

Effect of Hepatitis G Virus Infection on Progression of HIV Infection in Patients with Hemophilia

Anthony E.T. Yeo, MD, MPH, PhD;
Akihiro Matsumoto, MD, PhD; Michie Hisada, MD, ScD;
James W. Shih, PhD; Harvey J. Alter, MD; and
James J. Goedert, MD, for the Multicenter Hemophilia
Cohort Study*

Background: Infection with hepatitis G virus (HGV), also known as GB virus C, is prevalent but is not known to be associated with any chronic disease. Infection with HGV may affect the risk for AIDS in HIV-infected persons.

Objective: To compare AIDS-free survival in patients with and those without HGV infection during 16 years of follow-up after HIV seroconversion.

Design: Subanalysis of a prospective cohort study.

Setting: Comprehensive hemophilia treatment centers in the United States and Europe.

Patients: 131 patients with hemophilia who became HIV-positive between 1978 and 1985.

Measurements: Age, *CCR5* genotype, HIV and HCV viral loads, CD4⁺ and CD8⁺ lymphocyte counts, and 12-year AIDS-free survival by HGV positivity (viremia [RNA] or anti-E2 antibodies).

Results: Compared with HGV-negative patients, the 60 HGV-positive patients (46%), including 22 who were positive for HGV RNA, had higher CD4⁺ lymphocyte counts (difference, 211 cells/mm³ [95% CI, 88 to 333 cells/mm³]) and 12-year AIDS-free survival rates (68% compared with 40%; rate difference, 1.9 per 100 person-years [CI, -0.3 to 4.2 per 100 person-years]), despite similar ages and HIV viral loads. In multivariate proportional hazards models, risk for AIDS was 40% lower for HGV-positive patients independent of age, HIV and HCV viral loads, CD4⁺ and CD8⁺ lymphocyte counts, and *CCR5* genotype.

Conclusions: Patients with past or current HGV infection have higher CD4⁺ lymphocyte counts and better AIDS-free survival rates. The mechanism of this association is unknown.

Hepatitis G virus (HGV), also known as GB virus C, is a newly discovered member of the *Flaviviridae* family and is therefore distantly related to hepatitis C virus (HCV) (1). It is transmitted by transfusion, from mother to infant, and probably with low efficiency by sexual contact (1–5). Persistent HGV infection, defined as detection of viremia (HGV RNA) in serum, is present in 1% to 2% of healthy volunteer blood donors and 10% to 20% of populations at high risk for parenteral exposure (1, 2, 6). The prevalence of antibody to the viral envelope (anti-E2) is twofold to fourfold higher. Remarkably, HGV does not seem to cause clinically significant hepatitis (2, 6).

Researchers searching for an HGV-related disease have suggested that persons infected with both HIV and HGV progress to AIDS more slowly than those infected only with HIV (7–9). Toyoda and coworkers (7) reported lower HIV viral load and AIDS incidence with detection of HGV RNA in serum. Conversely, Sabin and colleagues (8) found an increased risk for AIDS and death with detection of HGV RNA or anti-E2 antibodies. The differences were not statistically significant in either of these studies. Lefrère and coworkers (9) noted significantly lower HIV viral load, higher CD4⁺ lymphocyte count, and better AIDS-free survival in patients with HGV RNA than in those without HGV RNA or anti-E2 antibodies.

Our objective was to determine the effect of HGV on AIDS-free survival in a well-characterized cohort of patients with hemophilia, controlling for age, HIV viral load, and the highly influential 32-nucleotide deletion in the C-C chemokine receptor 5 polymorphism (*CCR5* Δ32) (10–12).

Methods

Patients

Between 1982 and 1996, patients with hemophilia or a related coagulation disorder were invited to join the Multicenter Hemophilia Cohort Study (MHCS), as reported elsewhere (10, 11). The study particularly sought to understand the cause and natural history of HIV infection and AIDS. Our analysis focused on the effect of HGV on AIDS-free survival in a defined subset of HIV-positive hemophilic men (5, 13). Patients were evaluated semi-annually with a standardized physical examination, abstraction of medical records, and phlebotomy. Serum or plasma was separated by centrifugation and stored at -70 °C until used. Samples for our analyses were taken between 1986 and 1996 (median, 1988), when 120 patients were receiving no anti-retroviral therapy, 10 were receiving only nucleoside

Ann Intern Med. 2000;132:959-963.

For author affiliations, current addresses, and contributions, see end of text.

* For a list of collaborators in the Multicenter Hemophilia Cohort Study, see the Appendix.

reverse transcriptase inhibitors, and 1 was receiving highly active combination therapy (14). Institutional review boards at each participating institution reviewed and approved the protocol of the MHCS, and signed informed consent was obtained from each patient.

Laboratory Assays

Antibodies to HIV and HCV were detected by enzyme immunoassay and immunoblotting, and viral loads were quantified with commercial kits (Amplacor HIV-1 Monitor, Roche Molecular Systems, Inc., Branchburg, New Jersey; Quantiplex HCV RNA 2.0 Assay [branched DNA], Chiron Corp., Emeryville, California) (10, 11, 13). Genotyping of CCR5 was performed by using single-stranded conformation polymorphism–heteroduplex analysis (12). Hepatitis G virus RNA was detected by using reverse transcriptase polymerase chain reaction with the Enzymun-Test DNA (Boehringer Mannheim Corp., Indianapolis, Indiana), and anti-E2 antibodies were detected by using the Enzymun-Test Anti-HGenv (Boehringer Mannheim Corp.) (5).

Statistical Analysis

The date of primary HGV infection could not be determined or imputed because patients with hemophilia were repeatedly exposed to bloodborne viruses and only one sample from each patient was tested. Therefore, HGV status (HGV-positive with detectable HGV RNA or anti-E2 antibodies, or HGV-negative) was assumed to be fixed at the time of HIV seroconversion. We defined AIDS as the development of a life-threatening opportunistic infection or malignant condition. The Kaplan–Meier method was used to estimate the effect of HGV infection on AIDS-free survival, and median values were used to define subgroups for further analysis. Groups were compared by using log-rank tests. The effects of other variables were evaluated with multivariate proportional hazards models. All models conformed to the proportional hazards assumption. Continuous variables were described with mean values and 95% CIs. Analyses were performed by using SAS software, version 6.12 (SAS Institute, Cary, North Carolina), and BMDP software, version 7.0 (Statistical Software, Inc., Los Angeles, California).

Role of the Funding Source

The funding source exercised no direct control over the analysis or the decision to submit the paper for publication.

Results

Of the 131 patients with hemophilia who were infected with HIV and HCV, HGV RNA and anti-

E2 antibodies were detected in 3, HGV RNA alone was detected in 19, and anti-E2 alone was detected in 38. Therefore, 60 of 131 patients (46%) were infected with HGV. Hepatitis G virus was present in 4 of the 11 patients receiving antiretroviral therapy (36%); 3 had anti-E2 antibodies, and 1 had HGV RNA. At the approximate time of HGV sampling, HGV-positive patients had significantly higher CD4⁺ lymphocyte counts (mean, 529 cells/mm³ compared with 318 cells/mm³; mean difference, 211 cells/mm³ [95% CI, 88 to 333 cells/mm³]) than HGV-negative patients. We found that CD4⁺ lymphocyte counts were similar in patients who were positive for HGV RNA (mean, 510 cells/mm³) and those who were positive for anti-E2 antibodies (mean, 528 cells/mm³). Patients who were HGV-positive had marginally higher CD8⁺ lymphocyte counts than HGV-negative patients (878 cells/mm³ compared with 716 cells/mm³; mean difference, 161 cells/mm³ [CI, –69 to 392 cells/mm³]) and were older (30 years compared with 27 years; mean difference, 3.5 years [CI, –0.2 years to 7.3 years]).

Viral loads for HCV were similar in patients who were positive for HGV RNA (mean, 6.91 log₁₀ equivalents/mL) and those who were positive for anti-E2 antibodies (mean, 6.92 log₁₀ equivalents/mL). However, HGV-negative patients had slightly lower HCV viral loads (mean, 6.65 log₁₀ equivalents/mL; mean difference, 0.27 log₁₀ equivalents/mL [CI, –0.03 to 0.56 log₁₀ copies/mL]) than those who were HGV-positive. Viral loads for HIV were similar in HGV-negative patients (mean, 4.32 log₁₀ copies/mL), HGV RNA–positive patients (mean, 4.21 log₁₀ copies/mL), and anti-E2 antibody–positive patients (mean, 4.35 log₁₀ copies/mL).

During a mean follow-up of 11.2 years, when most patients received no antiretroviral treatment or zidovudine alone, 72 patients developed an AIDS-defining opportunistic illness. In univariate Kaplan–Meier analysis, risk for AIDS was significantly lower among HGV-positive patients ($P = 0.03$) (**Figure**); AIDS incidence in these men was 3.9 per 100 person-years compared with 5.9 per 100 person-years in HGV-negative patients (difference, 1.9 per 100 person-years [CI, –0.3 to 4.2 per 100 person-years]). The 19 patients who were positive for HGV RNA and the 38 patients who were positive for anti-E2 antibodies had better 12-year cumulative AIDS-free survival rates (72% [CI, 50% to 93%] and 66% [CI, 51% to 82%], respectively) than HGV-negative patients (40% [CI, 28% to 52%]).

After adjustment for age, HIV viral load, and CD4⁺ and CD8⁺ lymphocyte counts in a proportional hazards model, risk for AIDS was approximately 40% lower for HGV-positive patients than for HGV-negative patients (**Table**, model 1). When added to this model, HCV viral load was not pre-

dictive of AIDS and did not substantially affect relations of the other variables (data not shown). One hundred of 131 patients had available *CCR5* genotypes. In a proportional hazards model that included *CCR5* genotype, age, and HIV viral load (Table, model 2), risk for AIDS was significantly reduced in patients with HGV infection (hazard ratio, 0.48 [CI, 0.26 to 0.87]).

Discussion

We found that HGV infection decreased the risk for AIDS among HIV-infected men with hemophilia, an association that was independent of age and *CCR5* genotype. Because few patients were receiving antiviral drugs, the association was not confounded by therapy.

Our findings are similar to and expand on previous findings. In a study of Japanese patients with hemophilia, HIV viral load and AIDS incidence were lower in those who had HGV RNA in serum. However, the difference was not statistically significant (7), and patients with HGV RNA were slightly younger, a characteristic associated with better prognosis (10, 11). In age-matched and age-unmatched analyses, HIV-infected French adults

with HGV RNA had significantly lower HIV viral loads, higher CD4⁺ lymphocyte counts, and better AIDS-free survival rates than patients who were negative for HGV RNA and anti-E2 antibodies (9). We found a similar reduction of AIDS risk in patients with HGV RNA or anti-E2 antibodies. Contrary results were found in British patients with hemophilia (8), but the reason for this is unknown. Prevalent cohort studies like ours cannot determine whether HGV truly decreases risk for AIDS among HIV-infected patients or is merely a surrogate for some other causal event. Nonetheless, we found no evidence of bias by age or duration of follow-up that might provide a trivial explanation.

The rate at which immune deficiency and AIDS develop varies greatly among HIV-infected patients. Younger patients and those with *CCR5* Δ32 heterozygosity have substantially better rates of AIDS-free survival (10–12), as do patients receiving highly active antiretroviral therapy and *Pneumocystis carinii* pneumonia prophylaxis. Because the MHCS was begun early in the AIDS epidemic, relatively few participants received antiretroviral therapy or prophylaxis until recently (14). In our study, the effect of HGV infection on AIDS-free survival was independent of *CCR5* genotype. Nonpharmacologic exogenous factors that affect AIDS risk remain poorly

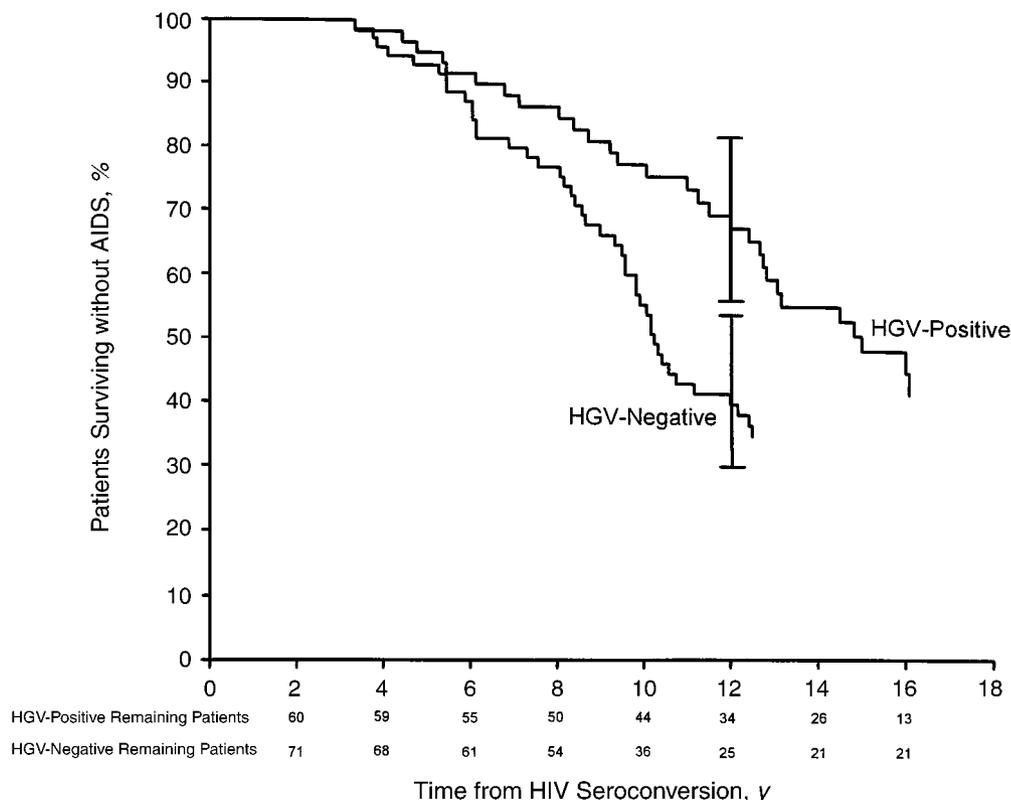


Figure. Product-limit AIDS-free survival (Kaplan–Meier method) measured from estimated dates of HIV seroconversion for 131 patients in the Multicenter Hemophilia Cohort Study. Error bars represent 95% CIs. Twelve-year AIDS-free survival was significantly better in patients who were positive for the hepatitis G virus (HGV) (68% [CI, 55% to 81%]) than in those who were HGV-negative (40% [CI, 28% to 52%]) ($P = 0.03$).

Table. Multivariate Proportional Hazards Models of the Effect of Hepatitis G Virus Infection on the Risk for AIDS*

Variable	Total Patients	Patients Developing AIDS	Hazard Ratio (95% CI)	P Value†
	n	n (%)		
Model 1‡				
Viral infection				
HIV without HGV	71	43 (61)	1.00 (referent)	
HIV with HGV	60	29 (48)	0.59 (0.36–0.96)	0.03
CD4 ⁺ count				
<350 cells/mm ³	66	47 (71)	1.00 (referent)	
≥350 cells/mm ³	65	25 (39)	0.47 (0.28–0.79)	0.004
CD8 ⁺ count				
<670 cells/mm ³	67	44 (66)	1.00 (referent)	
≥670 cells/mm ³	64	28 (44)	0.57 (0.35–0.95)	0.03
HIV viral load				
<4.30 log ₁₀ copies/mL	66	28 (42)	1.00 (referent)	
≥4.30 log ₁₀ copies/mL	65	44 (68)	2.72 (1.66–4.46)	<0.001
Age at HIV seroconversion				
<27 y	67	30 (45)	1.00 (referent)	
≥27 y	64	42 (66)	2.04 (0.98–3.41)	0.003
Model 2§				
Viral infection				
HIV without HGV	56	31 (55)	1.00 (referent)	
HIV with HGV	44	20 (46)	0.48 (0.26–0.87)	0.01
HIV viral load				
<4.30 log ₁₀ copies/mL	52	20 (39)	1.00 (referent)	
≥4.30 log ₁₀ copies/mL	48	31 (65)	2.47 (1.38–4.42)	0.002
Age at HIV seroconversion				
<27 y	50	20 (40)	1.00 (referent)	
≥27 y	50	31 (62)	1.51 (0.84–2.74)	0.17
CCR5 genotype				
Wild-type/wild-type	83	45 (54)	1.00 (referent)	
Wild-type/Δ32	17	6 (35)	0.76 (0.31–1.83)	>0.2

* HGV = hepatitis G virus.

† P values derived from likelihood ratio tests for inclusion of each variable in the model.

‡ Includes all 131 patients, of whom 72 developed AIDS.

§ Includes the 100 patients with available CCR5 genotypes, of whom 51 developed AIDS. Follow-up was truncated at 16.6 years to meet the proportional hazards assumption.

defined. Co-infection with cytomegalovirus, for example, seems to have little or no effect, except possibly in infants (15, 16).

Hepatitis G virus viremia is cleared in more than 50% of acute infections. This is followed by the appearance of anti-E2 antibodies, which usually persist over the long term (6). Remarkably, although HGV viremia often lasts for years, it does not seem to cause chronic disease (2, 6, 17). Like HCV, its distant flavivirus relative, HGV infects but has little replication in lymphocytes (18) and could therefore interfere with HIV within lymphocytes. Alternately, HGV could indirectly affect AIDS risk through induction of various chemokines and other soluble factors (19) or by altered expression of chemokine receptors, which are essential co-receptors for HIV (20). Investigation of the direct and indirect effects of HGV infection on chemokines, other soluble factors, and chemokine receptors could provide a mechanism for our observation of decreased risk for AIDS.

Appendix

The following institutions and investigators participated in the Multicenter Hemophilia Cohort Study:

J.J. Goedert, T.R. O'Brien, P.S. Rosenberg, C.S.

Rabkin, E.A. Engels, M. Hisada, E. Maloney, M.H. Gail, S.J. O'Brien, M. Dean, M. Carrington, M. Smith, and C. Winkler, National Cancer Institute, Rockville, Maryland, and Frederick, Maryland; B. Konkle, Cardeza Foundation Hemophilia Center, Philadelphia, Pennsylvania; M. Manco-Johnson, Mountain States Regional Hemophilia and Thrombosis Program, University of Colorado, Aurora, Colorado; D. DiMichele and M.W. Hilgartner, Hemophilia Treatment Center, New York Presbyterian Hospital, New York, New York; P. Blatt, Christiana Hospital, Newark, Delaware; L.M. Aledort and S. Seremetes, Hemophilia Center, Mount Sinai Medical Center, New York, New York; K. Hoots, Gulf States Hemophilia Center, University of Texas at Houston, Houston, Texas; A.L. Angiolillo, N.L.C. Luban, Hemophilia Center, Children's Hospital National Medical Center, Washington, D.C.; A. Cohen and C.S. Manno, Hemophilia Center, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; C. Leissinger, Tulane University Medical School, New Orleans, Louisiana; G.C. White II, Comprehensive Hemophilia Center, University of North Carolina, Chapel Hill, North Carolina; M.M. Lederman, S. Purvis, and J. Salkowitz, Case Western Reserve University School of Medicine, Cleveland, Ohio; C.M. Kessler, Georgetown University Medical Center, Washington, D.C.; A. Karafoulidou and T. Mandalaki, Hemophilia Center, Second Regional Blood Transfusion Center, Laikon General Hospital, Athens, Greece; A. Hatzakis and G. Touloumi, National Retrovirus Reference Center, Athens University Medical School, Athens, Greece; W. Schramm and F.

Rommel, Medizinische Klinik Innenstadt der Maximilian, Universitaet Muenchen, Munich, Germany; P. de Moerloose, Haemostasis Unit, Hôpital Cantonal Universitaire, Geneva, Switzerland; S. Eichinger, University of Vienna Medical School, Vienna, Austria; K.E. Sherman, University of Cincinnati Medical Center, Cincinnati, Ohio; D. Whitby and D. Waters, Scientific Applications International Corp., Frederick, Maryland; and V. Lamprecht and B.L. Kroner, Research Triangle Institute, Rockville, Maryland.

From the National Institutes of Health, Bethesda, Maryland.

Acknowledgments: The authors thank Dr. Frances Yellin (Computer Science Corp.) for computer programming and Virginia Lamprecht and Dr. Barbara Kroner (Research Triangle Institute) for study management. They especially thank the study participants, the hemophilia center staff, and the collaborators of the Multicenter Hemophilia Cohort Study for their tireless contributions.

Contract Support: In part by National Cancer Institute contract N01-CP-33002 with Research Triangle Institute.

Requests for Single Reprints: James J. Goedert, MD, Viral Epidemiology Branch, National Cancer Institute, 6120 Executive Boulevard, Room 8012 MSC 7248, Rockville, MD 20852; e-mail, goedertj@mail.nih.gov.

Requests To Purchase Bulk Reprints (minimum, 100 copies): Barbara Hudson, Reprints Coordinator; phone, 215-351-2657; e-mail, bhudson@mail.acponline.org.

Current Author Addresses: Drs. Yeo, Shih, and Alter: National Institutes of Health, Warren Grant Magnuson Clinical Center, Department of Transfusion Medicine, Room 1C711, MSC 1184, Bethesda, MD 20892.

Dr. Matsumoto: Second Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano-ken 390-8621, Japan.

Drs. Hisada and Goedert: Viral Epidemiology Branch, National Cancer Institute, 6120 Executive Boulevard, Room 8012 MSC 7248, Rockville, MD 20852.

Author Contributions: Conception and design: J.W. Shih, H.J. Alter, J.J. Goedert.

Analysis and interpretation of the data: A.E.T. Yeo, M. Hisada, H.J. Alter, J.J. Goedert.

Drafting of the article: A.E.T. Yeo, H.J. Alter, J.J. Goedert.

Critical revision of the article for important intellectual content: A.E.T. Yeo, A. Matsumoto, H.J. Alter.

Final approval of the article: M. Hisada, H.J. Alter, J.J. Goedert.

Statistical expertise: A.E.T. Yeo, M. Hisada, J.J. Goedert.

Obtaining of funding: J.J. Goedert.

Administrative, technical, or logistic support: J.W. Shih, J.J. Goedert.

Collection and assembly of data: A. Matsumoto, M. Hisada, J.J. Goedert.

References

1. Linnen J, Wages J Jr, Zhang-Keck ZY, Fry KE, Krawczynski KZ, Alter H, et al. Molecular cloning and disease association of hepatitis G virus: a transfusion-transmissible agent. *Science*. 1996;271:505-8.
2. Alter HJ, Nakatsuji Y, Melpolder J, Wages J, Wesley R, Shih JW, et al. The incidence of transfusion-associated hepatitis G virus infection and its relation to liver disease. *N Engl J Med*. 1997;336:747-54.
3. Zanetti AR, Tanzi E, Romano L, Principi N, Zuin G, Minola E, et al. Multicenter trial on mother-to-infant transmission of GBV-C virus. The Lombardy Study Group on Vertical/Perinatal Hepatitis Viruses Transmission. *J Med Virol*. 1998;54:107-12.
4. Wu JC, Sheng WY, Huang YH, Hwang SJ, Lee SD. Prevalence and risk factor analysis of GBV-C/HGV infection in prostitutes. *J Med Virol*. 1997;52:83-5.
5. Yeo AE, Matsumoto A, Shih JW, Alter HJ, Goedert JJ. Prevalence of hepatitis G virus in patients with hemophilia and their steady female sexual partners. *Sex Transm Dis*. 2000;27:178-82.
6. Alter HJ. G-pers creepers, where'd you get those papers? A reassessment of the literature on the hepatitis G virus. *Transfusion*. 1997;37:569-72.
7. Toyoda H, Fukuda Y, Hayakawa T, Takamatsu J, Saito H. Effect of GB virus C/hepatitis G virus coinfection on the course of HIV infection in hemophilia patients in Japan. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;17:209-13.
8. Sabin CA, Devereux H, Kinson Z, Griffioen A, Brown D, Dusheiko G, et al. Effect of coinfection with hepatitis G virus on HIV disease progression in hemophilic men. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;19:546-8.
9. Lefrère JJ, Roudot-Thoraval F, Morand-Joubert L, Petit JC, Lerable J, Thauvin M, et al. Carriage of GB virus C/hepatitis G virus RNA is associated with a slower immunologic, virologic, and clinical progression of human immunodeficiency virus disease in coinfecting persons. *J Infect Dis*. 1999;179:783-9.
10. Goedert JJ, Kessler CM, Aledort LM, Biggar RJ, Andes WA, White GC 2d, et al. A prospective study of human immunodeficiency virus type 1 infection and the development of AIDS in subjects with hemophilia. *N Engl J Med*. 1989;321:1141-8.
11. O'Brien TR, Blattner WA, Waters D, Eyster E, Hilgartner MW, Cohen AR, et al. Serum HIV-1 RNA levels and time to development of AIDS in the Multicenter Hemophilia Cohort Study. *JAMA*. 1996;276:105-10.
12. Dean M, Carrington M, Winkler C, Huttley GA, Smith MW, Allikmets R, et al. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. *Science*. 1996;273:1856-62.
13. Hisada M, O'Brien TR, Rosenberg PS, Goedert JJ. Viral load and risk of heterosexual transmission of human immunodeficiency virus and hepatitis C virus by men with hemophilia. *J Infect Dis*. 2000;181:1475-8.
14. Rosenberg PS, Gail MH, Schragger LK, Vermund SH, Creagh-Kirk T, Andrews EB, et al. National AIDS incidence trends and the extent of zidovudine therapy in selected demographic and transmission groups. *J Acquir Immune Defic Syndr*. 1991;4:392-401.
15. Rabkin CS, Hatzakis A, Griffiths PD, Pillay D, Ragni MV, Hilgartner MW, et al. Cytomegalovirus infection and risk of AIDS in human immunodeficiency virus-infected hemophilia patients. National Cancer Institute Multicenter Hemophilia Cohort Study Group. *J Infect Dis*. 1993;168:1260-3.
16. Kovacs A, Schluchter M, Easley K, Demmler G, Shearer W, La Russa P, et al. Cytomegalovirus infection and HIV-1 disease progression in infants born to HIV-1-infected women. Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection Study Group. *N Engl J Med*. 1999;341:77-84.
17. Goedert JJ, Steinmeyer LA, Nakatsuji Y. Hepatitis G infection. *N Engl J Med*. 1997;337:277.
18. Mellor J, Haydon G, Blair C, Livingstone W, Simmonds P. Low level or absent in vivo replication of hepatitis C virus and hepatitis G virus/GB virus C in peripheral blood mononuclear cells. *J Gen Virol*. 1998;79(Pt 4):705-14.
19. Woitas RP, Rockstroh JK, Beier I, Jung G, Kochan B, Matz B, et al. Antigen-specific cytokine response to hepatitis C virus core epitopes in HIV/hepatitis C virus-coinfecting patients. *AIDS*. 1999;13:1313-22.
20. O'Brien TR, Goedert JJ. Chemokine receptors and genetic variability: another leap in HIV research. *JAMA*. 1998;279:317-8.