked donor-recipient pairs, such as the NHLBI RADAR (REDS [Retrovirus Epidemiology Donor Study] Allogenic Donor and Recipient) repository [29], would be required to rule out rare transmission events.

In contrast with these US results, HHV-8 has been shown to be transmitted via blood transfusion in Uganda [14], with ~3% of HHV-8–seropositive units causing infection. If there were a comparable risk in the TTVS, we would have expected to see ~3.8 (3% of 128) infections resulting from blood transfusion, rather than the zero that we observed (for the difference between the observed vs. the expected, $P = .035$). The transfusion risk may be higher in Uganda because of a higher prevalence of immunosuppression, a higher risk of exposure and reinfection, and a higher frequency of viremia among HHV-8–seropositive individuals. In addition, donor-deferral guidelines in Uganda were less stringent, testing for HCV was not done, and leukoreduction was not performed. Furthermore, blood was often stored for short periods of time, perhaps allowing virus to remain viable.

The lack of evidence for HHV-8 transmission via blood transfusion is unlikely to be explained by assay deficiencies. We used an IFA and a dilution (1:80) that have been validated and used in previous studies [13, 14] and that have been shown to have high sensitivity and specificity. The assay detected HHV-8 in 96.3% of specimens from control patients with KS (specimens were randomly and blindly inserted among the TTVS specimens), including KS specimens that had been found to have relatively low levels of antibodies by other assays [30, 31]. Our low seroprevalence among blood donors (2.8%) was consistent with the findings of other studies [2, 3] and suggested high assay specificity. The higher seroprevalences among the transfusion recipients and the surgical control patients without transfusions (7.1% and 7.7%, respectively) were consistent with their older age and health status (i.e., surgical patients may be less healthy than the general population). Furthermore, our results for longitudinal follow-up specimens were highly coherent, with results remaining consistent throughout follow-up among postsurgery specimens for >95% of the presurgery specimens with a positive or

negative result (table 2). For the small number of patients with incoherent longitudinal reactivity patterns, a few explanations may pertain. First, a single positive serum specimen among a series of negative specimens (e.g., 2D, 2F, 4F, and 4H in figure 2) is likely the result of nonspecific reactivity or a specimen-labeling error. Second, up-and-down reactivity patterns (e.g., 2A–2C and 2E in figure 2) may be the result of periodic nonspecific reactivity or, more likely, low levels of HHV-8 antibody fluctuating above and below the lower limit of detection of the assay.

Screening of blood donors for HHV-8, if warranted, faces important technical challenges. Currently, there is no consensus on a standard HHV-8 assay that has known high sensitivity and specificity. The IFA used in the present study is time-consuming and could not be readily standardized across laboratories in the implementation of a screening program. Enzyme-linked immunosorbent assay formats, which might be more amenable to the high throughput demanded by a screening program, may be less sensitive. The main challenge is that the HHV-8 antibody response in healthy individuals is relatively weak, and most of the current assays have inadequate sensitivity and specificity.

In conclusion, the present study does not provide evidence of transmission of HHV-8 via blood transfusion in the United States. Rates of seroconversion in the transfusion and nontransfusion groups were not statistically different, and the historical nature of the cohort suggests that any current transfusion transmission is rare. However, much larger studies would be required to rule out rare transmission events. Nevertheless, if such transmission is shown to occur in the United States, universal screening of blood donors may not be warranted, because HHV-8 seldom causes disease in immunocompetent populations. If suitable assays become available, screening of blood for HHV-8 may be beneficial for immunosuppressed populations. However, the challenges associated with reliably detecting HHV-8 antibody or HHV-8 DNA in a healthy blood-donor population remain a substantial barrier, one that must be crossed before the costs and benefits of HHV-8 blood screening can be appropriately weighed.

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医薬品
医薬部外品　研究報告　調査報告書
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研究報告の概要

ゴリラ起源の新型のヒト免疫不全ウイルス：
我々は、カメルーンの首都ヤウンデ近郊に住んでいた62歳の女性が、2004年に渡仏した際にHIV感染が発覚し、彼女から連続的に採取した血液分析により、HIV-1(SIVgor)に密接に関連した新型のヒト免疫不全ウイルスを同定した。
新型のヒト免疫不全ウイルスは、密接にゴリラ・サル免疫不全ウイルス（SIVgor）に関係があり、他のHIV-1系統で組換えの証拠を示さない。これまでに知られているチンパンジー由来のウイルス（種を超え交差伝播した(SIVcpzPtt)）とは異なり、最近ヒト感染に必要な生物学的特性の多くを持っているSIV（SIVgor）が野生のゴリラ（Gorilla gorilla gorilla）で発見されている。
発見された新型HIV-1変異株は現在確認されているHIVの3つの亜種（M、NおよびO）とは異なっている。我々はHIV-1グループPと称することを提案する。
Strain RBF168（subject number）は血清学的そして非特異的な分子試験で古典的なHIV-1の挙動を示すことより、気づかれずにカメルーンやその他の地域ですでに感染が広がっている可能性があることを示唆する。
結論として、我々の知見はゴリラがチンパンジーに加えて、HIV-1の有望な起源であることを示す。
この新しいHIV-1系統の発見は、特に西中央アフリカは全ての既存のHIV-1グループの起源であることより、新しいHIV変異株の出現を継続して見守る必要があることを強調する。

使用上の注意記載状況・その他参考事項等

代表としてヘプスブリンIH静注1000単位の記載を示す。
2. 重要な基本的注意
(1)本剤の原材料となる血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体陰性で、かつALT（GPT）値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV及びHCVについて核酸増幅検査(NAT)を実施し、適合した血漿を本剤の製造に使用しているが、当該NATの検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した高力価の抗HBs抗体を含有する血漿を原料として、Cohnの低温エタノール分画で得た画分からポリエチレングリコール4000処理、DEAEセファデックス処理等により抗HBs人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において60℃、10時間の液状加熱処理及びびろ過膜処理（ナノフィルトレーション）を施しているが、投与に際しては、次の点に十分注意すること。

報告企業の意見

新たに発見された亜型ウイルス(HIV-1 グループ P)は、カメルーンからパリに移住した62歳の女性の血液サンプルから発見されたという報告である。
HIV-1ウイルスは、レトロウイルス科レンチウイルス属に属し、成熟ウイルスの粒子直径約100nmのエンベロープを持つ一本鎖RNAウイルスである。HIV-1は塩基配列により3群に分類され、グループM（Major）、グループO（Outlier）、グループN（non-M/non-O）に分けられるが、世界的に分布しているウイルスの多くがグループMに属している。現在、原料血漿に実施されているスクリーニング(抗体検査、ミニプールNAT)によりこの新たなHIVが検出可能か否かは不明であるものの、もし原料血漿にHIV-1グループPが混入したとしても、HIV-1をモデルウイルスとしたウイルスバリデーション試験成績から、製造工程において十分に不活化・除去されると考えている。

今後の対応

本報告は本剤の安全性に影響を与えるものではないと考えるので、特段の措置はとらない。

8

nature medicine

BRIEF COMMUNICATION

BENESIS2009-1

A new human immunodeficiency virus derived from gorillas

Jean-Christophe Plantier[1], Marie Leoz[1], Jonathan E Dickerson[2], Fabienne De Oliveira[1], François Cordonnier[3], Véronique Lemée[1], Florence Damond[4], David L Robertson[2] & François Simon[5]

We have identified a new human immunodeficiency virus in a Cameroonian woman. It is closely related to gorilla simian immunodeficiency virus (SIVgor) and shows no evidence of recombination with other HIV-1 lineages. This new virus seems to be the prototype of a new HIV-1 lineage that is distinct from HIV-1 groups M, N and O. We propose to designate it HIV-1 group P.

HIV-1, the virus principally responsible for the AIDS pandemic, arose through cross-species transmission of a retrovirus (SIVcpzPtt) found in chimpanzees (*Pan troglodytes troglodytes* (*Ptt*))[1,2]. Another SIV (SIVgor), recently discovered in wild-living gorillas (*Gorilla gorilla gorilla*)[3], has many of the biological properties necessary for human infection[4]. We have now identified a new human immunodeficiency virus closely related to SIVgor in a Cameroonian woman. This new HIV-1 variant is distinct from the three established groups of HIV-1, namely M (major or main), N (non-M, non-O) and O (outlier)[5,6].

Since 2001, a French network of reference laboratories has been monitoring HIV genetic diversity. Infection with an unusual variant is suspected when RNA viral load assays or molecular tests are negative in an individual with acquired immunodeficiency and of antiretroviral therapy. As part of these surveillance activities, we analyzed serial samples from a 62-year-old woman (subject number RBF168), who was found to be HIV seropositive in 2004, shortly after moving to Paris from Cameroon (Supplementary Methods). Several HIV-1 screening tests were all reactive, and western blot with HIV-1 group M proteins showed weak reactivity against the envelope glycoprotein 120 and no reactivity against Gag p18 protein (Supplementary Methods and Supplementary Fig. 1). She currently has no signs of AIDS, remains untreated and has a stable $CD4^+$ cell count of about 300 cells per mm^3 (Supplementary Fig. 2). Her viral load has been consistently high since diagnosis (4.4 to 5.3 log copies per ml) in nonspecific group M and O PCR commercial assays (HIV-1 HIV RNA Quantitative and RealTime HIV1, Abbott) and in an in-house real-time RT-PCR assay[7] (Supplementary Fig. 2). The virus replicates in cultured human donor peripheral blood mononuclear

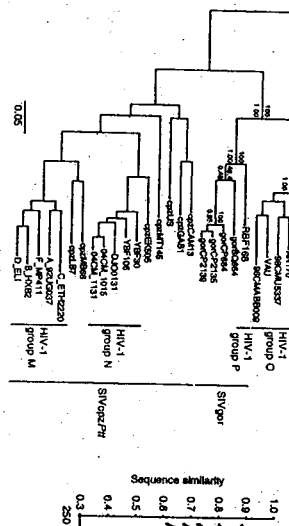

Figure 1 Evolutionary relationship of strain RBF168 to HIV-1, SIVcpz and SIVgor. (**a**) Maximum likelihood phylogeny inferred from concatenated amino acid alignments corresponding to the partial sequences available for SIVgorBQ564 (ref. 4), 1,052 amino acid positions remained after stripping gap-containing sites. The support values (indicated for key nodes only) in black above the branches are from 1,000 maximum likelihood bootstraps (shown as percentages), whereas posterior probabilities from amino acid Bayesian analysis are shown in blue below the branches (shown as proportions). (**b**) Average sequence similarity (250 amino acid windows, 100-amino-acid increments) of RBF168 with representative strains of HIV-1 groups M, N and O, SIVgor, SIVcpz from *Pan troglodytes schweinfurthii* (SIVcpzPts) and SIVcpzPtt across the concatenated translated gene sequence alignments. Similar results were obtained with the nucleotide sequence alignment (data not shown).

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