An Epidemic of Hepatitis C Virus Infection While Treating Endemic Infectious Diseases in Equatorial Africa More than a Half Century Ago: Did It Also Jump-Start the AIDS Pandemic?

G. Thomas Strickland

Division of International Health, Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore

(See the articles by Pépin et al, on pages 768–776 and 777–784.)

Two articles in this issue of *Clinical Infectious Diseases* by Pépin et al [1, 2] report how intravenous and intramuscular prophylaxis and treatment of endemic infectious diseases led to hepatitis C virus (HCV) and human T lymphotropic virus (HTLV)–1 infection in Equatorial Africa. Both of the rural areas, in southeast Central Africa Republic (where there was a high incidence of trypanosomiasis) [2] and in southern Cameroon (where there was extensive use of parenteral therapy for malaria and other endemic infectious diseases) [1], are near sites where SIV_{cpz}, believed to be the precursor of human immunodeficiency virus (HIV)–1, has been isolated from chimpanzees [3, 4]. Thus, they hypothesize that these iatrogenic exposures may have jump-started the HIV pandemic from a few isolated cases of infected persons exposed to "bush meat." This markedly increased the reservoir of infection and led to sustained human-to-human sexual transmission of HIV.

The populations studied were elderly local inhabitants. The conclusion in the Central Africa Republic study was that mass trypanosomiasis therapy before 1951 caused iatrogenic transmission of HCV genotype 4 and that population-wide use of intramuscular pentamidine chemoprophylaxis for trypanosomiasis in 1947–1953 may have transmitted HTLV-1. Their data showing markedly excessive mortality among patients with trypanosomiasis treated before 1951 suggest that SIV_{cpz}/HIV-1 could have also been iatrogenically transmitted [2].

The conclusion of the Cameroon study was that medical interventions, including intravenous treatment with antimalarial drugs, transfusions, and to a lesser extent traditional circumcision of young males in groups, were associated with an increased level of HCV transmission during the first half of the 20th century [1].

These data also support their HIV transmission hypothesis. Because both HCV and HTLV-1 are 2 blood-borne viral infections that are compatible with prolonged survival, the authors use the presence of HCV antibodies (anti-HCV) and RNA and HTLV-1 antibodies as proxy biomarkers for putative HIV transmission.

The data on iatrogenic transmission of HCV and HTLV-1 in Central Africa Republic are convincing [2]. Differences among different age groups of predicted prevalence of trypanosomiasis before 1951 based on historical data and prevalence based on a 2006 interview strongly suggest that its treatment was associated with greatly increased mortality. These people could have died of the trypanosomiasis itself or its treatment, HCV-related complications, or other blood-borne infections. However, the difference in estimated historical and interview-detected mortality rates was large in the 65–69-year age group and became even greater in the older groups (cohort effect). This provides strong evidence that a killer, such as HIV, was transmitted. Because these exposures occurred 55–75 years before and all who were infected died decades ago of causes (eg, tuberculosis and other infections) that could not be traced back to HIV, it is impossible to confirm that the excess mortality was due to HIV-1.

The authors of the Cameroon article conducted a cross-sectional survey of residents 60 years and older in southern Cameroon and tested for prior infection

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Reprints or correspondence: Dr G. Thomas Strickland, Div of International Health, Dept of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, 660 W Redwood St, Baltimore, MD 21201 (tstrick@epi.umaryland.edu).

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(antibodies) and current infection (RNA) with HCV [1]. The 451 individuals participating in the study provided a venous blood sample and answered a questionnaire on potential exposures and past medical events. The study focused on parenteral therapy of infectious diseases. They tested for anti-HCV using 2 third-generation enzyme immunoassays and reverse-transcriptase polymerase chain reaction to detect HCV-RNA; 252 (56%) had anti-HCV. HCV-RNA was detected in 179 (71% of those with HCV antibody) and they genotyped 171 viruses; 31 were genotype 1, 47 were genotype 2, and 93 were genotype 4. Molecular clock analysis showed that each genotype underwent exponential growth during the first half of the 20th century. For genotypes 1 and 2, it started in ~1920, continuing until their effective population stabilized during the 1940s. The effective population size of genotype 4 increased exponentially from ~1910. Genotype 1 was uncommon among those born after 1945, perhaps because this population had been saturated with HCV infection. I estimate the HCV infection rate was much greater than 56% because (1) they excluded patients who did not test positive in both enzyme immunoassay tests (which would omit many whose anti-HCV had waned during the half century); (2) all infected with both HIV and HCV would be dead; (3) many could have died of chronic complications of HCV; and (4) the virus could have cleared up in some of those infected, leaving only an HCV-specific T cell response to mark the exposure [5, 6].

Although a history of intravenous treatment of malaria ($P = .03$) was the only significant therapeutic risk associated with the prevalence of anti-HCV, injection therapy for syphilis, leprosy, and trypanosomiasis prophylaxis and blood transfusions had increased the crude odds ratios. However, the sample sizes of these events were too small to reach statistical significance. Their hypothesis before conducting the study was that the Cameroon HCV epidemic had been driven by campaigns against yaws. Parenteral treatment of yaws was not a risk for anti-HCV, and they speculate that this may be because only 16 received intravenous therapy among the 146 recalling injection therapy for yaws [1]. Also, yaws therapy was usually given to children, and many in this group may not have yet had HIV infections, and their blood may not have been infectious to others being treated at the same time. They report 2 other significant risks for anti-HCV (ie, girls attending a specific grammar school [$P = .02$] and vaccine scar on the right arm [$P = .005$]), for which I am unable to provide additional speculation beyond their discussion.

I believe these 2 articles support the conclusion that parenteral therapy for endemic infectious diseases >50 years ago transmitted HIV-1. The circumstances described meet several requirements for iatrogenic blood-borne infection epidemics.

1. Reuse of needles and syringes contaminated with infectious blood. At that time disposable syringes and needles were not available and it was unknown that human blood could transmit infections. In fact, patients with relapsing cases of trypanosomiasis were given 10 mL of whole blood intramuscularly from convalescent patients [2].
2. Older persons (potentially infectious) and children (who can be infected) treated at the same location. This is why immunizations are less likely to cause blood-borne infection epidemics because those being immunized are usually young children. Mass treatment campaigns for schistosomiasis in Egypt were particularly risky because a child could have received intravenous tartar emetic in the same setting as a grandparent [7].
3. Courses requiring multiple treatments. In the Egyptian HCV epidemic, during which tartar emetic was given intravenously for 10–12 weeks, a person being treated could be infected and then pass on the infection to a second person during the therapy [7]. This same situation could have happened in Equatorial Africa during the treatment of trypanosomiasis. From 1928 until 1953, the standard course of therapy was either 12 weekly subcutaneous or intravenous injections of orsanine or, if cerebrospinal fluid was altered, 12 weekly intravenous injections of tryparsamide [2].
4. Infectious agent in the blood of those receiving parenteral therapy. Genotype 4 HCV was circulating in the blood of some patients in Egypt, Central Africa Republic, and Cameroon when endemic infectious diseases were being treated. However, fortunately for Egypt, HIV-1 was not present in that country at the time intravenous antischistosomal therapy was administered to a large proportion of its rural population [7].
5. Treating many persons at the same time. Although treatment of malaria was usually given with intravenous quinine to individuals based on the health care practitioner's diagnosis, during the high transmission season several sick persons could have been treated with the same quinine-filled syringe [1]. In Central Africa Republic,

> [Pentamidine] was used as chemoprophylaxis of sleeping sickness from 1946 until the late 1950s. Hoping to eradicate the disease, intramuscular injections were given to all inhabitants of endemic foci (except pregnant women and infants) every 6 months, for several years.... Pentamidine was available in bottles of 25 g, enough for 100 injections. A contemporary description gives a flavor of the potential for transmission of blood-borne pathogens: 'principles of mass production and time and motion study should be invoked to ensure the maximum speed and efficiency in getting through, say, 250 injections in a morning. The man actually giving the injection should merely have to turn half around in order to hand over his used syringe and take a freshly charged one. As he turns back again, a freshly iodinated buttock, and the appropriate dose, should present themselves before him [2, p 782].

This description is reminiscent of the

one Christiana Frank found in the World Health Organization Archives in which Professor Brian Maegraith described treatment of bilharziasis in Egypt in 1964:

> Patients are grouped according to weight and appropriate dose and lined up in queues for administration in turn for injection.... The stranger to mass therapy with Tartar Emetic is certainly to be confounded by the speed and apparent safety of the administration of the drug.... The skillful doctor began injecting at 9:20 and had completed 504 injections of men, women, and children by 10:10 am. Allowing for a 10-min rest, the time taken for each injection was thus under 5 seconds.... This remarkable performance is being repeated at various tempos all over Egypt [7, p 890].

Furthermore,

> The used syringe is placed in an 'out' tray, from which it is taken by the nurse, washed through, and boiled for a minute or two. As soon as the syringe is cold, it is filled with a volume of the drug solution.... It is then placed in the "in tray."... There are usually 20 to 30 syringes in rotation [7, p 890].

6. Other factors influencing bloodborne epidemics include infectivity and virulence of the organism, the dose of infectious inoculums, site and extent of parenteral exposure (eg, penetrating wound or injection [intravenous, intramuscular, or subcutaneous]), and protective immunity of the host populations, including prior exposure and preexisting immunity.

The hypothesis that transmission of HIV-1 during parenteral therapy of endemic infectious diseases during the first half of the last century jump-started the HIV pandemic in Equatorial Africa is exceedingly insightful. However, these 2 articles also provide data showing that these events caused an iatrogenic epidemic of HCV in the same areas, which in addition to being a proxy for HIV-1 is a huge public health burden. Worldwide hepatocellular carcinoma is increasing in incidence, and the primary reason for this increase is cirrhosis caused by chronic HCV infection [8, 9].

The Egyptian Ministry of Health and Population had the best intentions when it launched mass-treatment campaigns with intravenous tartar emetic to control what they considered to be the country's most important disease, schistosomiasis [7]. Likewise, French Colonial doctors in the CAR and Cameroon also had the best of intentions 50–80 years ago when they treated patients for endemic infectious diseases, including frequently fatal sleeping sickness and malaria: good intentions that led to serious, though unintended, global health consequences.

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