Changes in the prevalence of hepatitis C virus genotype among injection drug users: a highly dynamic process - Reply : letter

Bruisten, S.M.; van Asten, L.C.H.I.; van der Laar, T.; Prins, M.

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Changes in the Prevalence of Hepatitis C Virus Genotype among Injection Drug Users: A Highly Dynamic Process

To the Editor—With great interest we have read the article by van Asten et al. in *The Journal of Infectious Diseases* [1]. An important aspect of their study is its detailing of the introduction and spread of "new" hepatitis C virus (HCV) genotypes among injection drug users (IDUs).

Changes of subtype distributions in a given population were shown, for the first time, by our group several years ago [2]. In that study, it was demonstrated that subtype 1b was the prevailing subtype in the German population until subtype 1a started spreading in the early 1980s [2]. This led to a substantial change of the most prevalent HCV subtype, especially in younger people. To highlight the question of whether this change was a single effect, a multicenter study was performed 2 years ago [3]. In that study, we demonstrated that the epidemiology of HCV genotypes in IDUs is subjected to highly dynamic changes. Profound changes in the prevalence of different HCV genotypes were noted between 1994–1995 and 2000–2001, when large populations of IDUs ($n = 144$ and $n = 172$, respectively) were compared. These changes are summarized in figure 1. The introduction of genotypes that were formerly unknown in this risk population (4 and 2a/b) and the ability of these genotypes to establish significant prevalence within a period of only 6 years are remarkable.

The theory of 2 independently developing HCV epidemics had been proposed elsewhere [4], because the epidemiology of HCV subtype 3a and other subtypes seemed to be very different between IDUs and non-IDUs. However, there are indications that the dynamics observed among IDUs also influence the genotypic distribution among the entire population of patients. Although subtype 3a was detected nearly exclusively among IDUs in 1994–1995, ~45% of patients infected with subtype 3a had never been IDUs. In the majority of these people, high-risk sexual behavior (HRSB) was the most probable risk factor for acquiring HCV infection [3]. It can be assumed from these data that the higher the prevalence of a certain genotype among the population of IDUs, the higher is the risk of this genotype spreading beyond the boundaries of the IDU scene. This is most probably due to HRSB, which, today, is one of the major risk factors for acquiring HCV [3, 5]. On the other hand, new genotypes can be introduced in the population of IDUs. This has been demonstrated very convincingly for genotype 4, which was introduced by immigrants from northern Africa and the Arabian peninsula [1, 3], and for genotype 2 [3]. In our population of patients, these genotypes established a prevalence of 7% and 8%, respectively, within only 6 years (figure 1). In analogy to the findings for subtype 3a, these genotypes may also spread over the boundaries of the IDU scene with increasing prevalence.

However, knowledge of these dynamic changes of the distribution of HCV genotypes provides information regarding not only the epidemiology, but also the treatment, of HCV. In a population with a high risk of repeated HCV infections, the probability of infection with different HCV genotypes is associated with the speed of changes of the genotype distribution. We have shown that, in at least 18% of IDUs with long-term follow-up (up to 7 years), multiple HCV infections detected by intraindividual changes of the predominant HCV genotype occurred [6].

It is well known that, in patients infected with multiple HCV genotypes, one of the infecting virus strains establishes predominance, and, by use of polymerase

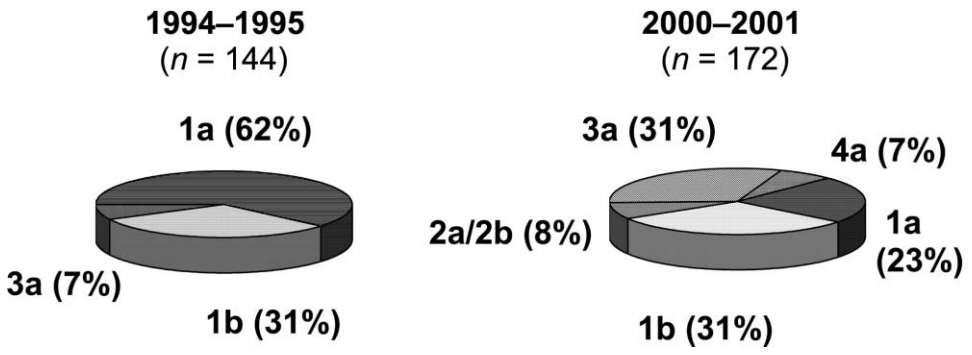

Figure 1. Comparison of the genotype distribution among injection drug users, over a period of 6 years

chain reaction–based methods, usually only the actual prevailing strain can be detected in these patients [7]. However, minor strains do not become eliminated, and we have demonstrated in various patients that these minor strains can reappear [6, 8]. These findings are of importance, especially in the context of therapy with pegylated interferon and ribavirin. It has been shown that reemergence of minor strains is a possible cause for failure of therapy [6, 8]. Therefore, the recommendation was made to repeat genotyping in patients who do not respond to therapy as expected. This enables adjustment of the regimen to the actual predominant HCV genotype.

These findings underline the importance of the described dynamic changes of the epidemiological distribution of HCV genotypes among IDUs They are important for better understanding (1) the epidemiology of HCV and (2) possible factors influencing outcome of therapy.

Matthias Schröter, Bernhard Zöllner, Rainer Laufs, and Heinz-Hubert Feucht

Zentrum für Klinisch-Theoretische Medizin I, Institut für Infektionsmedizin, Universitätsklinikum Hamburg Eppendorf, Hamburg, Germany

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Reprints or correspondence: Dr. Matthias Schröter, Zentrum für Klinisch-Theoretische Medizin I, Institut für Infektionsmedizin, Universitätsklinikum Hamburg Eppendorf, Martinistr. 52, 20246 Hamburg, Germany (mschroet@uke.uni-hamburg.de).

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Reply to Schröter et al.

To the Editor—We agree with Schröter et al. [1] that tracking of hepatitis C virus (HCV) genotypes and studying the dynamic changes is of importance for both of the reasons they mentioned. The well-documented fact that HCV genotypes 1 and 4 are more difficult to treat effectively, combined with the observed increase in the prevalence of genotype 4 in Europe, is a reason for concern. Schröter et al. [1] describe an increase of subtype 4a to 7% in the northern German population of injection drug users (IDUs), whereas we previously found a gradient for subtype 4d of >24% in southern European countries to nearly 7% in northern European countries [2]. The difference in subtypes is possibly explained by the use of different regions of the HCV genome for typing, although it could also reflect real regional differences in the distribution of subtypes 4a and 4d.

The idea of a spillover from IDUs to the total population is reasonable. We do not agree, however, that high-risk sexual behavior (HRSB) is a plausible explanation for this spillover [1, 3]. Transmission of HCV has been documented to occur mainly, and perhaps exclusively, by parenteral exposure. We are currently comparing the phylogenetic relations between current HCV-infected young drug users (DUs) and HCV-infected blood donors whose donations were obtained during the same calendar period, analogous to a study that was performed for hepatitis B virus (HBV) [4]. In that study, the discrimination of HBV genotypes between identified risk groups and those found among (potential) blood donors was not possible; in other words, there seems to be only 1 epidemic for HBV. Whether the same holds true for HCV remains to be established. Potential blood donors, as representatives of the low-risk population, may receive HCV-seropositive test results because of a single injection drug use episode or through previous exposure to infected blood or blood products. Alternatively, a different set of HCV genotypes may be present among the low-risk population, compared with that among young DUs, which would strengthen the hypothesis of independent HCV epidemics. It has been postulated that, among DUs, the incidence of HCV has decreased because of reduced needle use and less sharing of injection equipment [5]. The majority of the HCV infections occurred some 20–30 years ago. Because HCV-related disease and active virus replication can emerge years after infection, the burden of disease is now an increasing problem worldwide. Therefore, recording the dynamic changes of HCV genotypes, as was done by Schröter et al. [1], is important, in combination with collecting epidemiological information, preferably among recently infected individuals, for identifying new trends in the HCV epidemic. This should help in developing measures to decrease transmission of HCV.

Sylvia Bruisten, Liselotte van Asten, Thijs van de Laar, and Maria Prins

Gemeentelijke Geneeskundige en Gezondheidsdienst, Municipal Health Service, Amsterdam, The Netherlands

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Reprints or correspondence: Dr. Sylvia Bruisten, Gemeentelijke Geneeskundige en Gezondheidsdienst, Municipal Health Service, Nieuwe Achtergracht 100, 1018 WT Amsterdam, The Netherlands (sbruisten@gggd.amsterdam.nl).

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