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Open Forum Infectious Diseases

MAJOR ARTICLE

Estimating the Time to Diagnosis and the Chance of Spontaneous Clearance During Acute Hepatitis C in Human Immunodeficiency Virus-Infected Individuals

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Background. Hepatitis C virus (HCV) infection is often asymptomatic, and the date of infection is almost impossible to determine. Furthermore, spontaneous clearance (SC) may occur, but little is known about its time of occurrence.

Methods. Data on human immunodeficiency virus (HIV)-HCV coinfected individuals were used to inform a stochastic simulation model of HCV viral load kinetics, alanine aminotransferase (ALT), and HCV antibodies during acute hepatitis C. The dates of diagnosis and potential SC were estimated through a Bayesian approach. Hepatitis C virus diagnosis was assumed to be based on an elevated ALT level detected during a control visit for HIV-infected individuals, which occurred every 3 months (scenario A) or every 6 months (scenario B).

Results. We found that HCV diagnosis occurred after a median of 115 days and 170 days of infection in scenarios A and B, respectively. Among spontaneous clearers, SC occurred after a median time of 184 days after infection. Seven percent (scenario B) to 10% (scenario A) of SCs appeared more than 6 months after diagnosis, and 3% (both scenarios) of SCs appeared more than 1 year after diagnosis.

Conclusions. Acute hepatitis C diagnosis occurs late in HIV-HCV coinfected individuals. Screening for HCV in HIV-infected individuals should be performed frequently to reduce delays. Our findings about late occurrence of SC support "wait and see" strategies for treatment initiation from an individual basis. However, early treatment initiation may reduce HCV transmission.

Keywords. agent-based modeling; HCV antibodies; late diagnosis; natural history; viral load.

The acute phase of hepatitis C infection is defined as the first 6 months after the infection [1, 2]. Patients with acute hepatitis C (AHC) may develop symptoms such as jaundice but are more often asymptomatic [3–5]. As a result, except for cases related to a known exposure to hepatitis C virus (HCV) such as occupational exposures to HCV, determining the time of HCV infection is a challenge for clinicians. Patients with HCV infection might spontaneously clear the virus, which allows for potential recovery without use of anti-HCV drugs [6]. Accordingly, in the past era of rather toxic Peginterferon-ribavirine combination therapy, most clinicians considered a delay in HCV treatment initiation. However, the time at which spontaneous clearance (SC) occurs remains unclear and probably varies from patient to patient. These 2 sources of uncertainty concerning the time of infection and the time of potential SC make the clinicians' task very difficult when making decision about treatment initiation.

With the increasing availability of interferon-free direct-acting antiviral regimens, HCV treatment efficacy during the chronic stage of the disease is expected to be close to 100%. Therefore, treating patients at the acute stage of the disease where direct-acting antivirals are currently not recommended in most countries is probably less tempting at an individual level because response rates in the chronic phase have improved tremendously. To avoid costly treatment, it is probably even more efficient to delay the initiation of anti-HCV therapy until patients reach the chronic stage of HCV infection when they are less likely to clear the virus spontaneously. However, in the men who have sex with men (MSM) population, given the current HCV infection epidemic [7–9] at a population level, early treatment of infection with highly efficacious and well tolerated regimens should be considered to avoid transmission to

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partners. As a result, early diagnosis of infections should be promoted. Consequently, the timing of AHC diagnosis will remain an issue.

In this study, we aimed to improve the characterization of the natural history of HCV infection in human immunodeficiency virus (HIV)-HCV coinfected patients. Using individual data on AHC from 3 different European cohorts of HIV-HCV coinfected patients, data from the medical literature, and a mathematical model, we estimated (1) the time from HCV infection to HCV diagnosis and (2) the distribution of the times of SC after infection.

METHODS

Individual Data

We gathered individual data on 286 HIV-HCV coinfected individuals from 3 different European cohorts of patients diagnosed with AHC between 2002 and 2012. Cohort A comprised 211 patients enrolled into the observational European AHC cohort of the European AIDS Treatment Network. Patients were followed prospectively beginning in 2002. Retrospective enrollment of cases was possible provided that data on their follow-up were available as requested. Cohort B comprised 38 patients diagnosed in 3 centers in Paris, France, between 2003 and 2007, and followed up for 15 months. This cohort was described in detail by Schnuriger and colleagues [10]. Cohort C was composed of patients followed in the HIV clinic of Saint-Antoine Hospital, Paris, who presented with AHC during the course of HIV management between 2010 and 2012.

In cohort A, AHC diagnosis was either based on (1) a positive HCV-ribonucleic acid (RNA) test and prior negative anti-HCV antibody or HCV-RNA test within 12 months or (2) an elevated alanine aminotransferase (ALT) within the past 12 months with prior normal ALT during the previous year. In cohorts B and C, AHC was diagnosed on ALT elevation during routine monitoring of HIV infection and confirmed by 2 consecutive positive HCV-RNA detections in patients previously HCV-RNA or HCV-antibody negative within the past 8 months.

General Approach

A mathematical model was used to simulate key characteristics of the natural history of HCV infection. In particular, the model incorporates HCV viral load (HCV-VL) dynamics, date of seroconversion, and timings of ALT elevation and ALT peak. The model parameters were generated through a Bayesian process involving a likelihood that was based on the individual data described above as well as published estimates from the literature. The resulting model was then used to estimate the time from HCV infection to diagnosis as well as the times to SC.

Viral Load, Seroconversion, and Alanine Aminotransferase Peak

Based on the available literature relating to hepatitis C viral dynamics [11–20], we assumed that the variation pattern of HCV-VL can be decomposed in successive phases. That is, the HCV-VL was assumed to increase exponentially after infection (not explicitly modeled), until reaching its maximal level. Then, we considered that the VL is stable during a plateau phase, which ends when antibodies appear, because this event is expected to trigger a drop in the HCV-VL. In the model, the corresponding drop was modeled as a linear decrease of log(HCV-VL) in spontaneous clearers, and the date of SC was defined as the time that the HCV-VL becomes lower than 1 IU/mL. In our data, the maximal level of HCV-VL was assumed to be the highest level measured before antibodies appearance, and the gradient of HCV-VL was estimated by measuring the time elapsed between the start of the drop phase and the first undetectable HCV-VL.

We undertook a parallel analysis of HCV-VL dynamics and ALT levels in the 25 patients that presented a drop in HCV-VL and found that in 23 (92%) of them, the peak of ALT—defined as the highest measured ALT level—was observed when the drop in VL started. In the 2 remaining individuals, this trend was less clear but did not contradict the affirmation that the peak in ALT coincides with the beginning of the drop phase (data shown in Supplementary Figure S1). Accordingly, we assumed that the date of ALT peak coincides with the date of seroconversion in our model because the drop was assumed to begin at seroconversion.

The time from HCV infection to seroconversion was not available in our data. However, detailed estimates for this variable in HIV-infected individuals have been published by Vanhommerig et al [21]. We used graph digitizer software (Plot Digitizer version 2.6.8) to obtain quantitative estimates of the time from HCV infection to antibodies appearance from the survival curve and the associated confidence intervals that were reported in this publication.

Dating the Diagnosis of Hepatitis C Virus Infection

In the model, the diagnosis of HCV was assumed to be based on the detection of an elevated ALT level during a routine follow-up visit of an HIV-positive individual. Our individual data allowed estimation of the duration between ALT elevation—defined as ALT level higher than the upper normal limit (40 IU/L)—and peak of ALT in 20 patients. Therefore, the date of ALT elevation (t_{ALT}) was retrospectively calculated by subtracting this duration to the date of ALT peak that coincides with seroconversion (see previous paragraph). In the model, 2 scenarios were explored regarding the frequency of HIV follow-up routine visits: 3 months (Scenario A) and 6 months (Scenario B). Accordingly, the date of diagnosis was randomly generated from a uniform distribution on the interval [t_{ALT}, t_{ALT} + 3 months] under Scenario A and [t_{ALT}, t_{ALT} + 6 months] under Scenario B.

Bayesian Analysis

A stochastic model was defined to generate a profile of natural history of HCV infection based on 4 independent characteristics: (1) the time to seroconversion; (2) the time from ALT elevation

to ALT peak; (3) the maximal level of HCV-VL; and (4) the negative gradient of HCV-VL in spontaneous clearers. We used the statistical distributions listed in Supplementary Table S1 to generate the different parameter values associated with the model. Instead of using fixed parameter values for these statistical distributions, we used a Metropolis-Hastings algorithm to explore wide parameter spaces and only retain the statistical models that are compatible with the measures performed in the data. Figure 1 presents a diagram explaining the global method used to generate the model estimates. A total of 100 000 combinations of statistical models were accepted and then used to generate as many profiles of natural history of HCV infection. Censoring was used to avoid negative values of HCV-VL and diagnosis that occurs before infection. In the event that a parameter set was censored, another parameter set was generated. The Metropolis-Hastings algorithm as well as the likelihood on which it is based are described in details in the Supplementary Data. We used R version 3.2.1 for running the simulations.

Uncertainty Around Seroconversion Times

The exact date of infection is almost impossible to estimate accurately because AHC is often asymptomatic; therefore, a common approach to its estimation is to use the midpoint between the last negative and the first positive RNA test [21]. To account for the uncertainty in such estimates, we used the 95% confidence intervals reported on the survival curves of Vanhommerig et al [21] to consider alternate scenarios for the seroconversion times. Namely, "early seroconversion" scenarios were considered by assuming that antibodies always appeared at the reported lower estimates. The corresponding scenarios are denoted A1 and B1 when follow-up visits are settled every 3 months and 6 months, respectively. In contrast, "delayed seroconversion" was considered by assuming that seroconversion always occurred at the reported upper estimates. Scenarios A2 and B2 designate such scenarios when follow-up visits are settled every 3 months and 6 months, respectively.

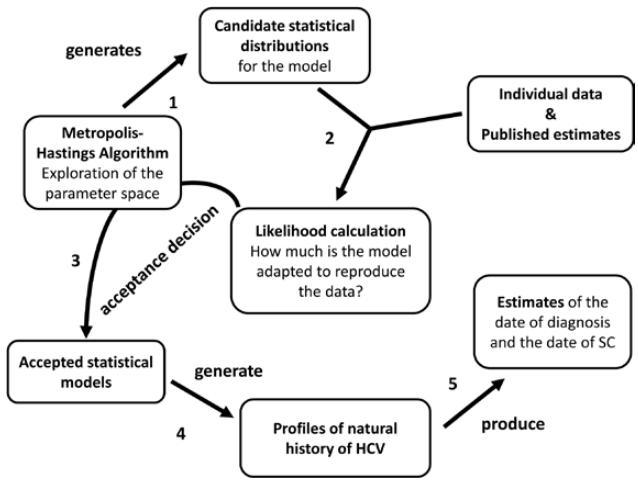

Figure 1. Diagram illustrating the general modeling approach. HCV, hepatitis C virus; SC, spontaneous clearance.

RESULTS

Exploitation of the Data

The characteristics of the cohorts A, B, and C are presented in Table 1. The mean maximal level of HCV-VL assessed in 48 patients of the cohorts A and B was estimated at 6.37 log IU/mL (standard deviation [SD] = 0.75). The duration between elevation and peak of ALT was available in 20 patients and its mean was estimated at 56 days (SD = 32 days). Our data allowed for estimation of the gradient of log(HCV-VL) in 13 patients. This quantity was found to range between 0.05 and 0.21 log(UI/mL)/day with a mean of 0.11 log(UI/mL)/day (interquartile range [IQR], 0.07–0.18). The outputs of the Metropolis-Hastings simulation as well as the parameters used to generate the profiles of HCV natural history are presented in Supplementary Figures S2 and S3.

Model Outputs

Dates of Diagnosis

Alanine aminotransferase elevation appeared after a median duration of 33 days of infection (IQR, 1–88), leading to a median time from infection to diagnosis of 115 days (IQR, 72–180) in scenario A and 170 days (IQR, 110–235) in scenario B. The distribution of diagnosis dates over time obtained from the model are represented in Figure 2a and 2b for scenarios A and B, respectively. We note that even for individuals with a regular follow-up of 1 visit every 3 months, HCV diagnosis may occur after 1 year of infection. This corresponds to individuals in which ALT elevation is strongly delayed.

Dates of Spontaneous Clearance

The distribution of the times from infection onset to SC occurrence is presented in Figure 3a. We estimated the median time from infection to SC occurrence to be 184 days (IQR, 123–276), indicating that half of the SCs occur after 6 months of infection. Earliest SCs were recorded after 1 month of infection, whereas the model showed SC occurrences after 1 year of infection in 13% of the total SC cases. Twelve percent of SCs occurred in the first 3 months of infection, whereas 50% of them appeared before 6 months of infection. Figure 3b presents the distribution of the times from diagnosis to SC occurrence. The median time from diagnosis to SC was 54 days in scenario A. The scenario B led to a shorter median duration of 17 days, which is explained by the fact that individuals were generally diagnosed later in this scenario. We found that 14% (scenario A) to 40% (scenario B) of SCs occurred before the diagnosis, 7% (scenario B) to 10% (scenario A) of SCs appeared more than 6 months after diagnosis, and 3% (scenarios A and B) of them occurred later than 1 year after diagnosis.

Table 1. Characteristics of the 3 Different European Cohorts of HIV-HCV Coinfected Individuals[a]

Clinical Measure	Total (n = 286)	Cohort A (n = 211)	Cohort B (n = 38)	Cohort C (n = 37)
Demographics				
Age	40 (36–45)	40 (35–44)	44 (37–51)	41 (37–48)
Gender (Male/Female/Missing)	284/1/1	209/1/1	38/0/0	37/0/0
HIV-HCV characteristics				
HCV genotype				
1	161 (56%)	136 (64%)	10 (26%)	15 (41%)
2	13 (5%)	10 (5%)	1 (3%)	2 (5%)
3	27 (9%)	18 (9%)	3 (8%)	6 (16%)
4	74 (26%)	39 (18%)	23 (61%)	12 (32%)
Missing	11 (4%)	8 (4%)	1 (3%)	2 (5%)
CD4 level (cells/mm^3)	532 (387–645)	505 (368–625)	559 (417–655)	643 (497–731)
Symptoms				
Symptomatic	86 (30%)	74 (35%)	12 (32%)	NA
Asymptomatic	154 (54%)	129 (61%)	25 (66%)	NA
Unknown	46 (16%)	8 (4%)	1 (3%)	37 (100%)
HCV-RNA level at HCV diagnosis (log IU/mL)	5.72 (5.17–6.47)	5.75 (5.16–6.38)	5.60 (5.25–6.67)	5.69 (5.33–6.52)
Maximal ALT (IU/L)	602 (186–804)	637 (194–853)	415 (151–577)	NA
Treated	n = 191	n = 146	n = 22	n = 23
Time from diagnosis to therapy initiation (days)	92 (34–121)	74 (28–102)	162 (110–205)	134 (42–189)
Bi-therapy (PegIFN-α ribavirin)	135 (71%)	112 (77%)	NA	23 (100%)
SVR (Yes/No/Missing)	99/47/45	72/38/36	10/6/6	17/3/3
Untreated	n = 86	n = 58	n = 16	n = 12
Spontaneous clearance (% of untreated/% of overall)				
All HCV genotypes	34 (40%/12%)	24 (41%/11%)	5 (31%/13%)	5 (42%/14%)
Genotype 1	20 (43%/12%)	15 (42%/11%)	2 (50%/20%)	3 (50%/20%)
Genotype 2	1 (50%/8%)	1 (100%/10%)	0 (0%/0%)	0 (0%/0%)
Genotype 3	4 (57%/15%)	3 (60%/17%)	0 (0%/0%)	1 (100%/17%)
Genotype 4	5 (19%/7%)	3 (23%/8%)	2 (22%/9%)	0 (0%/0%)

Abbreviations: AHC, acute hepatitis C; ALT, alanine aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PegIFN, Peg-interferon; RNA, ribonucleic acid; SVR, sustained virologic response.

[a]Cohort A gathers patients enrolled into the observational European AHC cohort of the European AIDS Treatment Network; Cohort B gathers patients prospectively recruited in 3 centers in Paris and followed for 15 months; Cohort C is composed of patients from the HIV clinic of Saint-Antoine Hospital, Paris, who presented with AHC during HIV follow-up. Measures are given as means; interquartile ranges are provided in parentheses.

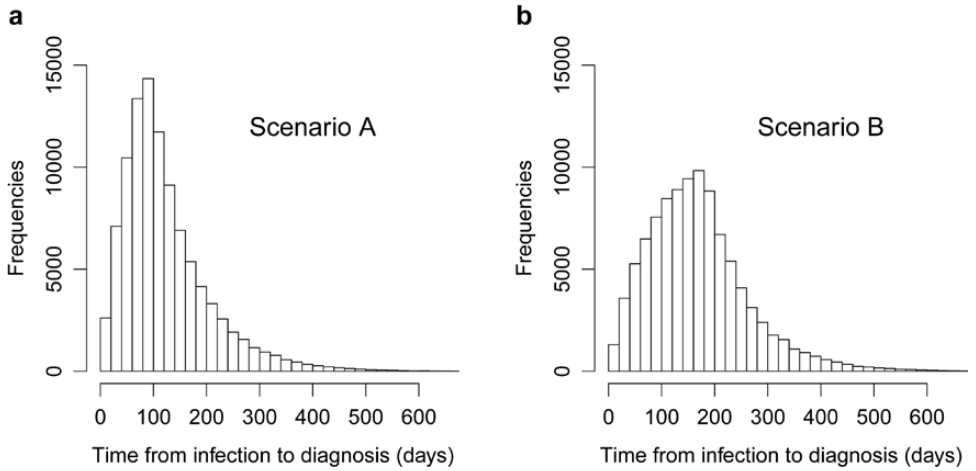

Figure 2. Distributions of the times from infection to diagnosis. Routine visits of human immunodeficiency virus-positive patients are assumed to occur every 3 months in scenario A (a) and every 6 months in scenario B (b).

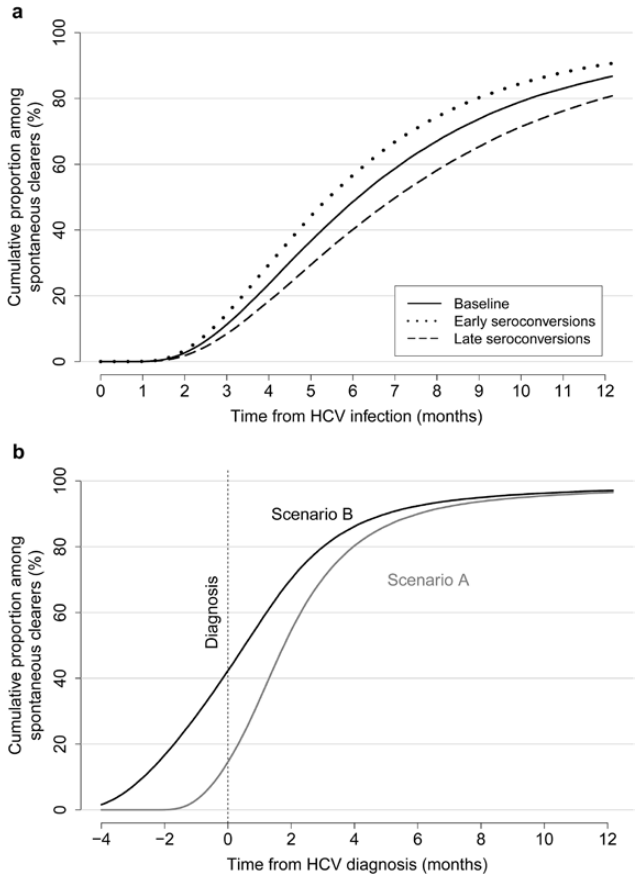

Figure 3. Cumulative frequency of spontaneous clearance occurrence among spontaneous clearers over time. (a) The time reference is the date of hepatitis C virus (HCV) infection. The solid line represents the baseline analysis, whereas the dotted line represents the scenario A1 (only early seroconverters), and the dashed line represents the scenario A2 (only delayed seroconverters). (b) The time reference is the date of HCV diagnosis. The gray line shows the results for the scenario A (every 3 months routine visits of human immunodeficiency virus [HIV]-positive patients), whereas the black line corresponds to the scenario B (every 6 months routine visits of HIV-positive patients). The vertical dashed line indicates the date of HCV diagnosis.

Sensitivity Analysis

Under the early seroconversion scenarios, diagnosis occurred after a median duration of 103 days (IQR, 68–158) when HIV-positive patients were seen every 3 months (scenario A1) or 158 days (IQR, 102–215) of infection when HIV-positive patients were seen every 6 months (scenario B1). When considering the delayed seroconversion scenarios, these median durations reached 133 (IQR, 83–220) and 187 (IQR, 123–274) days for scenarios A2 and B2, respectively (Figure 3a). Results on the time from infection to diagnosis, time from infection to SC, and time from diagnosis to SC are also presented in Table 2.

DISCUSSION

Our study highlights 2 main findings concerning AHC infection in HIV-infected individuals. First, we suggest that diagnosis of HCV often occurs late because half of the cases are detected more than 4 months after HCV infection when HIV-infected patients are screened every 3 months for ALT levels. This delay in diagnosis reaches a median of 6 months when patients are screened every 6 months. Next, we demonstrate that in HIV-HCV coinfected individuals, half of the SCs occur after more than 6 months of infection and that a substantial proportion of SCs (13%) even appear after more than 1 year of infection.

Many HIV-infected patients in whom acute HCV infection occurs are under antiretroviral therapy and therefore present an undetectable HIV-VL. Consequently, a high proportion of HIV-infected individuals do have unprotected sex, especially MSM [22, 23]. This population is now identified as at high risk of acquiring sexually transmitted infections in general and hepatitis C in particular [24, 25].

Our results suggesting late diagnosis of HCV raise important concerns about the screening of HCV infection in HIV-infected individuals. In particular, they highlight the importance of performing frequent ALT measures, especially in groups known to be at higher risk of HCV such as HIV-infected MSM. It also remains critical that such screenings are completed with further investigation of HCV infection using HCV serology and HCV-RNA testing in case of ALT elevation. However, the frequency of these visits as well as the nature of the tests performed and the threshold considered to define ALT elevation should be evaluated through a formal cost-effectiveness analysis. Such an evaluation may be critical as recent guidelines for HIV-infected patients care recommend less and less frequent follow-up visits, with frequencies that depend on the patients' clinical status and CD4 cell count but not on their risk of exposure to HCV and other sexually transmitted infections [26, 27].

Our results concerning the possibility of very late elimination of HCV are supported by previous studies [28, 29]. In particular, Vispo et [29] al demonstrated that 24% of SCs occurred after 1.3 years of HCV infection in their cohort of HIV-infected individuals. The fact that HIV-HCV coinfected patients who spontaneously clear HCV infection are likely to do so in the late stages of HCV infection supports the "wait and see" strategies regarding treatment initiation at an individual level. Indeed, even in the era of highly effective direct-acting antiviral regimens, this approach could avoid the use of expensive drugs. However, such strategies can only be envisaged provided that the patient is aware of his infectiousness and that preventive measures are taken to avoid transmission. In general, one may consider that wait and see strategies for treatment initiation may not be efficient at a population level because of the risk of transmission during this period, whereas treating earlier is likely to decrease the risk of HCV transmission.

It is important to remember that our results concerning the chances of SC are presented as a cumulative distribution of dates among spontaneous clearers only and not among the entire infected population. The probability of SC for the patient was

Table 2. Results of the Baseline and Sensitivity Analysis[a]

Scenario	Visits Frequency	Median Time From Infection to Diagnosis (Days)	Median Time From Infection to SC (Days)	Median Time From Diagnosis to SC (Days)
Baseline				
Scenario A	3 months	115 (72–180)	184 (123–276)	54 (17–102)
Scenario B	6 months	170 (110–235)	184 (123–276)	17 (−38 to 73)
Sensitivity analysis				
Scenario A1	3 months	103 (68–158)	163 (111–242)	49 (15–95)
Scenario B1	6 months	158 (102–215)	163 (111–242)	12 (−42 to 67)
Scenario A2	3 months	133 (83–220)	210 (138–321)	58 (21–111)
Scenario B2	6 months	187 (123–274)	210 (138–321)	21 (−35 to 79)

Abbreviations: HIV, human immunodeficiency virus; SC, spontaneous clearance.

[a]The visits frequency corresponds to the time interval between 2 visits in the usual follow-up of an HIV-positive individual. The scenarios A1 and B1 consider only early seroconverters, whereas scenarios A2 and B2 consider only delayed seroconverters. Interquartile ranges are provided in parentheses.

not estimated in our study, but previous works indicated that approximately 15%–20% of HIV-HCV coinfected individuals clear infection spontaneously [13, 30, 31]. However, these probabilities might constitute underestimates of the overall chance of SC because patients generally receive therapy while they might potentially still have a chance to spontaneously clear the HCV infection. Besides, it was demonstrated that the probability of SC depends on host characteristics such as polymorphism upstream of interleukin-28B (IL28B) [32]. Namely, individuals with a type CC for IL28B are more likely to clear the HCV infection spontaneously than those with a type CT or TT. Unfortunately, our data did not allow for further exploration of the impact that IL28B may have on the dynamics of acute HCV because this information was available in only 9% of the patients.

In our sensitivity analysis, we demonstrated that time to SC significantly depends on the scenario regarding the time to seroconversion. In particular, we noted that SC occurred approximately 50 days earlier when considering the scenario of early seroconversion compared with the scenario of late seroconversion. The early seroconversion scenario could reflect the configuration of HCV monoinfected individuals in whom antibodies appear earlier [28]. Thus, this highlights the fact that our results related to the possibility of very late SC are specific to HIV-HCV coinfection and that they may not directly lead to recommendations concerning the management of HCV monoinfection.

One limitation of our study is that despite the large number of cases (286) in our combined dataset, not all data were used to calibrate the model. Indeed, the required information was not always available due to missing data and because patient details were not reported in the exact same way across the 3 cohorts. Nevertheless, the Bayesian approach, based on the generic statistical model that we used, allowed us to account for the uncertainty linked to the small sample sizes and permitted us to generate patterns that were not effectively observed in the data.

Another limitation is that we modeled HCV-RNA level over time using a model that is based on successive specific phases. In the real world, viral kinetics may in fact present infinity of particularities that could not be reproduced by a model. However, the stochastic approach used to generate the parameter values certainly provides a reliable insight. Similarly, we only considered 2 scenarios regarding the interval between 2 follow-up visits for HIV-infected individuals (3 months and 6 months), whereas in the real world this duration may be different and not fixed even for a same patient. Nevertheless, this approach was sufficient to highlight the importance of settling on frequent visits to limit the delay in HCV diagnosis.

CONCLUSIONS

In conclusion, our study demonstrates that diagnosis of acute HCV infection often occurs late, and it therefore suggests that screening for HCV in HIV-infected individuals should be performed frequently, in particular in patients at risk of transmitting HCV such as MSM. Our model also shows that a nonnegligible proportion of SC is observed at an advanced stage of HCV infection (more than 6 months), supporting the wait-and-see strategy for treatment initiation at an individual level but probably not at a population level because of the risk of transmission during this period.

Supplementary Data

Supplementary material is available at *Open Forum Infectious Diseases* online.

Acknowledgments

Author contributions. R. R., S. D.-B., and Y. Y. designed the study. C. B., J. K. R., M. G., and K. L. gathered the individual data. R. R., S. D.-B., and J. G. designed the model. R. R. coded the model. All authors interpreted the results. R. R., S. D.-B. and Y. Y. wrote the first draft of the manuscript. All authors reviewed and approved the final report.

Potential conflicts of interest. S. D.-B. served as a speaker for Bristol-Myers Squibb, Gilead, and Janssen, acted as a consultant for Abbvie, Bristol-Myers Squibb, Gilead, HEVA, Janssen, MSD, and Public Health Expertise, and received research funding from Janssen and MSD. C. B. received honoraria for consulting or educational lectures from abbvie, BMS, Gilead, MSD, and ViiV. J. G. acted as a consultant for Gilead. Y. Y. served as a speaker and as a consultant for Abbott, Bristol-Myers Squibb, Gilead, MSD, Roche, Tibotec, and ViiV Healthcare.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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