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### APPENDIX 1. TAHOD-TASER Study Members

- A. Kamarulzaman, Sharifah Faridah Syed Omar, Sasheela Vanar, Iskandar Azwa, and L.Y. Ong, University Malaya Medical Center, Kuala Lumpur, Malaysia;
  - C.K.C. Lee, B.L.H. Sim, and R. David, Hospital Sungai Buloh, Sungai Buloh, Malaysia;
  - C.V. Mean, V. Saphonn, and V. Khol, National Center for HIV/AIDS, Dermatology and STDs, Phnom Penh, Cambodia;
  - E. Yuniastuti\*, D. Imran, and A. Widhani, Working Group on AIDS Faculty of Medicine, University of Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia;
  - F.J. Zhang, H.X. Zhao, and N. Han, Beijing Ditan Hospital, Capital Medical University, Beijing, China;
  - J.Y. Choi, S. Na, and J.M. Kim, Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea;
  - M. Mustafa and N. Nordin, Hospital Raja Perempuan Zainab II, Kota Bharu, Malaysia;
  - N. Kumarasamy, S. Saghayam, and C. Ezhilarasi, YRG Centre for AIDS Research and Education, Chennai, India;
  - O.T. Ng, P.L. Lim, L.S. Lee, and M.T. Tan, Tan Tock Seng Hospital, Singapore, Singapore;
  - M.P. Lee, P.C.K. Li, W. Lam, and Y.T. Chan, Queen Elizabeth Hospital and KH Wong, Integrated Treatment Centre, Hong Kong, China;
  - P. Kantipong and P. Kambua, Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand;
  - P. Phanuphak, K. Ruxrungtham, A. Avihingsanon, P. Chusut, and S. Sirivichayakul, HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand;
  - R. Ditangco\*, E. Uy, and R. Bantique, Research Institute for Tropical Medicine, Manila, Philippines;
  - R. Kantor, Providence, Brown University, RI;
  - S. Oka, J. Tanuma, and T. Nishijima, National Center for Global Health and Medicine, Tokyo, Japan;
  - S. Pujari, K. Joshi, and A. Makane, Institute of Infectious Diseases, Pune, India;
  - S. Kiertburanakul, S. Sungkanuparph, L. Chumla, and N. Sanmeema, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand;
  - T.P. Merati†, D.N. Wirawan, and F. Yuliana, Faculty of Medicine, Udayana University and Sanglah Hospital, Bali, Indonesia;
  - R. Chaiwarith, T. Sirisanthana, W. Kotarathititum, and J. Praparatanapan, Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand;
  - T.T. Pham, D.D. Cuong, and H.L. Ha, Bach Mai Hospital, Hanoi, Vietnam;
  - V.K. Nguyen, V.H. Bui, and T.T. Cao, National Hospital for Tropical Diseases, Hanoi, Vietnam;
  - W. Ratanasuwan and R. Sriodee, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand;
  - W.W. Wong, W.W. Ku, and P.C. Wu, Taipei Veterans General Hospital, Taipei, Taiwan;
  - Y.M.A. Chen and Y.T. Lin, Kaohsiung Medical University, Kaohsiung City, Taiwan;
  - A.H. Sohn, N. Durier, B. Petersen, and T Singtoroj, TREAT Asia, amfAR—The Foundation for AIDS Research, Bangkok, Thailand;
  - D.A. Cooper, M.G. Law, A. Jiamsakul, and D.C. Boettiger, The Kirby Institute, University of New South Wales, Sydney, Australia.
- \*Current Steering Committee Chairs.  
†Co-chairs.

## Stabilizing Incidence of Hepatitis C Virus Infection Among Men Who Have Sex With Men in Amsterdam

To the Editors:

### INTRODUCTION

Since 2000, there has been an unexpected and substantial increase in the incidence of hepatitis C virus (HCV) among HIV-1-infected men who have sex with men (MSM).<sup>1–3</sup> Prevalence of HCV among HIV-uninfected MSM has remained low.<sup>1</sup> HIV may enhance sexual transmission of HCV through increased infectiousness and increased susceptibility.<sup>1,3</sup> In combination with increased high-risk sexual behavior, these factors most likely allowed HCV to spread sexually.<sup>1,3</sup>

The Multicenter AIDS Cohort Study (MACS) in the United States reported significantly higher HCV incidence rates (IRs) among MSM recruited in 2001–2003 compared with earlier periods.<sup>4</sup> Studies from Switzerland, Spain, and Japan showed an ongoing increase in new HCV infections among HIV-infected MSM from 2008 till 2011/2012.<sup>5–7</sup> In contrast, data collected during bi-annual surveys at the sexually transmitted infection clinic in Amsterdam, the Netherlands, suggested that the prevalence of HCV among HIV-infected MSM has stabilized in recent years.<sup>8</sup> We therefore updated our previous analysis in the Amsterdam Cohort Study (ACS) among MSM<sup>9</sup> to examine recent changes in HCV incidence.

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## METHODS

### Participants

The ACS among MSM is an open, ongoing prospective study initiated in 1984.<sup>10</sup> Participation is voluntary and informed consent is obtained at intake. Participants return every 3–6 months for follow-up. Since 1999, the follow-up of nearly all HIV-infected MSM has been relocated to HIV treatment centers, where collection of behavioral data is limited.

We included all HIV-infected and HIV-uninfected MSM with  $\geq 2$  study visits between October 1984 and January 2012. HCV status of each participant up to January 2003 has been retrospectively determined as described previously.<sup>9</sup> New participants since 2003, and HIV-uninfected MSM with a negative HCV status who have remained in follow-up, were (again) tested for HCV antibodies at their first visit after October 2008. To update the HCV status among HIV-infected MSM with a negative HCV status in our previous study, we obtained all available HCV screening results from the clinical records of HIV treatment centers attended by ACS participants. If no test result was available after January 2009, the last available sample before January 2012 was tested for HCV antibodies. On finding incident HCV infection, samples from earlier visits were tested to minimize width of seroconversion interval.

### Laboratory Methods

HCV antibody testing was performed using a commercial microparticle enzyme immunoassay (AxSYM HCV 3.0; Abbott Laboratories, Abbott Park, IL) and confirmed by immunoblot (Chiron RIBA HCV 3.0 SIA; Ortho-Clinical Diagnostics Raritan, NJ) and transcription-mediated amplification (TMA Versant; Siemens Medical Solutions Diagnostics, Tarrytown, NY).

### Statistical Analysis

Participants contributed follow-up time from the date of study entry until the date of the last negative HCV antibody test, or until the estimated date of HCV infection (ie, the midpoint between the last negative and the first positive HCV test). IRs were calculated per year, and trends over time

were analyzed using Poisson regression. Restricted cubic splines allowed for smoothly varying trends in the modeled incidence.<sup>11</sup> In a bivariate analysis for incident HCV infection among HIV-infected MSM, adjusting for calendar period of follow-up, the effects of age, CD4 cell count, nadir CD4 cell count, HIV viral load (modeled as log<sub>10</sub> increment above 1000 copies/mL), and combination antiretroviral therapy (cART) use were evaluated using Poisson regression. Variables subject to change were treated as time-updated covariates. Statistical software packages STATA Intercooled 11.2 (STATA Corp College Station, TX) and R 2.15.2<sup>12</sup> were used for analysis.

## RESULTS

The ACS enrolled 2457 MSM between October 1984 and January 2012, of whom 2104 had  $\geq 2$  study visits and HCV test results. Median age of the 2104 MSM at study entry was 30.3 years (interquartile range: 25.9–37.1) and 78.8% had Dutch nationality. At study entry, 539 (25.6%) of 2104 MSM were HIV infected; an additional 222 MSM seroconverted during follow-up. At study entry, 2080 of 2104 MSM were HCV negative and contributed to 17,310 person-years (PYs) of follow-up; median follow-up time was 7.4 years (interquartile range: 3.2–12.0). Of the 422 HIV-infected MSM followed up after 1996, 345 were ever on cART.

Twenty-nine incident HCV infections were documented during the observation period. All incident cases were infected with HIV before HCV infection and none of them reported injection drug user (IDU) at study entry. Based on 6422 PYs of follow-up among HIV-infected MSM, the overall observed HCV incidence was 4.52/1000 PYs [95% confidence interval (CI): 3.02 to 6.49]; the effect of calendar time was significant ( $P < 0.001$ ). Before 2000, only 3 incident HCV infections were documented, resulting in an IR varying between 0.73 and 3.60/1000 PYs (Fig. 1A). A significant increase in HCV incidence was observed after 2000 (IR<sub>2005</sub> vs. IR<sub>2000</sub>: incidence rate ratio [IRR] 3.41; 95% CI: 1.58 to 7.34;  $P = 0.002$ ). After 2005, however, HCV incidence stabilized at around 12/1000 PYs (IR<sub>2010</sub> vs. IR<sub>2005</sub>: IRR, 0.94; 95% CI: 0.38 to 2.36;  $P = 0.906$ ).

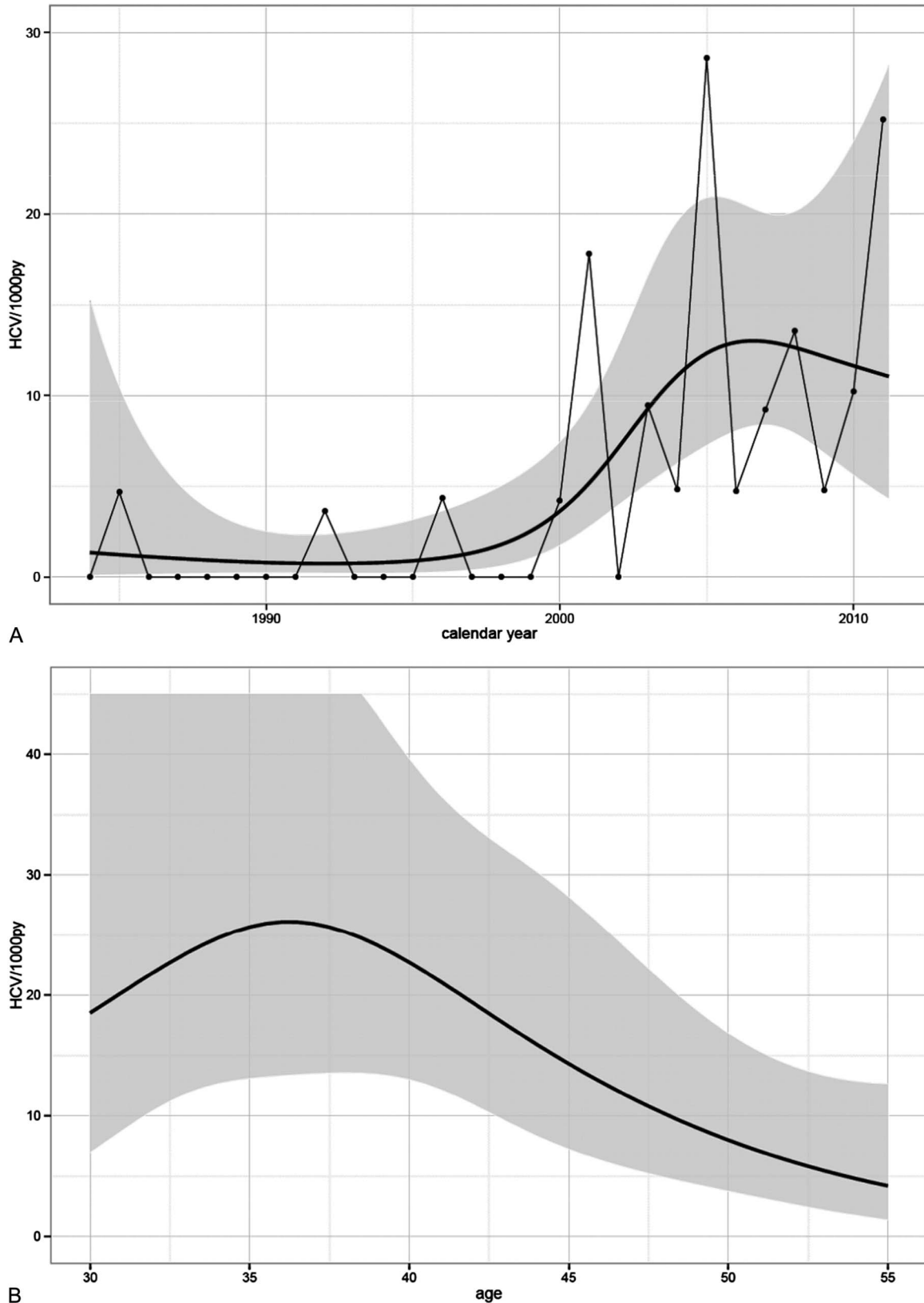
In Poisson regression, younger age was associated with incident HCV infection (age 50 vs. 35 years: relative risk [RR], 0.31; 95% CI: 0.11 to 0.89;  $P = 0.041$ ; Fig. 1B). Of the other evaluated risk factors, none were significantly associated with HCV infection after adjusting for calendar year: CD4 count (800 vs. 300 cells/ $\mu$ L: RR, 0.96; 95% CI: 0.33 to 2.79), nadir CD4 count (300 vs. 150 cells/ $\mu$ L: RR, 1.09; 95% CI: 0.46 to 2.58), HIV viral load (30,000 vs. 1,000 copies/mL: RR, 2.27; 95% CI: 0.82 to 6.29), and cART use (RR: 0.80, 95% CI: 0.34 to 1.88).

Infections were mostly of genotype 1 (14/29; 48.3%), followed by genotype 4 (7/29; 24.1%), in line with our previous study.<sup>9</sup> Infection with genotype 2b ( $n = 3$ ) was observed after 2008 only and might indicate the introduction of a new HCV genotype among HIV-infected MSM in the Netherlands. No statistically significant time trend in genotype distribution was found.

## DISCUSSION

We describe incidence of HCV infection among MSM in Amsterdam over the course of almost 3 decades. HCV incidence rose sharply among HIV-infected MSM between the years 2000 and 2005 but seems to have stabilized at a higher level of around 12/1000 PYs thereafter, although CIs were wider in the years 2005–2011. Our observation of stabilizing incidence corresponds with findings from the Amsterdam sexually transmitted infection clinic and may partly result from increased HCV testing and treatment uptake and increased HCV awareness leading to a reduction of risk behavior and a saturation effect in the group at highest risk for HCV infection.<sup>8</sup> No incident HCV infections were documented among HIV-uninfected MSM, despite more than 10,000 PYs of follow-up, which supports earlier findings that HCV mainly spreads among HIV-infected MSM.<sup>1,3</sup> Sexual transmission of HCV has occurred among a few HIV-uninfected MSM.<sup>1</sup>

Our findings show a leveling off in HCV incidence among HIV-infected MSM rather than an ongoing increase, in contrast to studies from Switzerland, Spain, Japan, and the United States.<sup>4–7</sup> However, the HCV epidemic and the subsequent public health response



**FIGURE 1.** Observed and fitted HCV IR per 1000 PYs of follow-up. A, HCV IR among 761 HIV-infected MSM participating in the Amsterdam Cohort Studies, 1984–2011. The shaded area is the 95% CI. B, HCV IR by age, among HIV-infected MSM participating in the Amsterdam Cohort Studies (in 2008). The shaded area is the 95% CI.

among MSM in the Netherlands may have started earlier.

The HCV epidemic in the MACS cohort (with 4 study sites across the United States) seems to differ from the epidemic in the Netherlands.<sup>4</sup> Continuous incident infections have occurred from the mid-80s onwards, with majority of infections (ie, 67/92; 73%) during the period 1985–1995 among both HIV-infected and HIV-uninfected MSM. The incident HCV infections in these early years might be attributed to IDU (reported by 5%) and blood transfusion (reported by 3%). Besides, the majority of MSM with incident HCV infection (ie, 67/115; 58%) reported only 1 anal sex partner, suggesting transmission routes other than sexual contact play a major part. The actual outbreak of sexually transmitted HCV may have started later on, but unfortunately, the authors do not differentiate sexually acquired and nonsexually acquired HCV infections over time.

Also study design and methods differ between the MACS and ACS and could partly explain differences in trends. The MACS is a closed cohort with 3 separate enrolment periods, whereas the ACS has inclusion throughout the study period. In contrast to the ACS, in the MACS, 22 MSM with possible incident HCV infection tested HCV antibody positive for the first time at their last study visit were classified as HCV-free, as the MACS definition required 2 consecutive positive visits.<sup>4</sup> In addition, HCV seroconverters with a wide seroconversion interval ( $\geq 4$  years) were excluded.

Since the start of the HCV epidemic among HIV-infected MSM, multiple HCV genotypes have been introduced and continued to circulate in this population. Because of the relatively few incident infections in our study, we had limited power to test for trends in HCV genotype distribution over time. Genotype 2b is known to be transmitted mainly through invasive procedures, blood transfusion, and IDU,<sup>13</sup> but the current spread among MSM is most likely through sexual transmission.<sup>14</sup>

The initial scope of the ACS was to study the HIV epidemic; hence data on risk factors for HCV were limited. In addition, data on sexual risk behavior were limited after 1999 as described in

our Methods section. Recently initiated HCV-specific cohort studies among MSM in the Netherlands, the United Kingdom, and Germany will be better able to provide insight into the role of traditional and sexual risk factors for HCV infection and reinfection among MSM.<sup>15–17</sup>

In conclusion, the incidence of HCV infection among HIV-infected MSM in Amsterdam seems to have stabilized after an initial increase until 2005. The overall disease burden is likely to remain high because studies in the cART era show that HIV–HCV co-infection results in an increased risk of both HCV and HIV mortality.<sup>18–20</sup> Infected individuals will benefit from the swiftly changing landscape of HCV treatment. Continued follow-up is needed to see if the HCV epidemic among HIV-infected MSM will also stabilize in other regions of the world.

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**Joost W. Vanhommerig, MSc\*†**

**Ineke G. Stolte, PhD\***

**Femke A.E. Lambers, MD\***

**Ronald B. Geskus, PhD\*‡**

**Thijs J.W. van de Laar, PhD§**

**Sylvia M. Bruisten, PhD\***

**Janke Schinkel, MD, PhD†**

**Maria Prins, PhD\*||**

\*Department of Research, Cluster of Infectious Diseases, Public Health Service, Amsterdam, the Netherlands

†Department of Medical Microbiology, Section of Clinical Virology, Academic Medical Center, Amsterdam, the Netherlands

‡Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, the Netherlands

§Department of Blood-Borne Infections, Sanquin Blood Supply Foundation, Amsterdam, the Netherlands

||Department of Internal Medicine, Center of Infectious Diseases and Immunology, Amsterdam, Academic Medical Center, Amsterdam, the Netherlands

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