A Genome Wide Association study (GWAS) on susceptibility to sexual transmission of HCV among HIV-1+ MSM

Published: 18-01-2017
Last updated: 12-04-2024

To identify genetic host factors associated with HCV susceptibility among HIV-infected MSM.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Observational non invasive

Summary

ID

NL-OMON47171

Source
ToetsingOnline

Brief title
HCV susceptibility study

Condition

- Viral infectious disorders

Synonym
Hepatitis C

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,AMC (beleids OIO);materiaalkosten GWAS: winstreserve bij AMR uit diverse projecten

Intervention

Keyword: GWAS, HCV, MSM, transmission

Outcome measures

Primary outcome

Differences in the genetic profile of cases and controls

Secondary outcome

N/A

Study description

Background summary

With an estimated 180 million people infected, hepatitis C virus (HCV) presents a major health problem globally. Ongoing inflammation of the liver during chronic HCV infection may ultimately progress to liver cirrhosis and hepatocellular carcinoma, resulting in 700,000 HCV-associated deaths each year (1, 2). The recent availability of *direct acting antivirals* heralded a remarkable improvement in treatment outcome, with >95% of patients achieving viral clearance and reduction of side effects. However, despite this tremendous improvement, the burden of disease will remain substantial for a variety of reasons. Firstly, cirrhotic patients remain at risk for hepatocellular carcinoma, also after successful antiviral treatment. Secondly, chronically infected patients are usually unaware of their HCV-positive status during the long asymptomatic phase of the infection. Last but not least, diagnostics are unavailable and treatment is unaffordable in many parts of the world, creating huge challenges to eliminate HCV globally.

Since blood products in general have become safe, people who inject drugs (PWID) remain the predominant risk-group for incident HCV infection. However, since the beginning of this millennium, HCV is also spreading by sexual transmission among HIV infected *men who have sex with men* (MSM), which is remarkable as sexual transmission of HCV was considered very rare for a long time. In the Netherlands, where the epidemic among PWID has declined due to needle-exchange programs and changes in injecting drugs behaviour, HIV infected MSM are currently the main risk-group for incident infection, with high rates of reinfection following successful treatment of primary infection (3*5) . With the arrival of pre-exposure prophylaxis (PreP) for HIV, there is concern that Hepatitis C will spread to HIV negative MSM as well. Indeed, an HCV prevalence

of 4% among HIV negative MSM was observed during a HIV PreP pilot project in Amsterdam, which is substantially higher than the prevalence of 0.2% in the general population (6).

Nevertheless, despite high-risk behavior facilitating HCV transmission and substantial prevalence in the population, some individuals remain uninfected (multiple exposed uninfected, MEU), suggesting that host factors play a role in HCV susceptibility . In a small pilot study among participants of the Amsterdam Cohort Studies and the MOSAIC cohort, specifically studying HCV entry factors, we indeed found a few genetic polymorphisms that appeared to be associated with HCV acquisition. Linking specific host genotypes with risk of HCV acquisition and identifying the inhibitory mechanism will undoubtedly lead to new host molecules that antivirals can target. The best example of such an approach is the development of Maraviroc, a drug blocking the HIV-1 CCR5 co-receptor which was found to be dysfunctional in high-risk uninfected individuals.

Aim of the study proposed here is to perform a genome wide association study (GWAS) on individuals at high risk for acquiring HCV, to identify polymorphisms in host genes which influence HCV susceptibility.

Study objective

To identify genetic host factors associated with HCV susceptibility among HIV-infected MSM.

Study design

The study is a case-control study. Cases are HIV-infected MSM with current or past HCV infection. Controls are HIV-infected MSM without HCV infection. Controls will be asked to fill out a questionnaire which enables assessment of risk behavior. In the final GWA study, only controls with high risk behavior (as evidenced by a risk score >= 2, see below) will be included for genetic testing.

This study will be done in collaboration with several locations in Amsterdam, New York and Berlin. DNA will be collected prospectively by buccal dry cotton swabs. The HCV status will be determined by HCV antibody testing, ALT levels and/or HCV RNA detection. Also will the participants be asked to fill in a questionnaire on risk behavior for acquiring HCV. The swabs collected outside the Netherlands will be stored in transport medium at room temperature and shipped to the Netherlands for DNA isolation. We aim to analyze a minimum of 500 cases and 500 controls, which is sufficiently powered to identify SNPS with ORs between 1.5 and 2, depending on the gene frequency. The GWAS will be performed at a GWAS facility at the EMC in Rotterdam. On the array 700.000 SNPs will be analyzed and up to 4 million can be computed from that data. These SNPs

will have a minor allele frequency (MAF) score ranging between 0.05-0.5. Data analysis and statistics will be performed in collaboration with Michael Tanck from the data analysis department at the AMC. A logistic regression (additive, dominant and no genetic model) will be performed on the data to estimate the Odds Ratio for specific SNPs and HCV. Controlling for multiple testing to accurately estimate significance the generally accepted 5 x 10^-8 threshold will be used. For the analysis we will be supported by the biostatistics department of the AMC (Michael Tanck)

Recruitment will take place between January 1st 2017 and August 1st 2017. Data-analysis and writing of manuscript deadline is 31st December 2017.

Study burden and risks

The inclusion can happen after regular poli visit so no extra visit to the hospital has to be made.
Inclusion will take about 15 minutes of a participants time.
The questionnaire consists of very personal questions wich can be experienced as unpleasant. However, there is always the option to skip a particular question.
Buccal swabs will be taken from the patient. This is a minimally invasive method.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- male
- HIV-1 infected
- MSM (men who have sex with men) risk group

Exclusion criteria

non-consent

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-02-2017
Enrollment:	930

Type:	Actual

Ethics review

Approved WMO Date:	18-01-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL59688.018.16