PREVALENCE AND NATURAL HISTORY OF HEART FAILURE IN OUTPATIENT HIV-INFECTED SUBJECTS: RATIONALE AND DESIGN OF THE HIV-HEART STUDY*

Till Neumann1, Stefan Esser1, Anja Porthoff5, Sabine Pankuweit1, Anja Neumann1, Frank Breuckmann1, Katrin Neuhaus1, Jana Kondratev1, Thomas Buck1, Thomas Müller-Tasch1, Rolf Wachter1, Christiane Prentin1, Gröz Gelbracht3, Wolfgang Herzog1, Burkert Piekske1, Mathias Rauchhaus4, Markus Lößler7, Bernhard Maisch1, Andreas Mürger1,11,12, Jürgen Wasmann1, Guido Gerken1, Norbert H. Brockmeyer2, Raimund Erbel1 for the HIV-HEART Study Investigative Group

on behalf of the Competence Network of Heart Failure and the Competence Network for HIV/AIDS

Essen, Bochum, Berlin, Göttlingen, Heidelberg, Marburg, Leipzig

Departments of Cardiology1, Gastroenterology2, and Dermatology3, University Hospital Essen; Department of Cardiology4, Chartis, University Hospital Berlin; the Department of Dermatology5, University Hospital Bochum; the Department of Cardiology6, University Hospital Marburg; the Department of Cardiology7, University Hospital Göttlingen; the Department of Clinical and Psychosomatic Medicine8, University Hospital Heidelberg; the Institute for Clinical Trials Leipzig9, University of Leipzig; the Department of Cardiology10, University Hospital Bochum; the Alfred Krupp von Bohlen und Halbach Foundation-Institute for Health Systems Management11, University of Duisburg-Essen, Germany

Abstract

Background: HIV infection is a global public health issue that is frequently associated with cardiac involvement. However, myocardial dysfunction and heart failure are often clinically occult or attributed incorrectly to other non-cardiac disease processes even a heightened awareness and knowledge for these cardiac diseases in HIV-infected patients may lead to earlier detection and a reduction in morbidity and mortality. The present study evaluates the frequency and clinical course of myocardial dysfunction and heart failure in a HIV-infected population.

Methods: The HIV-HEART (HIV-infection and HEART disease) study is a prospective, longitudinal cohort study. The study is designed and powered to define prevalence and natural history of chronic heart failure. Following a pilot-study of 105 HIV-infected subjects the HIV-HEART trial will contain 802 HIV-infected males and females with and without antiretroviral therapy in an urban population. HIV-HEART is performed by using non-invasive techniques for the quantification of exercise intolerance and ventricular dysfunction, including concentration of B-type natriuretic peptide (BNP), transitionary echocardiography and endurance testing. Patients with BNP >100 pg/ml achieve a magnetic resonance tomography of the heart for characterization of myocardial dysfunction and type of cardiomyopathy. To determine incidence and natural history of myocardial dysfunction and heart failure, a 2 year follow-up started in September 2006.

Conclusions: The HIV-HEART study will define the significance of myocardial dysfunction and heart failure in a HIV-infected urban population and classify appropriate methods for identifying high-risk patients, the basis for risk stratification and therapy.

Key words: human immunodeficiency virus, antiretroviral therapy, heart failure, myocardial dysfunction

Introduction

A variety of previous reports demonstrate that HIV infection is associated with cardiovascular involvement. At the beginning of the epidemic spread, cardiovascular problems, in particular myocardial disorders, were expected to be prominent. However, cardiac diseases, of HIV-infected patients were often overlooked or attributed incorrectly to other non-cardiac disease processes because of the urgency of life-threatening HIV-related problems. In recent years the therapeutic options of HIV-infection increased and HIV-associated cardiac diseases developed to a considerable health problem. One of the most serious cardiac manifestations are myocardial diseases resulting in ventricular dysfunction and heart failure. However, left ventricular dysfunction does not only predict reduced life quality, it is also an independent predictor of mortality in HIV-infected patients.

* The HIV-HEART study is part of the German Heart Failure Network and supported by the sponsorship of the Federal Ministry of Education and Research Germany.
The HIV-HEART (HIV-infection and HEART disease) is the first prospective epidemiological study which evaluates frequency and clinical course of myocardial dysfunction and chronic heart failure in a HIV-infected urban population. This report focuses on the clinical background of the HIV-HEART study and the methods being applied.

**METHODS**

**OVERVIEW**

The study is part of the German Heart Failure Network. It is performed in the Ruhr area, one of the largest industrial areas, located in the heart of Europe. The overall study group is defined by subjects with a known HIV-infection. Therefore, a local association of physicians specialized in the treatment of HIV-infected patients has been established. This local net holds contact even by conservative estimation to more than 1200 outpatients with HIV-infection.

Of all subjects, participating at the study, a targeted assessment of medical history and physical examination is performed. The included tests are explained and performed during the initial visit. For further information, questionnaires covering a comprehensive risk-assessment as well as socioeconomic aspects are completed by the participants and blood is drawn for comprehensive laboratory tests. Subsequent, heart rate

and blood pressure measurements, resting electrocardiogram (ECGs), six-minute walk test and transthoracic echocardiography are performed, all in compliance with the standing operating procedures (SOPs) of the German Heart Failure Network. A Follow-up is obtained 2 years after entry, when the participants will be seen again for a repeat assessment. The synopsis of the HIV-HEART study is presented in Figure 1.

**AIMS AND END POINTS OF THE STUDY**

The underlying aim of the study is to evaluate the prevalence, etiology and clinical course of myocardial dysfunction and heart failure in HIV-infected subjects. Myocardial dysfunction is defined by dyscontractile, hypococontractile or acontractile parts of the myocardial wall. Heart failure is defined by a reduced ejection fraction of less than 50% (pysotolic heart failure) or a pathologic filling pattern (diastolic echocardiography) determined by echocardiography in combination with common symptom of heart failure. Different types of cardiomyopathy are defined by common guidelines published by the World Health Organization. Further and detailed study aims are listed in Table 2.

**EXCLUSION CRITERIA**

Based on the fact that the HIV-HEART study focuses on myocardial diseases in general HIV-infected popula-
Table 1. Cardiac diseases in HIV-infected patients.

Pericardial diseases
- Pericardial effusion and Pericarditis
- Neoplasms (Kaposi’s sarcoma, lymphoma)

Myocardial diseases
- HIV-associated cardiomyopathy
- Myocardin (acute or chronic)
- Drug side-effects (especially by antiretroviral therapy)

Endocardial diseases
- Infective endocarditis (bacterial, mycotic)
- Nonbacterial thrombotic endocarditis

Vascular diseases
- Atherosclerosis, Vasculitis, perivascularitis
- Pulmonary arterial hypertension

Table 2. Study aims.

Primary
- Incidence, prevalence and etiology of myocardial dysfunction and chronic heart failure in HIV-infected subject, in particular focusing on the effect of antiretroviral therapy

Secondary
- Incidence, prevalence and etiology of further cardiovascular diseases in HIV-infected subjects
- Frequency of fatal and nonfatal cardiac events, or hospitalization for cardiac diseases
- Analysis of economic aspects of cardiovascular diseases in HIV-infected patients
- Quality of life, depressive comorbidity

Table 3. Inclusion and exclusion criteria.

Inclusion criteria
- Appropriate written informed consent
- Known to be human immunodeficiency virus positive
- ≥18 years of age at the time of signing informed consent
- Stable health condition within 4 weeks before inclusion

Exclusion criteria
- Unstable cardiovascular status within the last 4 weeks
- Current clinical treatment
- Pregnancy

Table 4. Laboratory tests of cardiac and HIV-specific parameters.

Common cardiac laboratory parameters
- Cholesterol enzymatic method (cholesterol esterase and cholesterol oxidase)
- Triglyceride Fossati three-step enzymatic reaction
- HDL-cholesterol polyethylene glycol (PEG) modified enzymes
- LDL-Cholesterol enzymatic method (cholesterol esterase and cholesterol oxidase)
- Glucose Stein utilizing hexokinase and glucose-6-phosphatase dehydrogenase enzymes
- HbA1c latex agglutination inhibition assay
- BNP fluorescence immunoassay

HIV-specific laboratory parameters
- CD4 cell counts flow cytometry
- HIV RNA test's R-DNA hybridization assay (lowest detection rate 50 copies/ml)

BNP = B-type natriuretic peptide

Earlier reports on the relative risk associated with the development of myocardial diseases within a population of HIV-infection subjects vary substantially and are limited by study participants. However, with a sample size of 800 participants at baseline, the prevalence of chronic heart failure could be estimated with an accuracy of less than ± 3.5 percent at the 95% confidence level.

Behavioural risk factors, including nutrition, smoking, alcohol consumption, and physical activity are assessed in the current study. In addition, medical history, such as previous cardiac or cardiovascular diseases, family history, medication, and symptoms of heart diseases are also evaluated. For the quality of life assessment standardized questionnaire are used, including Short-Form-36 Health Survey (SF-36) and EuroQol (EQ-5D). 13,14 Depressive mood is evaluated by the 9 items of the depression section of the PHQ-D. Education and profession are evaluated, as social gradients in cardiac morbidity and mortality have been consistently demonstrated in economically developed countries.

LABORATORY TESTS

General health is evaluated by a number of tests, which in part are listed in Table 3. Venous blood is collected into serum specimen tubes and centrifuged at 2000 rpm for 15 minutes. An aliquot is withdrawn to identify causal risk factors of cardiovascular diseases. To quantify brain natriuretic peptide (BNP), virus load and CD4-count, blood is collected into EDTA specimen tubes. Additional aliquots are stored at -80°C for future analysis.

GENETIC POLYMORPHISMS

Genetic polymorphisms have received great interest because they can modify the susceptibility for dilated...
cardiomyopathy disease. In this study, functional alter-
ations in several candidate genes are examined in co-
operation with the German Heart Failure Network. Susceptibility genes are defined as genes in which
functional polymorphisms are distributed differently in
HIV patients with and without dilated cardiomy-
opathy.

**Blood Pressure Measurements, Resting Electrocardiogram, Transthoracic Echocardiography**

Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) are measured by oscillometric sphygmomanometer. A digital 12-lead surface ECG is recorded in all patients.

Echocardiography was included into the study pro-
tocol, because of its feasibility to visualize a majority of
cardiac disorders in particular systolic and diastolic
dysfunction. In the current study, echocardiography
examinations are performed according to the Guide-
lines of the German Society of Echocardiography.18
As functional parameters mitral inflow velocity pattern and left ventricular outflow velocity are recorded. To
detect left ventricular diastolic dysfunction, the move-
ment of the lateral mitral annulus is acquired by tissue
Doppler imaging (TDI).19 Additionally pulsed Doppler pulmonary vein flow and TDI-index are mea-
sured.20

**Six-Minute Walk Test**

Previous studies have shown that the six-minute walk
test gives a reliable assess of the exercise capacity and
is highly reproducible in patients with cardiac symp-
toms.21,22 The participants in the current study per-
form a six-minute walk test in a quiet corridor to as-
 sess their levels of physical fitness. Each participant is
rested individually and constantly observed by a physi-
cian. Blood pressure and heart rate are determined be-
fore and after walking.

**Magnetic Resonance Tomography**

In case, heart failure is suspected by increased levels of
BNP, a visualizing of structural and functional aber-
tations by magnetic resonance imaging (MRI) is per-
formed. All examinations were performed on a 1.5T
MR scanner equipped with high performance gradi-
ents (Magnetom Sonata, Siemens Medical Solutions,
Erlangen, Germany). The MRI protocol included se-
quencies for the assessment of the myocardial function
and myocardial edema. Additionally, an inversion re-
cover fast low angle shot sequence was acquired in
short and long axis views 10 min after injection of a
0.2 mmol/kg bodyweight of Gd-DTPA (Schering AG,
Berlin, Germany) for signs of delayed enhancement.

**Economic Aspects**

To get information about direct costs of illness, pa-
tients are - beside of medication – asked about con-
tacts to physicians, hospitalization, and rehabilitation.
Additionally, for the evaluation of indirect costs, the
questionnaire contains questions about impaired or
lost ability to work.

**Discussion**

The HIV-HEART study will provide a large database of cardiovascular diseases and events in the general
population of HIV-infected patients of industrialized
countries. The primary focus is the determination of
prevalence and natural history of asymptomatic and
symptomatic myocardial dysfunction in the population
of HIV-infected subjects. The study focuses on the
improvement of the detection of these diseases even
in an early state by efficient risk assessment.

Since new antiretroviral drugs, such as protease-in-
hibitors and non-nucleoside reverse-transcriptase in-
hibitors, have significantly reduced morbidity and mor-
bidity in the last years, HIV-associated manifestations,
including cardiovascular diseases, became more promi-
nent. In recent years a variety of cardiovascular dis-
cases in HIV-infected patients has been published (see
Table 1).

Especially myocardial alterations now appear to be
one of the most important cardiac disorders of HIV-
infected subjects in the industrialized countries. How-
ever, only limited data exist about frequency and etiol-
ogy of cardiac diseases in HIV-infected patients. My-
ocardial dysfunction and heart failure significantly im-
pair quality of life and are associated with a high de-
pression rate which also might imply prognostic impli-
cations in non HIV-infected patients.23-25 However, no
information exists about effects of myocardial mal-
function on quality of life and depression in the popu-
lation of HIV-infected subjects up to now.

Proposed causes of myocardial diseases in HIV-in-
festected subjects are manifold. Myocardial disorders,
such as cardiomyopathy, could result of a direct infec-
tion of the heart by HIV, effects of circulating or sys-
temic toxins, infection of the heart by opportunistic
pathogens, toxicity of illicit, self-prescribed pharma-
ceuticals or home remedies, and nutritional disorders.8
Additionally, more than one factor may be operative in
a single patient, opening the possibility of combined
effects or comorbidity.26-28

In recent publications, HIV-infection is increasingly
recognized as an important cause of especially myocard-
ial disorders, particular dilated cardiomyopathy.29-31
being described in up to 30-40% of patients with
AIDS in clinical-pathological studies performed in the
pre-HAART period.30 In times of effective antiretro-
viral therapy, it could be assumed, that the better con-
trol of opportunistic infections is an example of the
beneficial impact of HAART on incidence and clinical
course of HIV-associated heart diseases. In contrast, it
had been described that HIV-associated dilated car-
diomyopathy is, in particular, associated with antiretro-
viral therapy.32,33

The present study analyses HIV-specific reasons of
myocardial dysfunction, including type and duration of
antiretroviral therapy and concentration of the HIV-
virus. Additionally, common risk factors of HIV-nega-
tive people for coronary heart disease and heart failure
are evaluated, such as smoking or arterial hyperten-
sion. For further characterization, the type of car-
dysmorphia due to the common classification of the WHO will be defined by echocardiography and mag- netic resonance tomography, which provides further information for the etiology of HIV-associated my- ocardial function.34

Even a variety of non-invasive techniques are per- formed, there is still a theoretical limitation which should be considered: In clinical practice the diagnosis of chronic heart failure commonly depends on typical symptoms. These symptoms are heterogeneous and often not specific. Therefore, a variety of non-invasive techniques has been developed until now. However, none of these tests alone could be used as a standard for the diagnosis of heart failure. Even more, each of these techniques reflect only an aspect of the disease. Focusing this problem, the present study is based on clinical symptoms as well as on the most common non-invasive techniques to make a whole view for kind and status of myocardial diseases in the examined pop- ulation possible.

CLINICAL IMPLICATIONS

The results from the HIV-HEART study will help to define whether myocardial disorders and chronic heart failure will play a major role in a general population of HIV-infected subjects. In addition, the current study will help to classify HIV-infected subjects into groups with low, intermediate or high risk for myocardial dis- orders, not only due to common established methods for non-HIV infected persons, but also for HIV-spe- cific parameters, such as state and duration of HIV-infection as well as duration and type of antiretroviral therapy.

LITERATURE


