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Estimating past hepatitis C infection risk from reported risk factor histories: implications for imputing age of infection and modeling fibrosis progression

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Abstract

Background
Chronic hepatitis C virus infection is prevalent and often causes hepatic fibrosis, which can progress to cirrhosis and cause liver cancer or liver failure. Study of fibrosis progression often relies on imputing the time of infection, often as the reported age of first injection drug use. We sought to examine the accuracy of such imputation and implications for modeling factors that influence progression rates.

Methods
We analyzed cross-sectional data on hepatitis C antibody status and reported risk factor histories from two large studies, the Women’s Interagency HIV Study and the Urban Health Study, using modern survival analysis methods for current status data to model past infection risk year by year. We compared fitted distributions of past infection risk to reported age of first injection drug use.

Results
Although injection drug use appeared to be a very strong risk factor, models for both studies showed that many subjects had considerable probability of having been infected substantially before or after their reported age of first injection drug use. Persons reporting younger age of first injection drug use were more likely to have been infected after, and persons reporting older age of first injection drug use were more likely to have been infected before.

Conclusions
In studies of fibrosis progression, modern methods such as multiple imputation should be used to account for the substantial uncertainty about when infection occurred. The models presented here can provide the inputs needed by such methods. Using reported age of first injection drug use as the time of infection in studies of fibrosis progression is likely to produce a spuriously strong association of younger age of infection with slower rate of progression.
Background

Chronic hepatitis C virus (HCV) infection is prevalent both in the United States, with perhaps 3 million persons infected (1), and worldwide (2). It often causes progressive hepatic fibrosis. This can eventually become cirrhosis, causing hepatocellular carcinoma, liver failure, a need for liver transplant, or death. Fibrosis measured by liver biopsy is believed to provide the most accurate measurement of the extent of liver damage (3). Considerable effort has been devoted to estimating risk factors for infection (4-13), as well as rates of progression through fibrosis stages to cirrhosis (14-21). Studies of HCV progression often utilize liver biopsies from persons who may have been originally infected many years or decades earlier. The exact time of infection is often unknown, so the subjects’ self-reported risk factor histories are used to impute a presumed time of infection. A common practice is to assume that infection occurred at the time of first reported injection drug use (IDU) (14, 19, 22). Studies of infection risk factors support this practice to a limited extent by showing that IDU is a strong risk factor (4, 5, 7, 8, 12). Here, we assess in more detail how accurate such imputation is likely to be. We utilize cross-sectional HCV antibody status data and self-reported risk-factor histories, similar to the situation in progression studies where time of infection must be imputed. In contrast to the usual statistical modeling in risk factor studies, which utilizes logistic regression with potential risk factors modeled as fixed covariates, we use survival analysis methods with time-varying covariates. This is possible even though every observation is either left-censored (infection occurred at some unknown time in the past) or right censored (infection has not yet occurred). An advantage of this approach is that it permits reconstruction of past risk year by year, which facilitates assessment of possible biases or inaccuracies in the usual imputation strategy, along with the implications for modeling of factors that influence fibrosis progression.

Methods

Study population

We analyzed data from two large studies that performed HCV antibody (anti-HCV) testing and collected subject reports concerning history of IDU. The Women’s Interagency HIV Study (WIHS), as previously described (23, 24), includes women with or at risk for HIV infection. This study performed anti-HCV testing of initial participants, mainly in 1994-1995, and additional participants who were recruited in 2001-2002. The results used here were obtained using a second generation HCV enzyme immunoassay for most subjects, with a few of the newer recruits having data from a third generation test. The Urban Health Study (UHS) was composed of street-recruited injection drug users in the San Francisco Bay Area and has also been described previously (25-27). Participants included here were recruited from 1987 to 2002, and second generation anti-HCV testing was performed for specimens from 1987 and from 1998-2002, as well as the initial specimens regardless of year for all subjects who reported IDU duration of <10 years. For our analyses of both studies, we included only the first anti-HCV result from each participant and did not include any subsequent longitudinal follow up. This was to reduce cohort participation bias (12, 28, 29), and to approximate the common situation of patients presenting with chronic HCV infection with no prior HCV test results. We also required that subjects have valid data on: sex; race; HIV antibody; ages of first and last IDU, if any; age and calendar year of HCV test; and for those with a history of IDU, whether they typically injected every day. For UHS, we assumed that subject’s current injection frequency was typical of their entire IDU history, while WIHS subjects were asked to report typical frequency when they were injecting. Histories of needle sharing practices were not collected in either study. Because needle sharing behavior may have changed substantially over time due to the emergence of HIV and subsequent efforts to prevent its
spread, current sharing would not be an adequate surrogate for past practices; we therefore did not assess this risk factor. Data on blood transfusion history was not required for inclusion in our analyses because it was only partially ascertained in WIHS (transfusions in the years 1975-1985, only among those recruited in 1993-94) and was not collected in UHS.

Statistical methods

The available data indicate only whether or not each subject was infected with HCV at some point in the past, a form of information known in the statistical literature as current status data (30-33). We used maximum full likelihood to fit parameters of discrete-time survival models, using year of age as the time scale. Beginning with age 1 (where risk was very small in all models), the log-odds of HCV infection given no previous infection was modeled as a linear function of covariates that pertained to that year, including age, calendar year, and whether the subject used injection drugs during that year. The fitted log-odds were then converted to hazards and combined across years to obtain a predicted probability of being HCV seropositive at the age tested. The NLMIXED procedure in the SAS statistical package (version 9.1, SAS Institute, Cary, NC) was used to obtain the parameter estimates that maximized the resulting likelihood, along with their confidence intervals (CI) and p-values. This approach is similar to Cox’s discrete-time partial likelihood model (34), except that the role of time (in this case age) is modeled instead of being conditioned out in a partial likelihood. It can also be considered a form of pooled logistic regression (35) with a parsimonious model for the effect of time instead of an unstructured model. Estimated effects of covariates are presented as odds ratios (OR’s). We provide in Additional File 1 the SAS NLMIXED code for fitting one of the models presented below.

Because HCV risk associated with IDU may vary depending on duration of IDU (7, 12, 36), we defined separate time-varying indicator variables for the first year of use, the second or third year, and the fourth or greater year. In defining the hazard at each age, we assumed that IDU began in the middle of the reported age of first use; instead assuming that IDU began at the beginning produced qualitatively similar results, but may be a less accurate assumption. We also examined further breakdown of duration into fourth to tenth year versus 11th or greater year. For the time-varying numeric covariates age and calendar year, we examined linear models, quadratic models, and more flexible models based on parametric cubic splines defined by the ns() function in S-Plus (Insightful Corporation, Seattle, WA), choosing a model by likelihood ratio testing of nested alternatives. We examined plausible interactions one at a time by adding the product of the two predictors to the model with main effects only. To limit the complexity of interactions with IDU, we assumed common interactions for the first, second-third, and fourth or greater years of IDU.

We used the fitted multivariate models to calculate estimated distributions of age at HCV infection given each subject’s age at first positive HCV antibody test and reported risk factor profile. For each subject and each possible age of infection, this produced a probability that infection occurred at that age. To compare these to the usual imputation of age at HCV infection as the age of first IDU, we calculated the mean age at infection from the estimated probabilities and calculated the usual imputation’s bias as the age of first IDU minus this mean. We also calculated the probability that infection occurred at the age of first IDU or the next year, considering this to be the probability that the usual imputation would be reasonably accurate.

Results

Descriptive summaries

The characteristics of 2248 WIHS participants and 4623 UHS participants analyzed in this study are summarized in Table 1. Both studies contain sufficient numbers of HCV seropositive and
seronegative subjects to permit analysis of risk factors, but there are substantial differences between
the studies due to different target populations and inclusion criteria. Although WIHS enrolled 3766
women, IDU history was only assessed in enough detail for the present study 8 years after initial
enrollment. At that time, 2318 women provided information on ages of IDU, if any, and 70 of these
(3.0%) were excluded for lack of valid data on other key variables. Of 4734 potential UHS
participants, 111 (2.3%) were excluded due to lack of valid data on key variables.

Table 2 shows detailed data on HCV prevalence by total duration of IDU in the two studies. This shows increasing prevalence of HCV seropositivity even at long durations, suggesting continuing
risk among those who avoid infection early on. This also suggests that not everyone who is infected
with HCV due to IDU is infected in the first year, as is commonly assumed.

Models for HCV infection risk

Multivariate models of HCV risk for WIHS and UHS are shown in Table 3 and Figure 1. The
estimated background risk for these models was 0.0051 (95% CI 0.0028 to 0.0091) for WIHS and
0.034 (95% CI 0.021 to 0.055) for UHS. This is the fitted probability of being infected with HCV over
the course of a year at age 30 in 1975 for a previously HCV-uninfected, non-injecting, HIV-uninfected
Caucasian female in the San Francisco area. Fitted probabilities for other situations and types of
subjects are obtained by applying the OR’s shown in Table 3 and Figure 1 to these background rates.
Both cohorts produced some qualitatively similar results, including decreased risk at younger ages and
more recent calendar years, as well as highest risk in the first year of IDU. Despite these similarities,
there were too many quantitatively substantial differences to permit a simple model of both studies
pooled. These include the background risk when not injecting, the shape of the drop in risk as duration
of IDU increases, the role of daily IDU, the strength of the influence of age, and racial/ethnic
associations. The model shown in Figure 1b for UHS is a parametric spline with knots at 1980, 1990,
and 1995, because this provided an improved fit to the data compared to a quadratic model (p=0.0028),
even though its overall shape is roughly quadratic. The other curves in Figure 1 are all quadratic,
because these improved substantially over linear models (WIHS p=0.0003 for age and p=0.0054 for
calendar year; UHS p=0.018 for age), but parametric splines with up to 4 parameters did not appear to
substantially improve the fits further (all p>0.22).

We examined a number of possible additions or refinements to the models shown. Including
blood transfusion history in the WIHS model would result in losing 995 subjects with missing data for
this variable, and it did not appear to be an important predictor (OR 1.10, 95% CI 0.74 to 1.65,
p=0.64). Allowing for differing effects of age when injecting versus not injecting did not produce
substantially better fits to the data (WIHS p=0.38, UHS p=0.21 by likelihood ratio tests). Other
interaction terms examined included calendar year by IDU (WIHS p=0.64, UHS p=0.39), year by age
(WIHS p=0.37, UHS p=0.065), race by IDU (WIHS p=0.13, UHS p=0.29), and sex by IDU (UHS
p=0.54). We also examined models with IDU effects differing for the 4th to 10th years of IDU versus
beyond the 10th (WIHS p=0.33, UHS p=0.17). We note that the confidence intervals were not narrow
enough to rule out potentially important interactions, but in the absence of strong evidence for such
interactions we focus on the simpler models without them. One interaction that did reach statistical
significance was IDU by location in the WIHS study (p=0.029 overall). This was mainly due to IDU
being estimated to be less risky in the Bronx (IDU OR’s estimated to be smaller by a factor of 0.38,
95% CI 0.16 to 0.91) and Brooklyn (OR’s smaller by a factor of 0.42, 95% CI 0.16 to 1.14). The OR’s
for the main effects of these locations were higher when the interaction was included than those shown
in Table 3 (Bronx OR 2.3, Brooklyn OR 1.41). These differences make the Bronx and Brooklyn more
similar to the UHS model, with lower OR’s for IDU and a higher background risk. Nevertheless, the
OR for the first year of IDU in the Bronx remains nearly 3-fold larger than that in the UHS model.
Because we already show details for the UHS model, we do not provide any further details on this
WIHS model with interaction terms.
Reconstruction of yearly past infection probabilities for those infected

Table 4 summarizes the models’ fitted past risks for a number of situations and compares these to the age of first IDU, the usual imputed age at HCV infection. Scenarios 1-4 illustrate the impact of different ages at time of HCV antibody test and first IDU, while the remaining scenarios are based on extreme situations observed in the actual data sets. The alternatives at the bottom of the table illustrate the relatively minor impacts of different locations in WIHS and of male sex in UHS. Among all HCV seropositive subjects with IDU history, the median fitted probability that HCV infection occurred the year of first IDU or the next year was 0.77 for WIHS (range 0.23 to 0.93) and 0.56 for UHS (range 0.01 to 0.82). The lower values for UHS reflect its higher estimated background risk when not injecting and smaller OR’s for the effect of IDU (Table 3). When averaged over all subjects, mean bias was less than 1 year in both studies, because age of first IDU was sometimes too early and sometimes too late. There was, however, a strong correlation of bias with age of first IDU; the Pearson correlation was 0.78 (95% CI 0.73 to 0.81) in WIHS and 0.83 (95% CI 0.82 to 0.84) in UHS. Figure 2 illustrates this association.

Discussion

Using modern statistical methods and large data sets, we were able to obtain models for HCV infection risk that can be used to produce year-by-year estimates of past infection risk. Similar to many epidemiological studies, we found high risk in the first year of IDU (4, 5, 7, 8, 12) and decreasing risk in recent calendar years (22, 37-40). For a patient or research subject newly discovered to be HCV-infected, these models permit calculating the estimated probability that infection occurred at each year in the past based on IDU history and other characteristics. For the subjects studied here, results of such calculations suggest that the common assumption that infection occurred at the reported age of first IDU is unreliable.

Some implications for modeling of fibrosis progression

Although the average difference between reported age of first IDU and the fitted mean infection times from the models was small for both WIHS and UHS, this does not imply that modeling of fibrosis progression will be accurate if it assumes infection at age of first IDU. Large errors in one direction cancelled large errors in the other, and there was usually a considerable chance that infection occurred before or after the first reported year of IDU. Such uncertainty necessitates a multiple imputation strategy (41) or other advanced statistical method to avoid both biased estimates and inappropriately narrow confidence intervals. Most importantly, the strong correlation of errors with age at first IDU implies that the usual imputation can lead to spurious associations of fibrosis progression with age at first IDU. For example, consider one patient matching scenario 1 in Table 4 who shows Metavir (42) fibrosis stage 4 (cirrhosis) by liver biopsy at age 40, and another patient matching scenario 3 who shows fibrosis stage 2 at age 40. If we calculate progression rate as observed stage divided by duration of infection (14), we get very different comparisons depending on what we assume about age of infection. Using age of first IDU, the patient with first IDU at age 12 has a rate of 0.143 fibrosis points per year, while the one with first IDU at age 35 has a rate of 0.400, nearly three times as fast. But using the fitted means from the UHS model completely eliminates this difference, producing rates of 0.161 and 0.148.

The above bias toward making earlier age of HCV infection look spuriously protective against rapid progression is further compounded by other sources of bias. Many clinic-based progression studies have utilized patients whose HCV infection is discovered due to related symptoms. This may exaggerate progression rates compared to the entire population of HCV-infected persons (18), but it can also produce a spurious protective effect of earlier age of infection. Consider 4 persons who all would develop symptoms and have their HCV infection discovered once they reach fibrosis stage 3.
Two are fast progressors who reach stage 3 in 15 years, one infected at age 15 and one at age 40. The other two are slow progressors who will reach stage 3 in 45 years, again with one infected at age 15 and one at age 40. Among these 4 persons, progression is not associated with age at infection. Nevertheless, mortality risk unrelated to HCV makes the slow progressor infected at age 40 much less likely than the one infected at age 15 to ever be included in a clinic-based study, while the difference in unrelated mortality risk for the fast progressors is considerably less. This differential selection pressure implies that in clinic-based studies slow progressors will be under-represented among those infected at older ages compared to those infected at younger ages, producing an apparent protective effect of younger age at infection.

A third difficulty is distinguishing a fixed effect due to age at infection from a time-varying effect that changes as a patient ages. For example, progression may accelerate with increasing age so that the rate of progression is 2-fold faster at age 60 than it would be at age 30, given the same duration of disease and other characteristics. Those infected at younger ages would then have more of their disease course occur at younger ages when progression is slower, causing them to progress more slowly overall even if age at infection itself has no direct effect and even though they experience the same acceleration once they reach older ages. This again could produce a misleading protective effect of younger age at infection. Carefully distinguishing a fixed versus time-varying role for age in fibrosis progression will likely require multi-state modeling algorithms (20) that allow for time-varying covariates, which are currently not available. An analysis of similar issues concerning the role of age in variant Creutzfeldt-Jakob disease (43) required customized analysis to reveal that previous analyses had reached apparently mistaken conclusions. Similar efforts may be worthwhile for HCV.

Limitations

The current status data available in this cross-sectional study are less informative than knowing exact times of HCV infection from a longitudinal study, but the large sample sizes allowed our methods to produce models with many plausible features, reasonably narrow confidence intervals, and many small p-values. Importantly, this cross-sectional situation matches that of many progression studies where subjects are found to be chronically HCV infected without any direct information on when they became infected (14-21). Although potentially counterintuitive, this type of data does permit estimation of effects of calendar time before the year of the first HCV antibody test and of the background risk without IDU despite the lack of anyone with no IDU in the UHS study. This is because the current status data provide information about cumulative risk over all years before the measurement of the outcome, and because we had considerable variation in the ages, calendar years, and durations of IDU at the time of HCV antibody testing. For example, information on background risk when not injecting can be obtained by comparing the HCV prevalence of persons with 1 year of IDU tested at age 20 versus persons with 1 year of IDU tested at age 40, because they have different amounts of non-IDU time. This comparison also provides information on the risk of the first year of IDU, because this is the risk the two groups have in common after the difference in background risk is accounted for. Our analyses synthesize many such comparisons to produce the estimates.

The self-reported risk factor histories we have used may be inaccurate, due to inaccurate recall or social desirability bias. Indeed, some (or most) of the apparent background risk of infection in the absence of IDU could be due to inaccurate recall or report of ages of IDU. Some of the 8.6% prevalence of HCV seropositivity among WIHS subjects reporting no IDU could reflect infections caused by forgotten or unreported IDU. More importantly, the estimated risk in the absence of IDU is very high in UHS, much higher than in WIHS, reaching incidence of 3.4% per year for the riskiest calendar year and riskiest age. This is reflected in Figure 2b, where 31% of the predicted mean infection ages are before the reported age of first IDU (points above the horizontal line). Utilizing the entire fitted distributions instead of just the predicted means, we obtained an estimate of 17% of UHS subjects being infected before their reported age of first IDU. Although there is likely to be some risk
in the absence of IDU, particularly in this high-risk population, and one study found a similarly high prevalence of HCV infection among users of non-injection drugs [44], we believe that much of the risk predicted by the model may reflect inaccurate reporting of ages of first IDU. Thus, our models’ fitted background risks may reflect risk in the absence of reported IDU, but they may be inaccurate estimates of risk when there really is no IDU. Fortunately, this fits with our primary purpose of studying imputation of age of infection based on reported risk factor history, which is what must often be done in studies of fibrosis progression. For this purpose, it is irrelevant whether risk of infection before reported age of first IDU results from non-IDU sources of risk or from unreported IDU. In either case, imputation may be inaccurate.

One aspect that does not match the situation in progression studies is the use of HCV serology as the outcome. The reconstructed yearly risks summarized in Table 4 and Figure 2 are conditional on HCV seropositivity instead of being conditional on confirmed chronic HCV infection (by HCV RNA), which will be the case in progression studies. The proportion of HCV seropositive persons who clear the virus and become HCV RNA- is thought to be about 20% overall (45) and 15% among HIV-infected persons (46). A model of clearance probabilities utilizing age and other characteristics could in principle be synthesized with the models presented here to produce more relevant reconstructed past infection probabilities that are conditional on chronic HCV infection. In addition, some chronically HCV infected persons may test HCV seronegative, particularly by the second generation assay mainly used here. In one study of HIV-infected persons, 37 of 617 (6%) with HCV infection were observed to be HCV negative by second generation antibody assay (46). We note that some of these 37 cases may have been recently infected and not yet produced antibodies, which would not be typical of subjects in HCV progression studies. Exposure to HCV that results in neither chronic infection nor HCV seropositivity (47) does not affect the validity of our results, because such events do not initiate progression of HCV-related liver damage and are correctly treated as such in our analyses.

Being HIV positive was included as a fixed risk factor in multivariate models, because the timing of HIV infection was not known for most HIV-infected subjects. This assumption could make sense if HCV risk associated with being HIV infected was mainly due to other risk factors (such as membership in a risky social network) that are not directly available for modeling but are associated with HIV infection and were present even before HIV infection. If the mechanism of HIV-associated risk is directly causal, such as greater susceptibility to HCV when HIV infection is already present, then this effect would not be present before HIV infection occurred. In this case, our estimates based on HIV as a fixed risk factor would be attenuated compared to what would be estimated if the timing of past HIV infection were known.

Despite many qualitative similarities, the differences between the WIHS and UHS models leave considerable uncertainty about how to impute ages of infection for a progression study. Because inclusion of WIHS participants required retention in the study until IDU history was assessed, these may be less similar than UHS participants to cross-sectional progression study participants, while perhaps being more similar to subjects who are retained in longitudinal follow-up. A very desirable design would be a large cross-sectional study ascertaining chronic HCV infection and risk factor histories, followed by fibrosis progression measurement in those found to be HCV-infected. Infection models fit to the cross-sectional data would then be directly applicable to the progression modeling. In the absence of such directly relevant models of past risk, a sensible strategy may be to perform sensitivity analyses using both models presented here, along with the usual imputation based on first year of IDU. In addition, within each model different specific choices about whether to include and how to model each predictor, as well as whether to include some interaction terms, could in some cases be reasonable. This adds additional uncertainty about specific imputations, but additional uncertainty only adds further support for our conclusion that the common single-imputation strategy is dangerous.
Conclusions

We have shown that there is usually considerable uncertainty about when HCV infection may have occurred, even for patients or research subjects reporting a history of IDU. This should be accounted for in progression studies, preferably using modern methods such as multiple imputation (41). To facilitate use of such methods, we provide, in Additional File 2, code that produces individuals’ past infection probabilities year by year. Use of single imputation can not only produce confidence intervals that are too narrow and p-values that are too small, but also severely biased estimates of covariate effects. In particular, the usual strategy of imputing age of HCV infection as the age of first reported IDU is likely to produce bias toward finding slower progression associated with younger age of infection. This bias could be further exacerbated by differential selection effects according to age of infection, and by time-varying effects of current age being mis-modeled as fixed effects of age at infection. Some or all of the protective effect of younger age at infection (14, 19) found in cross-sectional studies of fibrosis progression could therefore be spurious.

Competing interests
None declared.

List of abbreviations used

CI – confidence interval
HCV – hepatitis C virus
HIV – human immunodeficiency virus
IDU – injection drug use
OR – odds ratio
RNA – ribonucleic acid
UHS – San Francisco Urban Health Study
WIHS – Women’s Interagency HIV Study

Competing interests
None declared.

Authors' contributions
PB conceived of the study, performed all analyses, and drafted and revised the manuscript. PCT, ECS, and MHA participated in the performance of the WIHS study and revised the manuscript for critical scientific content. TRO and MPB promoted and facilitated the performance of HCV testing in the UHS and revised the manuscript for critical scientific content. AHK and BRE led the performance of the UHS study, and revised the manuscript for critical scientific content. In addition, BRE raised issues leading to the conception of this study. All authors read and approved the final manuscript.
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Table 1. Characteristics of WIHS and UHS subjects analyzed for this study.

| Characteristic                  | N in category (% of total) |
|--------------------------------|----------------------------|
|                                | WIHS (N=2248) | UHS (N=4623) |
| HCV seronegative               | 1666 (74.1%)  | 576 (12.5%)  |
| HCV seropositive               | 582 (25.9%)   | 4047 (87.5%) |
| Year of HCV test               |               |              |
| 1987-1992                      | 0 (0.0%)      | 572 (12.4%)  |
| 1993                           | 29 (1.3%)     | 48 (1.0%)    |
| 1994                           | 844 (37.5%)   | 47 (1.0%)    |
| 1995                           | 306 (13.6%)   | 57 (1.2%)    |
| 1996                           | 2 (0.1%)      | 62 (1.3%)    |
| 1997                           | 4 (0.2%)      | 37 (0.8%)    |
| 1998                           | 76 (3.4%)     | 862 (18.6%)  |
| 1999                           | 15 (0.7%)     | 995 (21.5%)  |
| 2000                           | 24 (1.1%)     | 904 (19.6%)  |
| 2001                           | 635 (28.2%)   | 907 (19.6%)  |
| 2002                           | 313 (13.9%)   | 132 (2.9%)   |
| Age at HCV test                |               |              |
| <20                            | 58 (2.6%)     | 67 (1.4%)    |
| 20-29                          | 593 (26.4%)   | 488 (10.6%)  |
| 30-39                          | 1048 (46.6%)  | 1200 (26.0%) |
| 40-49                          | 486 (21.6%)   | 1925 (41.6%) |
| 50-59                          | 58 (2.6%)     | 810 (17.5%)  |
| 60+                            | 5 (0.2%)      | 133 (2.9%)   |
| Female                         | 2248 (100%)   | 1409 (30.5%) |
| Male                           | 0 (0%)        | 3214 (69.5%) |
| Race/Ethnicity                 |               |              |
| Caucasian                      | 275 (12.2%)   | 1684 (36.4%) |
| African American               | 1277 (56.8%)  | 2232 (48.3%) |
| Hispanic                       | 615 (27.4%)   | 401 (8.7%)   |
| Other                          | 81 (3.6%)     | 306 (6.6%)   |
Table 1. (Continued)

| Characteristic                  | WIHS (N=2248) | UHS (N=4623) |
|--------------------------------|---------------|--------------|
| Area                           |               |              |
| San Francisco                  | 340 (15.1%)   | 4623 (100%)  |
| Bronx                          | 459 (20.4%)   | 0 (0%)       |
| Brooklyn                       | 429 (19.1%)   | 0 (0%)       |
| Washington, DC                 | 320 (14.2%)   | 0 (0%)       |
| Los Angeles                    | 397 (17.7%)   | 0 (0%)       |
| Chicago                        | 303 (13.5%)   | 0 (0%)       |
| HIV-infected                   | 1627 (72.4%)  | 787 (17.0%)  |
| Ever IDU                       | 522 (23.2%)   | 4623 (100%)  |
| Age of First IDU               |               |              |
| Before 12                      | 4 (0.8%)      | 123 (2.7%)   |
| 12-15                          | 69 (13.2%)    | 972 (21.0%)  |
| 16-19                          | 163 (31.2%)   | 1520 (32.9%) |
| 20-29                          | 227 (43.5%)   | 1416 (30.6%) |
| 30-39                          | 56 (10.7%)    | 464 (10.0%)  |
| 40+                            | 3 (0.6%)      | 128 (2.8%)   |
| Year of First IDU              |               |              |
| Before 1960                    | 2 (0.4%)      | 198 (4.3%)   |
| 1960-1969                      | 78 (14.9%)    | 1174 (25.4%) |
| 1970-1979                      | 206 (39.5%)   | 1473 (31.9%) |
| 1980-1989                      | 173 (33.1%)   | 1015 (22.0%) |
| 1990-1995                      | 43 (8.2%)     | 459 (9.9%)   |
| After 1995                     | 20 (3.8%)     | 304 (6.6%)   |
| Daily IDU                      | 341 (65.3%)   | 2992 (64.7%) |


Table 2. HCV Antibody status by duration of injection drug use (IDU) at time of testing.

| Duration of IDU | HCV seropositive/Total (%) | WIHS | UHS   |
|-----------------|----------------------------|------|-------|
| None            | 148/1726 ( 8.6%)           |      |       |
| 1 year          | 5/9 (55.6%)                | 59/151 (39.1%) |       |
| 2 years         | 5/8 (62.5%)                | 56/104 (53.8%) |       |
| 3 years         | 6/11 (54.5%)               | 59/104 (56.7%) |       |
| 4-5 years       | 13/20 (65.0%)              | 138/209 (66.0%) |       |
| 6-7 years       | 15/21 (71.4%)              | 148/202 (73.3%) |       |
| 8-10 years      | 33/43 (76.7%)              | 275/335 (82.1%) |       |
| 11-15 years     | 84/102 (82.4%)             | 360/439 (82.0%) |       |
| 16-20 years     | 91/109 (83.5%)             | 497/556 (89.4%) |       |
| 21-30 years     | 167/184 (90.8%)            | 1345/1394 (96.5%) |       |
| >30 years       | 15/15 (100%)               | 1110/1129 (98.3%) |       |
Table 3. Multivariate models of HCV infection risk.

| Variable                                | Women’s Interagency HIV Study | San Francisco Urban Health Study |
|-----------------------------------------|-------------------------------|----------------------------------|
|                                         | Odds Ratio | 95% CI | p    | Odds Ratio | 95% CI | p    |
| Injection drug use (versus not injecting)|                       |     |     |            |     |     |
| 1st year of use                         | 310        | 163 to 588 | <0.0001 | 61        | 21 to 177 | <0.0001 |
| 2nd & 3rd year                          | 163        | 65 to 404 | <0.0001 | 9.8       | 1.94 to 50 | 0.0058  |
| 4th or later year                       | 7.2        | 2.1 to 24.2 | 0.0015  | 5.2       | 3.2 to 8.4 | <0.0001 |
| Daily IDU (versus less frequent IDU)    | 1.14       | 0.73 to 1.77 | 0.57    | 1.59      | 1.40 to 1.81 | <0.0001 |
| Male                                    |            |     |     | 0.76      | 0.67 to 0.85 | <0.0001 |
| Age                                     |            |     |     | <0.0001   | See Figure 1a | 0.0001  |
| Calendar Year                           |            |     |     | <0.0001   | See Figure 1b | <0.0001 |
| Race/ethnicity (versus Caucasian)       |            |     |     |            |     |     |
| African American                        | 1.50       | 1.05 to 2.1 | 0.027   | 0.86      | 0.76 to 0.97 | 0.014   |
| Hispanic                                | 1.64       | 1.09 to 2.5 | 0.018   | 1.44      | 1.15 to 1.81 | 0.0018  |
| Other                                   | 1.38       | 0.66 to 2.9 | 0.40    | 0.94      | 0.76 to 1.16 | 0.57    |
| Area (versus San Francisco)             |            |     |     |            |     |     |
| Bronx                                   | 1.41       | 0.96 to 2.1 | 0.080   |           |     |     |
| Brooklyn                                | 0.90       | 0.58 to 1.39 | 0.63    |           |     |     |
| Washington DC                           | 1.10       | 0.70 to 1.73 | 0.68    |           |     |     |
| Los Angeles                             | 0.80       | 0.51 to 1.26 | 0.33    |           |     |     |
| Chicago                                 | 1.70       | 1.11 to 2.6 | 0.015   |           |     |     |
| HIV infected                            | 1.56       | 1.16 to 2.1 | 0.0030  | 1.27      | 1.09 to 1.47 | 0.0017  |
Table 4. Summaries of fits from multivariate models described by Table 3 and Figure 1. Except as noted, area is San Francisco and sex is female.

| Scenario | Year of Birth | Age of First IDU | Age of Last IDU | HCV Ab+ | Daily IDU | Race/Ethnicity | Probability Accurate* | Age of First IDU Fitted Mean | Bias† | Probability Accurate* | Age of First IDU Fitted Mean | Bias† |
|----------|---------------|------------------|----------------|---------|-----------|----------------|-----------------------|-----------------------------|-------|-----------------------|-----------------------------|-------|
| 1        | 1960          | 12               | 40             | 40      | No        | Caucasian     | 0.38                  | 17.5                        | -5.5          | 0.52                  | 15.2                        | -3.2          |
| 2        | 1940          | 12               | 60             | 60      | No        | Caucasian     | 0.07                  | 29.2                        | -17.2         | 0.18                  | 22.4                        | -10.4         |
| 3        | 1960          | 35               | 40             | 40      | No        | Caucasian     | 0.66                  | 34.7                        | 0.3           | 0.39                  | 26.5                        | 8.5            |
| 4        | 1940          | 35               | 60             | 60      | No        | Caucasian     | 0.74                  | 35.5                        | -0.5          | 0.47                  | 32.3                        | 2.7            |
| 5        | 1943          | 14               | 50             | 52      | Yes       | Hispanic      | 0.30                  | 21.9                        | -7.9          | 0.58                  | 16.2                        | -2.2          |
| 6        | 1943          | 14               | 50             | 52      | No        | Caucasian     | 0.19                  | 25.4                        | -11.4         | 0.33                  | 20.5                        | -6.5          |
| 7        | 1972          | 21               | 22             | 22      | Yes       | Hispanic      | 0.96                  | 21.2                        | -0.2          | 0.71                  | 18.5                        | 2.5            |
| 8        | 1977          | 16               | 18             | 18      | Yes       | Caucasian     | 0.83                  | 16.7                        | -0.7          | 0.81                  | 15.5                        | 0.5           |
| 9        | 1942          | 56               | 57             | 57      | Yes       | African American | 0.09               | 34.3                        | 21.7          | 0.07                  | 31.4                        | 24.6          |
| 10       | 1917          | 15               | 70             | 70      | Yes       | African American | 0.01               | 41.2                        | -26.2         | 0.01                  | 39.4                        | -24.4         |
| 2 – LA‡  | 1940          | 12               | 60             | 60      | No        | Caucasian     | 0.07                  | 29.6                        | -17.6         |                      |                             |               |
| 9 - LA‡  | 1942          | 56               | 57             | 57      | Yes       | African American | 0.09               | 34.4                        | 21.6          |                      |                             |               |
| 2 – Ch§  | 1940          | 12               | 60             | 60      | No        | Caucasian     | 0.09                  | 28.0                        | -16.0         |                      |                             |               |
| 9 - Ch§  | 1942          | 56               | 57             | 57      | Yes       | African American | 0.08               | 34.0                        | 22.0          |                      |                             |               |
| 2 - Male | 1940          | 12               | 60             | 60      | No        | Caucasian     | 0.14                  | 24.1                        | -12.1         |                      |                             |               |
| 9 - Male | 1942          | 56               | 57             | 57      | Yes       | African American | 0.08               | 32.0                        | 24.0          |                      |                             |               |

* Fitted probability that infection occurred in either the year of first IDU or the year after.
† Age at first IDU minus the predicted mean age of infection from the model for that scenario.
‡ Los Angeles area
§ Chicago area
Figure 1. Estimated effects of age and calendar year for the multivariate models of HCV infection risk. WIHS: solid lines; UHS: dashed lines. Vertical bars are pointwise 95% confidence intervals. a) Estimated odds ratios for age. The reference age is 30, where the odds ratio is 1.0 by definition. b) Estimated odds ratios for calendar year. The reference year is 1975, where the odds ratio is 1.0 by definition.
Figure 2. Estimated biases resulting from imputing age at HCV infection as the age of first IDU. Bias is defined here as the age of first IDU minus the fitted mean from the multivariate models described by Figure 1 and Table 3. Circles below the horizontal line represent subjects who are likely to have been infected after their first IDU, while those above represent subjects likely to have been infected before their first IDU. We have added random numbers ranging from -0.4 to +0.4 to the integer ages in order to increase the visibility of distinct points. Included are HCV seropositive subjects with some history of IDU. a) WIHS data, n=434; b) UHS data, n=4047.
Additional files

Additional file 1 – SAS code for fitting a model

This gives the NLMIXED command used to fit the WIHS model described by Table 3 and Figure 1.

* Data set contains variables:
* hcv 1 if anti-hcv positive, 0 if negative
* calcbyr year of birth
* first age first at risk of HCV; 1 in all cases
* last age of anti-hcv antibody test
* agefinjj reported age of first injection drug use, last+1 if none
* agelinj reported age of last injection drug use, last if ongoing
* daily 1 if typical frequency of injection was at least daily, 0 if less
* black 1 if African American, 0 otherwise
* latino 1 if Hispanic, 0 otherwise
* othrace 1 if not Caucasian, AA, or Hispanic, 0 otherwise
* Bronx 1 if WIHS site was the Bronx, 0 otherwise
* Brooklyn 1 if WIHS site was Brooklyn, 0 otherwise
* dc 1 if WIHS site was Washington, DC, 0 otherwise
* la 1 if WIHS site was Los Angeles, 0 otherwise
* Chicago 1 if WIHS site was Chicago, 0 otherwise
* hiv 1 if HIV positive, 0 if negative;

proc nlmixed cov tech=nrridg absgcon=le-9[5] maxiter=100 maxfunc=10000;
* starting values for parameters ;
parms intercept=-5 inj1=0 inj23=0 inj4up=0
   age1=0 age2=0 dailyuse=0 year=0 year2=0
   blackk=0 latin=0 othrac=0 brnx=0 brook=0 atdc=0 atla=0 chicag=0
   hivpos=0;
surv=1;  * surv is the probability of remaining anti-HCV negative ;
* The following contribution to risk applies to every age ;
baselogit=intercept+blackk*black+latin*latino+othrac*othrace +hiv*hivpos + Bronx*brnx + Brooklyn*brook + dc*atdc + la*atla + Chicago*chicag;
do age=first to last; * accumulate risk over ages up to anti-HCV test ;
   yr=calcbyr+age-2000;  * calendar year, relative to 2000 ;
   * add risk contributions due to age and calendar year ;
   logithaz=baselogit+ age1*age+age2*age*age + year*yr+year2*yr*yr;
   if age<agefinj | age>=agelinj then chaz=1/(1+exp(logithaz));
   * chaz is 1 - hazard ;
injterm=dailyuse*daily;
   * Assume IDU started halfway through agefinj ;
if age=agefinj then do;
   chaz1=sqrt(1/(1+exp(logithaz)))); * first half of age, no IDU ;
   chaz2=sqrt(1/(1+exp(logithaz+inj1+injterm))); * IDU in 2nd half ;
   chaz=chaz1*chaz2;
end;
if age=agefinj+1 & age<=agelinj then do; * Similar calculations ;
   chaz1=sqrt(1/(1+exp(logithaz+inj1+injterm)));
   if age=agelinj then chaz2=sqrt(1/(1+exp(logithaz+inj23+injterm)));
   if age=agelinj then chaz2=sqrt(1/(1+exp(logithaz)));
   chaz=chaz1*chaz2;
end;
if age=agefinj+2 & age<=agelinj then do; * Similar calculations ;
   chaz1=sqrt(1/(1+exp(logithaz+inj23+injterm)));
   if age=agelinj then chaz2=sqrt(1/(1+exp(logithaz+inj23+injterm)));
   if age=agelinj then chaz2=sqrt(1/(1+exp(logithaz)));
chaz=chaz1*chaz2;
end;
if age=agefinj+3 & age<=agelinj then do;  * Similar calculations ;
    chaz1=sqrt(1/(1+exp(logithaz+inj23+injterm)));
    if age<agelinj then chaz2=sqrt(1/(1+exp(logithaz+inj4up+injterm)));
    if age=agelinj then chaz2=sqrt(1/(1+exp(logithaz)));
    chaz=chaz1*chaz2;
end;
if agefinj+3<age & age<=agelinj then do;  * Similar calculations ;
    chaz1=sqrt(1/(1+exp(logithaz+inj4up+injterm)));
    if age<agelinj then chaz2=sqrt(1/(1+exp(logithaz+inj4up+injterm)));
    if age=agelinj then chaz2=sqrt(1/(1+exp(logithaz)));
    chaz=chaz1*chaz2;
end;
* adjust risk for the age when the test occurred ;
if age=last then do; if agefinj<age<=agelinj then chaz=chaz1;
else chaz=sqrt(chaz); end;
surv=surv*chaz; * track the accumulating risk ;
end;  * end of loop through all years at risk ;
p=1-surv; * probability of anti-HCV+ ;
model hcv ~ binary(p);
title 'WIHS, quadratic calendar year and age';
run;
Additional file 2 – R / S-plus code for obtaining conditional densities

This gives code that runs in either R (http://CRAN.R-project.org/) or S-plus (http://www.insightful.com/products/splus/) that will produce fitted probabilities for HCV infection having occurred at each year of age up to the age of a positive HCV antibody test, based on subject characteristics and IDU history.

# Below is code that runs in either the S-Plus or R statistical packages. Use the Select Tool in Adobe Reader # to copy this and paste it into either S-plus or R. For someone with a positive test for HCV infection, this # returns fitted probabilities for when he or she was infected, based on information supplied in the vector # “preds”.

library("splines")  # Include this if running in R
wihsParams <- c(
-12.592143883, # 1  intercept
  5.736048710, # 2 inj1
  5.091128888, # 3 inj23
  1.972396705, # 4 inj4up
  0.127726176, # 5 dailyuse
  0.348384142, # 6 ageLinear
-0.005591044, # 7 ageQuadratic
-0.163715768, # 8 yearLinear
-0.003514481, # 9 yearQuadratic
  0, # 10 yearSpline1
  0, # 11 yearSpline2
  0, # 12 yearSpline3
  0, # 13 yearSpline4
  0, # 14 man
  0.403782049, # 15 blackk
  0.492086770, # 16 latin
  0.323003435, # 17 othrac
  0.345907244, # 18 brnx
-0.107515819, # 19 brook
  0.095883287, # 20 atdc
-0.222709684, # 21 atla
  0.529358756, # 22 chicag
  0.443385834) # 23 hivpos

uhsParams <- c(
-14.925894242, # 1 intercept
  4.112592320, # 2 inj1
  2.284821603, # 3 inj23
  1.648190843, # 4 inj4up
  0.463629622, # 5 dailyuse
  0.152336572, # 6 ageLinear
-0.002491117, # 7 ageQuadratic
  0, # 8 yearLinear
  0, # 9 yearQuadratic
  8.224213751, # 10 yearSpline1
  4.848163946, # 11 yearSpline2
  16.663527041, # 12 yearSpline3
-0.866023880, # 13 yearSpline4
-0.275295695, # 14 man
-0.150010414, # 15 blackk
yr4 <- ns(1917:2003,knots=c(1980,1990,1995))

conddens <- function(preds, params) {
  intercept <- params[1]
  inj1 <- params[2]
  inj23 <- params[3]
  inj4up <- params[4]
  dailyuse <- params[5]
  ageLinear <- params[6]
  ageQuadratic <- params[7]
  yearLinear <- params[8]
  yearQuadratic <- params[9]
  yearSpline1 <- params[10]
  yearSpline2 <- params[11]
  yearSpline3 <- params[12]
  yearSpline4 <- params[13]
  man <- params[14]
  blackk <- params[15]
  latin <- params[16]
  othrac <- params[17]
  brnx <- params[18]
  brooklyn <- params[19]
  atdc <- params[20]
  atla <- params[21]
  chicag <- params[22]
  hivpos <- params[23]
  
  # The block below specifies the covariate values that must be specified in order to
  # estimate a person’s past year-by-year risk of HCV infection from this model

  first <- preds[1]      # Age first at risk. This will be 1 for current status data.
  last <- preds[2]       # Age of HCV test result
  calcbyr <- preds[3]    # Calendar year of birth
  agefinj <- preds[4]    # Age of first IDU, set to last+1 if none
  agelinj <- preds[5]    # Age of last IDU (can be missing if agefinj>last)
  daily  <- preds[6]     # 1 if daily IDU when injected, 0 otherwise
  male   <- preds[7]     # 1 if male, 0 if female
  black  <- preds[8]     # 1 if black race, 0 otherwise
  latino <- preds[9]     # 1 if Hispanic, 0 otherwise
  othrace <- preds[10]   # 1 if race/ethnicity other than Caucasian, black, Hispanic
  bronx  <- preds[11]    # 1 if WIHS Bronx site, 0 otherwise
  brooklyn <- preds[12]  # 1 if WIHS Brooklyn site, 0 otherwise
  dc <- preds[13]        # 1 if WIHS Washington, DC site, 0 otherwise
  la <- preds[14]        # 1 if WIHS Los Angeles site, 0 otherwise
  chicag <- preds[15]    # 1 if WIHS Chicago site, 0 otherwise
  hiv <- preds[16]       # 1 if HIV infected, 0 if not

  baselogit <- intercept+blackk*black+latin*latino+othrac*othrace+male*man+
               bronx*brnx + brooklyn*brook + dc*atdc + la*atla + chicag*chicag+hivpos*hiv
chaz <- numeric()  # chaz is (1 - hazard)

for (age in (first:last)) {
  yr <- calcbyr+age-2000
  logithaz <- baselogit + ageLinear*age+ageQuadratic*age*age + yearLinear*yr +
    yearQuadratic*yr*yr +yearSpline1*yr[yr+84,1]+yearSpline2*yr[yr+84,2]+
    yearSpline3*yr[yr+84,3]+yearSpline4*yr[yr+84,4]
  if ((age<agefinj) | (age>agelinj)) chazup <- 1/(1+exp(logithaz))
  injterm <- dailyuse*daily
  if (age==agefinj) {
    chaz1 <- sqrt(1/(1+exp(logithaz)))
    chaz2 <- sqrt(1/(1+exp(logithaz+inj1+injterm)))
    chazup <- chaz1*chaz2
  }
  if ((age==agefinj+1) & (age<=agelinj)) {
    chaz1 <- sqrt(1/(1+exp(logithaz+inj1+injterm)))
    if (age<agelinj) chaz2 <- sqrt(1/(1+exp(logithaz+inj23+injterm)))
    if (age==agelinj) chaz2 <- sqrt(1/(1+exp(logithaz)))
    chazup <- chaz1*chaz2
  }
  if ((age==agefinj+2) & (age<=agelinj)) {
    chaz1 <- sqrt(1/(1+exp(logithaz+inj23+injterm)))
    if (age<agelinj) chaz2 <- sqrt(1/(1+exp(logithaz+inj23+injterm)))
    if (age==agelinj) chaz2 <- sqrt(1/(1+exp(logithaz)))
    chazup <- chaz1*chaz2
  }
  if ((age==agefinj+3) & (age<=agelinj)) {
    chaz1 <- sqrt(1/(1+exp(logithaz+inj23+injterm)))
    if (age<agelinj) chaz2 <- sqrt(1/(1+exp(logithaz+inj4up+injterm)))
    if (age==agelinj) chaz2 <- sqrt(1/(1+exp(logithaz)))
    chazup <- chaz1*chaz2
  }
  if (((agefinj+3)<age) & (age<=agelinj)) {
    chaz1 <- sqrt(1/(1+exp(logithaz+inj4up+injterm)))
    if (age<agelinj) chaz2 <- sqrt(1/(1+exp(logithaz+inj4up+injterm)))
    if (age==agelinj) chaz2 <- sqrt(1/(1+exp(logithaz)))
    chazup <- chaz1*chaz2
  }
  if (age==last) {
    if ((agefinj<age) & (age<=agelinj)) chazup <- chaz1
    if ((agefinj)>=age) | (age>agelinj)) chazup <- sqrt(chazup)
  }
  chaz  <-  c(chaz,chazup)
}  # end of age loop
surv <- cumprod(chaz)
surv  <-  c(1,surv[1:(length(surv)-1)])
dens  <-  (1-chaz)*surv
cbind(age=(first:last),cdens=(dens/sum(dens)))
}

# BELOW IS AN EXAMPLE, CORRESPONDING TO THE FIRST 4 LINES OF TABLE 4

tab4data <- rbind(
c(1,40,1960,12,40,rep(0,11)),
c(1,60,1940,12,60,rep(0,11)),
c(1,40,1960,35,40,rep(0,11)),
c(1,60,1940,35,60,rep(0,11)))

wihsdens <- apply(tab4data,1,conddens,params=wihsParams)
wihsdens <- as.array(wihsdens)

uhsdens <- apply(tab4data,1,conddens,params=uhsParams)
uhsdens <- as.array(uhsdens)

wihsCmean <- numeric()
wihsprob2 <- numeric()
uhsCmean <- numeric()
uhsprob2 <- numeric()

for (i in 1:4) {
  finj <- tab4data[i,4]
  densup <- wihsdens[i]
  wihsCmean <- c(wihsCmean,sum(densup[,1]*densup[,2]))
  wihsprob2 <- c(wihsprob2,sum(densup[c(finj,finj+1),2]))
  densup <- uhsdens[i]
  uhsCmean <- c(uhsCmean,sum(densup[,1]*densup[,2]))
  uhsprob2 <- c(uhsprob2,sum(densup[c(finj,finj+1),2]))
}

round(cbind(wProb2=wihsprob2,wMean=wihsCmean,wBias=tab4data[,4]-wihsCmean, uProb2=uhsprob2,uMean=uhsCmean,uBias=tab4data[,4]-uhsCmean),2)

# OUTPUT SHOULD BE AS BELOW:
#
#      wProb2 wMean  wBias uProb2 uMean  uBias
# [1,]   0.38 17.47  -5.47   0.52 15.17  -3.17
# [2,]   0.07 29.25 -17.25   0.18 22.44 -10.44
# [3,]   0.66 34.75   0.25   0.39 26.55   8.45
# [4,]   0.74 35.54  -0.54   0.47 32.32   2.68