Medical Costs and Resource Utilization for Hemophilia Patients With and Without HIV or HCV Infection

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ABSTRACT

BACKGROUND: Previous research has shown that hemophilia patients infected in the 1980s with human immunodeficiency virus (HIV) and/or hepatitis C virus (HCV) from the blood supply have increased morbidity and mortality. Although the possibility of contracting HIV or HCV through contaminated blood products has been virtually eliminated in the United States, approximately one third of hemophiliacs between the ages of 21 and 60 years are HIV infected.

OBJECTIVE: To determine the health care resource utilization of adult hemophilia patients with and without HIV and HCV infection in a commercially insured population in the United States.

METHODS: This was a retrospective claims analysis of the PharMetrics Patient-Centric database over an approximately 7-year period from January 1997 to April 2004. The database represents about 43 million members in commercial health plans. Male patients continuously enrolled for at least 6 months and >18 years of age were included in the study; female patients were excluded since they were likely to have von Willebrand disease. Hemophilia patients were identified if they had at least 1 claim with a primary diagnosis of hemophilia (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 286.XX) and at least 1 claim for a hemophilia drug (identified by National Drug Code number and J codes: J7190-J7199, Q0187 or Q2022). Clotting factor inhibitor patients identified through the dispensation of an activated prothrombin complex concentrate or recombinant factor VIIa were excluded from the study. Virally infected patients were identified as those hemophilia patients with at least 1 claim with a HIV diagnosis (ICD-9-CM codes 042.xx, 079.53) or HCV infection (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54). Four cohorts for analysis were established: hemophilia without HIV or HCV coinfection (H-only); hemophilia+HIV (H+HIV); hemophilia+HCV (H+HCV); and hemophilia+HIV+HCV (H+HIV+HCV). The index date was defined as the first day of enrollment. Follow-up lasted until the end of the patient's enrollment or the end of the study period. The main outcomes of the study were (1) annualized net costs paid by health plans (after subtracting member cost-share) associated with all pharmacy and medical claims and (2) office visit distribution overall and by physician specialty during the study period.

RESULTS: A total of 166 patients were identified for the study—73 with H-only, 12 with H+HIV, 44 with H+HCV, and 37 with H+HIV+HCV. The mean (median) annualized total cost of care in 2004 dollars was $90,942 ($63,613) for the H-only cohort versus $108,862 ($64,782, *P*=0.512) for the H+HIV cohort; $104,404 ($66,489, *P*=0.377) for the H+HCV cohort; and $144,462 ($111,542, *P*=0.005) for the H+HIV+HCV coinfected cohort. Clotting factor accounted for 78%-86% of total health care costs for all 4 groups of patients. Compared with the H-only cohort ($2,136), the H+HIV, H+HCV, and H+HIV+HCV cohorts had significantly higher mean non-hemophilia prescription drug costs ($8,239 [*P*=0.001]; $7,275 [*P*=0.034]; and $12,360 [*P*<0.001], respectively). The H+HIV+HCV cohort had significantly higher hospital inpatient costs than did the H-only cohort ($5,655 vs. $3,360, respectively, *P*=0.015). Mean annualized outpatient costs were higher in the H+HIV+HCV cohort ($12,897, *P*<0.001) and

H+HCV cohort ($7,233, *P*=0.016) than in the H-only cohort ($7,216). Mean annualized total numbers of office visits were higher for the H+HCV (11.18, *P*=0.003) and H+HIV+HCV (18.33, *P*<0.001) cohorts than for the H-only cohort (6.98). Compared with the H-only cohort, the H+HIV+HCV cohort had a greater mean annualized number of visits to infectious disease specialists (3.75 vs. 0.12, *P*<0.001) and to gastroenterology specialists (1.22 vs. 0.09, *P*<0.001).

CONCLUSION: The presence of HIV and HCV coinfection in hemophiliacs is associated with 59% (95% confidence interval, 34.8%, 82.9%) greater annual health care costs compared with costs for hemophilia alone. Coinfection with HIV and HCV is associated with significantly greater component costs for clotting factor, prescription drugs, inpatient services, and outpatient services.

What is already known about this subject

- Hemophilia is a chronic and expensive condition, with antihemophilic factor medications accounting for up to 93% of total medical cost, depending on severity.
- HIV and HCV coinfection has been associated with increased morbidity, mortality, and clotting factor utilization in hemophilia patients.

What this study adds

- This is the first study of hemophilia and coinfection with HIV and/or HCV in a U.S commercially insured population and the first to identify the sources and magnitude of component health care costs.
- Compared with the mean annualized cost in 2004 dollars for patients with H-only ($90,942, median=$63,613), HIV+HCV coinfection was associated with 59% greater costs ($144,462, median=$111,542, *P*=0.005).
- The health care services that contributed to greater total costs for hemophilia patients coinfected with both HCV and HIV than for patients with hemophilia only included antihemophilic (clotting factor) medication, outpatient costs, prescription drugs other than antihemophilic medications, and hospital inpatient costs.

By the early 1980s, most hemophilia patients had been exposed to the hepatitis B virus from plasma-derived factor VIII concentrates used for their treatment.[1] At that time, hepatitis was considered a manageable risk given the benefits of hemophilia treatment. However, the hepatitis C virus (HCV) was still uncharacterized, and despite the introduction of viral inactivation techniques in the mid-1980s, by the end of the decade most hemophilia patients were unknowingly infected.[2] In addition, the emergence of the human immunodeficiency virus (HIV) in the early 1980s severely affected the hemophilia population, mainly through contaminated blood products.[3] It has been estimated that of the approximately 15,500 hemophiliacs in the United States, about 9,465 (61%) were infected with HIV before the protective benefit of heat-treated factor VIII was widely known and accepted.[1] With the introduction of high-purity plasma-derived factor concentrates in the late 1980s and recombinant products in the early 1990s, the possibility of contracting HIV or HCV has been virtually eliminated; however, approximately one third of hemophiliacs in the United States between the ages of 21 and 60 years are HIV infected, and 80% are HCV infected.[4]

Mortality from liver disease in hemophilia due to HCV is almost 17 times higher than in the general population and is 6 times higher for liver cancer.[5] HIV has been shown to accelerate instances of HCV-related cirrhosis and liver failure, particularly when hemophilia is present.[6,7] Telfer et al. found that, on average, 15 years after initial exposure to factor concentrates, hemophilic patients coinfected with HIV and HCV were 21 times more likely to develop decompensated liver failure than were HCV mono-infected patients.[8] However, the effect of HCV on HIV progression has not been fully established. While some studies have found that HCV coinfection does not affect HIV progression,[9] other studies have found that HIV progresses faster in the presence of HCV.[10,11]

The presence of bidirectional interferences between HIV and HCV have complicated the treatment of coinfected individuals.[12] Frequent drug interactions, unique toxicities, and a greater likelihood of adverse events associated with antiviral therapy have been observed in coinfected individuals.[13] Partly because of the high prevalence of HCV coinfection in HIV patients, liver disease is the leading cause of death in HIV-infected individuals.[14]

A few studies have reported the effect of HIV infection on resource utilization in hemophiliacs. While Globe at al. did not find a statistically significant association between HIV positivity and the number of hospitalizations or the number of inpatient hospital days, Miners et al. found that HIV-positive hemophilia patients were more likely to have outpatient hospital visits than were hemophilia patients who were HIV negative.[15,16] Moreover, in hemophilia patients infected with HIV, a decrease in CD4+ counts has been associated with an increase in clotting factor utilization, with end-stage AIDS hemophilia patients consuming upward of 50% more clotting factor than when they are asymptomatic.[17]

Hemophilia is a chronic and expensive condition, with antihemophilic medications accounting for 45%-93% of total health care costs, depending on severity and treatment regimen.[18-20] In patients with inhibitors to factor VIII, clotting factor concentrates account for up to 99% of total costs.[21] Bohn et al. found that that the cost of hemophilia ranged from $30,820 per year for patients treated on demand to $87,865 for patients treated on prophylaxis,[19] while a study by Globe et al. estimated that the overall annual cost of hemophilia care in California was $139,102 in 1995.[18] The study found that higher total health care costs were correlated with HIV seropositivity, arthropathy, and inhibitors to factor VIII. In addition, they found that HIV infection was associated with significantly higher factor use. Molho et al. found that the mean annual treatment cost of patients with severe hemophilia, of whom 94.8% were HCV positive and 55.2% HIV positive, was US$73,029 in France in 1998.[22]

The slow response to act on the emerging HIV contamination of the blood supply led to devastating consequences for patients with hemophilia.[1] This was due in part to the costs and difficulty associated with the development and administration of appropriate interventions to protect the blood supply, such as screening and viral inactivation.[23] Poor vigilance of the emerging HIV and HCV threat resulted in a high rate of infection and consequently imposed a financial burden on health care payers and patients. Heemstra et al. found that while the annualized cost of hemophilia care for 17 boys treated between 1978 and 1998 in a Toronto children's hospital was Can$27,409 for severe patients with no viral transmission, it was approximately Can$85,448 for patients mono-infected with HIV and Can$111,809 for patients coinfected with HIV and hepatitis B or C.[24] Costs were underestimated because the study did not report drug costs related to HIV and HCV. Few other studies have attempted to quantify the economic impact of HIV and/or HCV coinfection in hemophilia patients. The purpose of this study is to determine the health care resource utilization of adult hemophilia patients with and without HIV and HCV infection in the United States.

■ Methods

Data

Data for this analysis were extracted from the PharMetrics Patient-Centric database from the approximately 7-year period from January 1997 to April 2004. The database is derived from at least 73 U.S. health plans (health maintenance organization [HMO], preferred provider organization [PPO], point-of-service [POS], and indemnity) and covers more than 43 million beneficiaries (with an average enrollment duration of 2 years). The data include a small number of Medicaid (approximately 8%) and Medicare (approximately 2%) patients who are enrolled in managed care organizations. The database includes patient demographic information (age, gender, type of insurance), medical
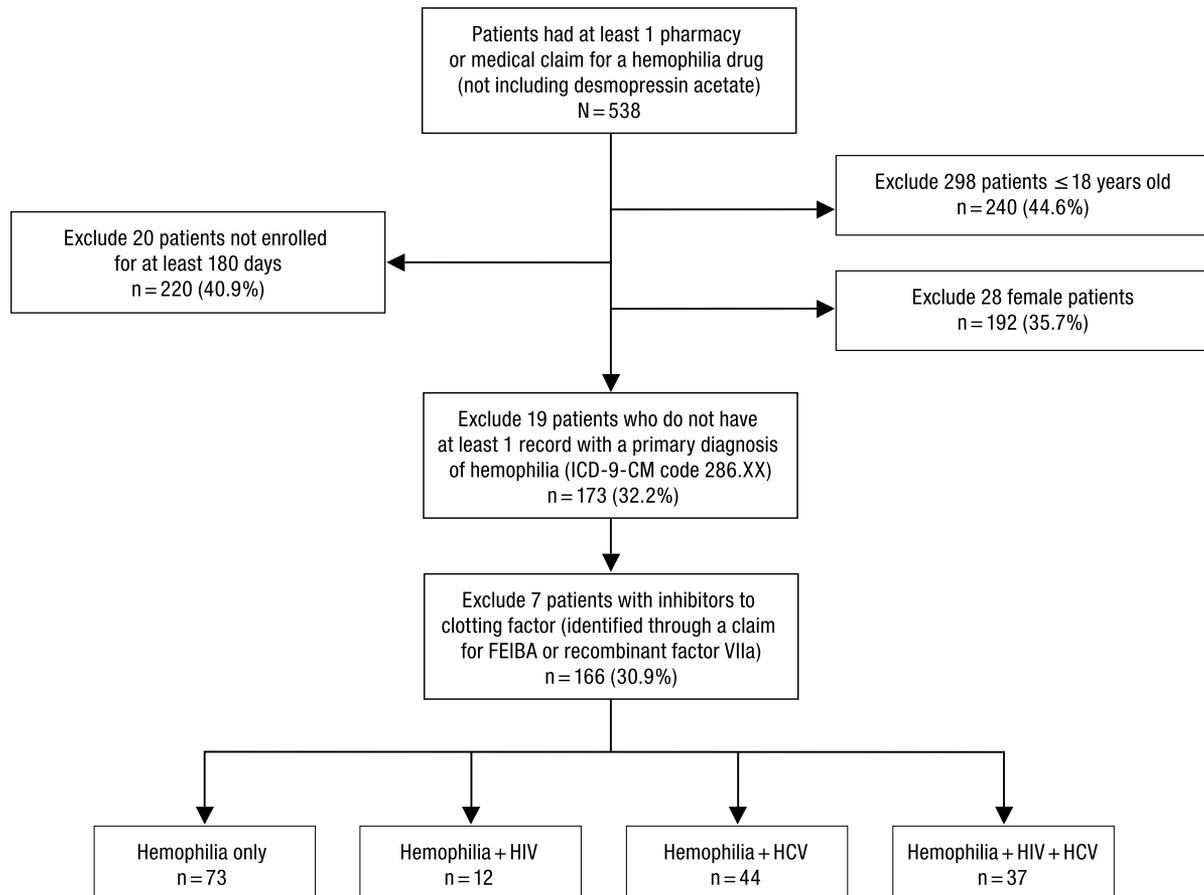
ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification.

claims data with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes; procedure codes (Current Procedural Terminology, 4th Edition [CPT-4] and Healthcare Common Procedure Coding System [HCPCS]); and pharmacy claims data, including National Drug Code (NDC) numbers, quantity, and days supply. Additional data elements in the administrative database include provider specialty, member eligibility, date of service, and plan cost. Plan cost is defined as the net plan cost after subtraction of member cost-share.

Patient Selection Criteria
Patients for this study were selected if they were continuously enrolled for at least 6 months, were >18 years of age, and male (Figure). Hemophilia patients were identified using ICD-9-CM, HCPCS, and NDC numbers. In an effort to overcome possible coding errors, hemophilia patients were identified if they (1) had

at least 1 medical claim with a primary diagnosis of hemophilia (ICD-9-CM codes 286.XX), (2) were male (to exclude cases of von Willebrand disease), and (3) had at least 1 pharmacy or medical claim for a hemophilia drug identified by NDC numbers (Table 1) and J codes: J7190-J7199, Q0187 or Q2022.

Patients having inhibitors to factor VIII or factor IX, identified through the dispensation of recombinant factor VIIa (rFVIIa), NovoSeven, or activated prothrombin complex concentrate (APCC), FEIBA VH, were excluded from the study. Virally infected patients were identified as those hemophilia patients with at least 1 medical claim with an HIV diagnosis (ICD-9-CM codes 042.xx, 079.53) or HCV infection (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54) in the primary, secondary, or tertiary diagnoses fields. Four patient cohorts were established: hemophilia without coinfection from either HIV or HCV (H-only); hemophilia+HIV (H+HIV); hemophilia+HCV (H+HCV); and

TABLE 1	Codes Used to Identify the Components of Health Care Utilization and Physician Specialty in the Claims Data
Service	**Identification**
Outpatient	Place of service code not = 01, 21, 23, 51, or 61, and no NDC in the claim and record type not pharmaceutical and procedure code not J7190-J7199,Q0187 or Q2022
Hospital inpatient	Place of service code = 21, 51, or 61, and no NDC in the claim and record type not pharmaceutical and procedure code not J7190-J7199,Q0187 or Q2022
Emergency room	Place of service code = 23 and no NDC in the claim and record type not pharmaceutical and procedure code not J7190-J7199,Q0187 or Q2022
Antihemophilic medication	NDC for 1 of the following drugs: Advate, Alphanate, Alphanine SD, Autoplex T, Bebulin VH, Benefix, Helixate, Helixate FS, Hemofil M Human, Humate-P, Humate-P Human, Hyate:C Anti-hemophilic Factor, Koate-Dvi, Koate-HP, Kogenate, Kogenate FS, Monarc-M, Monoclate-P, Mononine, Profilnine, Profilnine SD, Proplex T Factor IX Comp, Recombinate, Refacto; or HCPCS procedure codes J7190-J7199, Q0187 or Q2022
Prescription drugs	Pharmaceutical records not corresponding to the antihemophilic medications listed above where records were identified as pharmaceutical if they had a non-null NDC or had a procedure code for a drug (e.g., injectables)
Office visits	Place of service = 11
Physician specialty	Variable available in database when supplied by the employer or health plan

Place of service codes: 01=pharmacy; 11=office; 21=inpatient hospital; 23=emergency room; 51=inpatient psychiatric facility; and 61=comprehensive inpatient rehabilitation facility.
NDC=National Drug Code.

hemophilia+HIV+HCV (H+HIV+HCV). The index date was defined as the first day of enrollment and follow-up lasted until the end of the patient's enrollment or the end of the study period. Because of the limitations of the claims data, it was only known whether a test was ordered for a particular patient. Neither the laboratory test results nor hemophilia severity was available for the analysis. The study protocol was approved by the University of Southern California Institutional Review Board.

Outcomes Measures

Two main outcomes were measured from January 1997 through April 2004: (1) cost (net plan cost after subtraction of member cost-share) associated with all pharmacy and medical claims and (2) number of office visits overall and by physician specialty

during the study. Costs were annualized by computing the sum of total costs for each patient and dividing by the total number of patient months of eligibility multiplied by 12. Medical expenditures were adjusted to 2004 dollars using the medical consumer price index and were subdivided into outpatient, hospital inpatient, emergency room, antihemophilic medication, and non-hemophilia prescription drug costs (Table 1). Categorization of medical service claims into outpatient, hospital inpatient, and emergency room was based on place of service codes. Total costs were defined as the sum of the aforementioned costs.

Office visits were identified using place of service code 11 (office). For each cohort we computed the mean number of annualized office visits (categorized by physician specialty). Annualized office visits were computed as total visits incurred by each patient divided by the total number of enrollment months for that patient, multiplied by 12. The Charlson Comorbidity Index was used to assess the comorbidity of each cohort.[24]

Statistical Methods

Statistical analysis was performed using SAS 9 (SAS Institute, Cary, NC). All statistical tests were performed by comparing each coinfected cohort (H+HCV, H+HIV, H+HIV+HCV) against the H-only group. Differences in means were tested using the *t* test. The Mann-Whitney *U* test was used for nonnormally distributed data. Fisher's exact test was used to test the statistical significance of differences for categorical variables. Fisher's exact test was used instead of the Pearson chi-square test because of small counts in some of the cells.

◼ Results

Demographic characteristics of the study cohort are displayed in Table 2. After all inclusion and exclusion criteria were applied, 166 patients were identified for the study. H-only patients accounted for 44% of the patients (n=73), followed by patients with H+HCV (27%, n=44), H+HIV+HCV (22%, n=37), and H+HIV (7%, n=12). Patients who had H-only were on average 4 to 6 years younger than coinfected hemophilia patients. No statistically significant differences in payer mix or mean number of months enrolled were noted. As expected, all 3 coinfected cohorts had significantly higher comorbidity scores than the H-only cohort ($P<0.001$ for H+HIV and H+HIV+HCV, $P=0.001$ for H+HCV).

Annualized costs for the cohorts are displayed in Table 3. Mean (median) annual cost of care was $90,942 ($63,613) for the H-only cohort versus $108,862 ($64,782, $P=0.512$) for the H+HIV cohort, $104,404 ($66,489, $P=0.377$) for the H+HCV cohort, and $144,462 ($111,542, $P=0.005$) for the H+HIV+HCV cohort. Overall mean cost was approximately 59% (95% confidence interval [CI], 34.8%, 82.9%) higher for H+HIV+HCV patients than for H-only patients. Antihemophilic (clotting factor) medications accounted for approximately 78%-86% of total costs

TABLE 2 Patient Characteristics by Cohort
N = 166

Characteristics	H-only n = 73	H + HIV n = 12	P Value	H + HCV n = 44	P Value	H + HIV + HCV n = 37	P Value
Mean age* [SD]	31 [11]	36 [10]	0.147	37 [12]	0.005	35 [8]	0.006
Age categories†							
18-29	58%	25%		34%		30%	
30-39	15%	50%		18%		49%	
40-49	18%	17%	0.064	30%	0.075	14%	0.003
50-59	8%	8%		18%		8%	
60+	1%	0%		0%		0%	
Insurance status†							
Commercial	35.6%	58.3%		47.7%		40.5%	
Medicare/Medicaid	24.7%	0.0%	0.143	11.4%	0.207	16.2%	0.748
Self-insured	12.3%	16.7%		6.8%		16.2%	
Missing/unknown	27.4%	25.0%		34.1%		27.0%	
Charlson Comorbidity Index*§	0.2	6.2	<0.001	0.8	0.001	6.8	<0.001
Mean months enrolled‡ [SD]	30.24 [18.6]	27.12 [19.1]	0.394	31.68 [14.9]	0.237	33.72 [20.0]	0.273

*   t test computed versus hemophilia only.
†   Fisher's exact test for MxN tables versus hemophilia only.
‡   Mann-Whitney U test vs. hemophilia only.
§   Charlson Comorbidity Index computed using the Deyo et al. method.[25]

H-only = hemophilia only; H + HIV = hemophilia with HIV infection; H + HCV = hemophilia with HCV infection; H + HIV + HCV = hemophilia with HIV and HCV coinfection.

in all 4 study groups. Compared with the H-only group ($2,136), the H+HIV, H+HCV, and H+HIV+HCV infected cohorts had significantly higher mean annualized non-hemophilia prescription drug costs ($8,239 [P=0.001], $7,275 [P=0.034], and $12,360 [P<0.001], respectively). Mean clotting factor costs were approximately 45% higher for the H+HIV+HCV cohort than for the H-only cohort ($113,228 vs. $77,863, P=0.011). In addition, mean annualized outpatient costs were higher for the H+HCV ($7,233, P=0.016) and H+HIV+HCV ($12,897, P=0.001) cohorts than for the H-only cohort ($7,216).

The number of office visits by general practice and specialty type is shown in Table 4. The annualized mean office visits were higher for the H+HCV (11.18, P=0.003) and H+HIV+HCV (18.33, P<0.001) cohorts than for the H-only cohort (6.98). Compared with the H-only cohort, the H+HIV+HCV cohort had a greater mean annualized number of visits to infectious disease specialists (3.75 vs. 0.12, P<0.001) and to gastroenterology specialists (1.22 vs. 0.09, P<0.001).

■ Discussion

This study found that the presence of viral infection is associated with significantly increased treatment costs for hemophilia patients in commercial health plans. While previous studies attempted to quantify the cost of hemophilia in the United States, they did not report the relative difference in costs attributed to

viral infection. We found that total mean annualized costs in 2004 dollars ranged from $90,942 for the group with hemophilia only to $144,462 for hemophilia patients with both HIV and HCV coinfection. Since this study was conducted from the perspective of an insurer, the net plan cost after subtraction of member cost-share was used as the measure of health care resource cost.

As mentioned previously, Heemstra et al. found the same pattern—that costs increased with more transmitted diseases.[24] Differences in our estimates are likely because Heemstra had estimated annual inflation-adjusted Canadian costs between 1978 and 1998 for a cohort of 17 children in 1 hospital and did not include non-hemophilia prescription drug costs. Despite the rarity of hemophilia, even a few patients can impose substantial costs on a managed care organization. Viral coinfection substantially increases that financial burden.

Hemophilia patients with HIV and HCV were more likely to have a greater number of specialty physician visits than were hemophiliacs without similar infection. Costs for services provided with an inpatient place of stay were also somewhat higher for patients coinfected with HIV and HCV than for patients with hemophilia alone. However, both studies by Globe et al. and Miners et al. found no statistically significant association between occurrences of inpatient hospitalization and HIV status after adjusting for severity of hemophilia.[15,16] With current treatment of HIV effectively making it a chronic condition, it is possible that

TABLE 3	Annualized Cost per Patient by Cohort* N = 166							

Cost Category†	H-only n = 73	H+HIV n = 12	P Value	H+HCV n = 44	P Value	H+HIV+HCV n = 37	P Value
Outpatient							
Mean	7,216	9,398		7,233		12,897	
[SD]	[20,278]	[15,855]	0.220	[12,204]	0.016	[29,693]	0.001
Median	1,123	2,306		2,395		3,965	
% of total cost	7.9%	8.6%		6.9%		8.9%	
Hospital inpatient							
Mean	3,360	1,104		5,561		5,655	
[SD]	[11,561]	[3,823]	0.339	[18,261]	0.289	[15,476]	0.015
Median	0	0		0		0	
% of total cost	3.7%	1.0%		5.3%		3.9%	
Emergency room							
Mean	367	17		129		322	
[SD]	[1,646]	[60]	0.059	[469]	0.060	[1,287]	0.414
Median	0	0		0		0	
% of total cost	0.4%	0.0%		0.1%		0.2%	
Antihemophilic medication							
Mean	77,863	90,104		84,206		113,228	
[SD]	[100,350]	[149,739]	0.528	[112,385]	0.677	[102,705]	0.011
Median	43,104	42,374		41,867		88,173	
% of total cost	85.6%	82.8%		80.7%		78.4%	
Prescription drugs‡							
Mean	2,136	8,239		7,275		12,360	
[SD]	[5,178]	[5,802]	0.001	[30,244]	0.034	[10,732]	<0.001
Median	289	8,561		843		11,920	
% of total cost	2.3%	7.6%		7.0%		8.6%	
Total paid costs							
Mean	90,942	108,862		104,404		144,462	
[SD]	[101,366]	[147,805]	0.512	[117,668]	0.377	[127,463]	0.005
Median	63,613	64,782		66,489		111,542	

Computed as the sum of costs incurred by each patient divided by the total number of months enrolled by the patient multiplied by 12.

† Outpatient, inpatient, and emergency room costs were classified based on place of service codes.

‡ Prescription drugs, excluding hemophilia drugs.

P values were computed for the comparison of each coinfection category versus hemophilia only using the Mann-Whitney U test.

H-only=hemophilia only; H+HIV=hemophilia with HIV infection; H+HCV=hemophilia with HCV infection; H+HIV+HCV=hemophilia with HIV and HCV coinfection.

severity and age are the biggest predictors of hospitalization in coinfected hemophilia patients and attenuate the impact of viral coinfection.

We found that hemophilia patients coinfected with both HIV and HCV had significantly higher clotting factor utilization than did patients with hemophilia only. Other studies found that HIV status and decreasing CD4+ counts were significantly associated with increased clotting factor use.[17,18,24] Heemstra et al. found the weight-adjusted cost of factor VIII ranged from Can$1,000 per kg per year for severe hemophilia patients with no viral transmission to Can$2,206 per kg per year for severe patients with HIV and hepatitis B and/or C.[24] Several observational studies found that treatment of HIV-positive hemophilia patients treated with HIV protease inhibitors was associated with an increased incidence of bleeding episodes. While some individuals reported an increase

in frequency in bleeding in the same sites as before HIV protease inhibitor therapy was initiated, others reported new bleeds occurring at unusual sites, such as the small joints of the hand or the intraocular muscles.[26-29]

HIV and HCV coinfection in patients with hemophilia imposes a large increase in non-hemophilic prescription drug cost. The introduction of highly active antiretroviral therapy (HAART) significantly reduced new AIDS cases, mortality, and opportunistic infections in HIV-positive patients.[30,31] Although HAART substantially decreases inpatient hospitalization cost, it is accompanied by significantly higher pharmacy, laboratory, and outpatient care expenditures.[32] Purdum et al. estimated that the drug costs of HIV-infected patients in a managed care setting were approximately $15,768 and accounted for 78% of their total costs.[33] Drug costs were likely overstated because the study

TABLE 4 Mean Number of Annualized Office Visits by Physician Specialty Type for Each Cohort*
N = 166

	H-only n = 73	H + HIV n = 12	P Value	H + HCV n = 44	P Value	H + HIV + HCV n = 37	P Value
Primary care							
General practice	1.62	0.50	0.136	2.42	0.710	1.09	0.192
Internal medicine	0.19	1.90	0.747	1.03	0.005	0.63	0.026
Specialist							
Hemo-oncology	1.08	0.21	0.287	1.02	0.710	1.21	0.456
Orthopedic surgery	0.95	0.00	0.087	0.93	0.261	0.99	0.117
Chiropractic	0.28	0.00	0.564	0.17	0.316	3.93	0.991
Infectious disease	0.12	1.71	0.044	0.31	0.670	3.75	<0.001
Gastroenterology	0.09	0.00	0.564	0.76	<0.0001	1.22	<0.001
Other or unknown medical specialty	2.65	6.00	0.539	4.55	0.284	5.50	0.031
Total visits	6.98	10.31	0.133	11.18	0.003	18.33	<0.001

* Computed as the mean of the annualized patient records. Patient records were annualized by summing all office visits and dividing by the total number of patient months of eligibility times 12.
P values were computed against hemophilia only using the Mann-Whitney U test.
H-only = hemophilia only; H + HIV = hemophilia with HIV infection; H + HCV = hemophilia with HCV infection; H + HIV + HCV = hemophilia with HIV and HCV coinfection.

estimated these costs using average wholesale price. While we did not explicitly look at the component of drug costs related to HIV or HCV, we found that mean annualized non-hemophilia prescription drugs costs for the H+HIV and H+HIV+HCV groups were $8,239 and $12,360, approximately 4 to 5 times the prescription drug costs of the hemophilia-only group.

In addition to having an economic impact, HIV or HCV infection may also affect the health-related quality of life of hemophiliacs; however, there is currently no consensus on whether viral infection has a negative impact. While some studies reported that HIV or hepatitis comorbidity caused a significant decrease in HRQoL or health utility,[34-36] other studies did not find any effect of HIV status on HRQoL.[22,37] Several reasons for this contradiction have been put forward, including the possibility that (1) better treatment has reduced the impact of HIV comorbidity on HRQoL, (2) the instruments used to assess quality of life (e.g., Short Form 36, Health Utilities Index) are general scales not specific to hemophilia and may not be sufficiently sensitive to detect change in quality of life for a hemophilia patient, or (3) adaptation to the health state may have occurred.[38,39] It is possible that the marginal disutility of HIV, a second chronic condition, on a first chronic condition such as hemophilia may have been small. Further research is required to resolve this issue.

In the general hemophilia population, most hemophiliacs were infected with HIV and HCV through the blood supply.[2,3] Currently available hemophilia therapies have varying levels of exposure and vulnerability to contamination by blood-borne pathogens.[23] While the threat of HIV or HCV infection has been virtually eliminated, emerging pathogens such as variant Creutzfeldt-Jakob disease pose a risk to blood-derived products.[23] This study demonstrates the economic impact of HIV and HCV coinfection on a hemophilia population.

Limitations
First, because of the nature of claims data, we were unable to directly obtain several clinical markers that are relevant to hemophilia, such as severity and the development of inhibitors (antibodies to factor VIII). We identified inhibitor patients through the use of recombinant factor VIIa or APCC and excluded them from the study. The presence of inhibitors has been shown to dramatically increase the overall treatment cost for hemophilia and thus can confound the relationship between viral infection status and resource use.[40,41] Post hoc analysis of the inhibitor patients found that 4 of these patients were in the hemophilia-only group and 3 were in the HCV group, with a mean annualized total cost of $635,296. However, this methodology may not have captured inhibitor cases treated with immune tolerance induction therapy, which usually involves the daily infusion of large doses of FVIII over many months.

Second, there may have been under-reporting of HCV during the time frame of our study. HCV antibody testing was introduced in 1991 and was unlikely to have been disseminated widely into practice by 1997. However, since hemophilia patients are significant users of blood-derived products, the hemophilia

community has been acutely aware of the need to test for known viral pathogens such as HIV and HCV. Therefore, it is unlikely that HCV under-reporting would have materially affected the results of our study.

Third, we could not control for hemophilia severity between the cohorts. Since severe hemophilia patients have been shown to use more clotting factor concentrate than mild and moderate patients do,[18] severity can potentially account for the increased use of clotting factor in the virally infected cohorts. Fourth, clotting factor, the most costly component of hemophilia treatment, is administered by weight. Since weight data are not available in our database, the effect of this limitation on our results is unknown.

Fifth, this study was conducted using a retrospective claims database analysis. Although such databases provide a reasonably accurate estimate of direct medical costs, there is a possibility of miscoding and missing data. In order to guard against possible diagnosis coding errors, hemophilia patients were identified as patients who had at least 1 record of a primary hemophilia diagnosis and at least 1 claim for a hemophilia drug.

Sixth, because we based our medical service classifications only on place of service (e.g., without accounting for revenue codes or other more specific data about service use), it is possible that costs were misclassified; however, our analyses of total cost were unaffected by this problem. A related potential limitation is the coding of hemophilic factor in the hospital setting. It is possible and even likely that some clotting factor costs were assigned to the category of inpatient hospital costs, potentially biasing factor costs downward and inpatient hospitalization costs upward.

Seventh, although we used a database of approximately 43 million lives, we identified only 166 patients who met the study criteria across the 4 study cohorts. On the basis of national prevalence of 13.4 cases per 100,000 males, we would expect to identify approximately 2,880 patients versus the 538 cases that we identified before applying the exclusion criteria. Our requirement of at least 1 hemophilia drug dispensation excluded many mild and moderate hemophilia patients from all cohorts. In addition, for those managed care organizations that contract out with a specialty pharmacy to manage their injectable drugs benefit, clotting factor administrative claims data may not be available for analysis. Thus, we would have excluded these hemophilia patients because their FVIII claims were not accessible through either the managed care organization or pharmacy benefits manager. Using all available diagnosis positions, not just the primary diagnosis, would have identified only 4 more patients.

Eighth, the small sample size and high variability of health care costs, as reflected in high standard deviations, limited the statistical power of the data analysis. Thus, we were unable to detect any statistically significant differences in total costs between the hemophilia mono-infected cohorts (H+HCV and H+HIV) and the hemophilia-only cohort, although we did find significantly increased non-hemophilia prescription drug costs.

■ Conclusion

For patients with hemophilia, coinfection with both HIV and HCV is associated with greater total annual medical costs of approximately 59% (95% CI, 34.8%, 82.9%) in hemophiliacs. Coinfection with HIV and HCV is associated with significantly greater component costs for clotting factor, prescription drugs, inpatient services, and outpatient services.

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