

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

Till Neumann¹, Stefan Esser³, Anja Potthoff⁵, Sabine Pankuweit⁶, Anja Neumann¹², Frank Breuckmann¹, Katrin Neuhaus¹, Jana Kondratieva¹, Thomas Buck¹, Thomas Müller-Tasch⁸, Rolf Wachter⁷, Christiane Prettin⁹, Götz Gelbrich⁹, Wolfgang Herzog⁸, Burkert Pieske⁷, Mathias Rauchhaus⁴, Markus Löffler⁹, Bernhard Maisch⁶, Andreas Mügge¹⁰, Jürgen Wasem¹², Guido Gerken², Norbert H. Brockmeyer⁵, 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, Göttingen, Heidelberg, Marburg, Leipzig

Departments of Cardiology¹, Gastroenterology², and Dermatology³, University Hospital Essen;
Department of Cardiology⁴, Charite, University Hospital Berlin;
the Department of Dermatology⁵, University Hospital Bochum;
the Department of Cardiology⁶, University Hospital Marburg;
the Department of Cardiology⁷, University Hospital Göttingen;
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 Management¹², 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, long-term 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), transthoracic echocardiography and endurance testing. Patients with BNP >100 pg/ml achieve a magnetic resonance to-

mography 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.¹ At the beginning of the epidemic spread,² cardiovascular problems, in particular myocardial disorders, were expected to be prominent.³ 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.⁴

In recent years the therapeutic options of HIV-infection increased and HIV-associated cardiac diseases developed to a considerable health problem.³ One of the most serious cardiac manifestations are myocardial diseases resulting in ventricular dysfunction and heart failure.¹ However, left ventricular dysfunction does not only predict reduced life quality, it is also an indepen-

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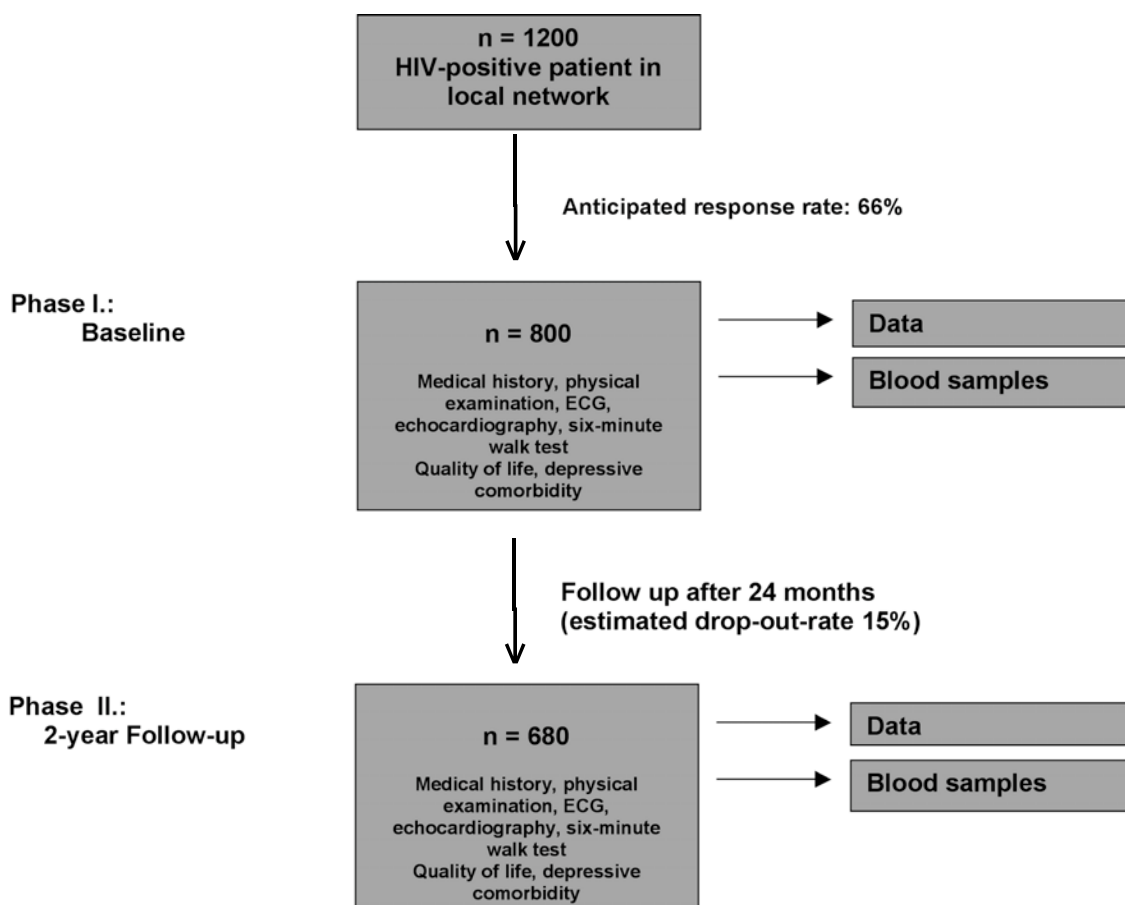


Fig. 1. Synopsis of the HIV-HEART study.

dent predictor of mortality in HIV-infected patients.

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, hypocontractile or acontractile parts of the myocardial wall. Heart failure is defined by a reduced ejection fraction of less than 50% (systolic 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

Table 1. Cardiac diseases in HIV-infected patients.

Pericardial diseases
<ul style="list-style-type: none"> • Pericardial effusion and Pericarditis • Neoplasm (Kaposi's sarcoma, lymphoma)
Myocardial diseases
<ul style="list-style-type: none"> • HIV-associated cardiomyopathy • Myocarditis (acute or chronic) • Drug side-effects (especially by antiretroviral therapy)
Endocardial diseases
<ul style="list-style-type: none"> • Infective endocarditis (bacterial, mycotic) • Nonbacterial thrombotic endocarditis
Vascular diseases
<ul style="list-style-type: none"> • Artherosclerosis, Vasculitis, perivasculitis • Pulmonary arterial hypertension

Table 2. Study aims.

Primary
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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 (cholesterinesterase and cholesteroloxidase)
• Glucose	Slein utilising 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 titre's	b-DNA hybridisation assay (lowest detection rate 50 copies/ml)

BNP = B-type natriuretic peptide

on myocardial diseases in general HIV-infected population, only a few exclusion criterias were previously defined. The exclusion criterias are unstable cardiovascular status with in the last four weeks prior to screening visit, current hospitalization, and pregnancy (Table 3).

SAMPLE SIZE

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.⁹⁻¹² 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.

QUESTIONNAIRES

Behavioral 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.¹⁵ Education and profession are evaluated, as social gradients in cardiac morbidity and mortality have been consistently demonstrated in economically developed countries.^{16,17}

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 alterations in several candidate genes are examined in cooperation 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 cardiomyopathy.

BLOOD PRESSURE MEASUREMENTS, RESTING
ELECTROCARDIOGRAM, TRANSTHORACIC
ECHOCARDIOGRAPHY

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

Echocardiography was included into the study protocol, 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 Guidelines 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 movement of the lateral mitral annulus is acquired by tissue Doppler imaging (TDI).¹⁹ Additionally pulsed Doppler pulmonary vein flow and Tei-index are measured.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 symptoms.^{21,22} The participants in the current study perform a six-minute walk test in a quiet corridor to assess their levels of physical fitness. Each participant is tested individually and constantly observed by a physician. Blood pressure and heart rate are determined before and after walking.

MAGNETIC RESONANCE TOMOGRAPHY

In case, heart failure is suspected by increased levels of BNP, a visualizing of structural and functional alterations by magnetic resonance imaging (MRI) is performed. All examinations were performed on a 1.5T MR scanner equipped with high performance gradients (Magnetom Sonata, Siemens Medical Solutions, Erlangen, Germany). The MRI protocol included sequences for the assessment of the myocardial function and myocardial edema. Additionally, an inversion recovery 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.

OECONOMIC ASPECTS

To get information about direct costs of illness, patients are - beside of medication - asked about contacts 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 industrial 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-inhibitors and non-nucleoside reverse-transcriptase inhibitors, have significantly reduced mortality and morbidity in the last years, HIV-associated manifestations, including cardiovascular diseases, became more prominent. In recent years a variety of cardiovascular diseases in HIV-infected patients had 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. However, only limited data exist about frequency and etiology of cardiac diseases in HIV-infected patients. Myocardial dysfunction and heart failure significantly impair quality of life and are associated with a high depression rate which also might imply prognostic implications in non HIV-infected patients.²³⁻²⁵ However, no information exists about effects of myocardial malfunction on quality of life and depression in the population of HIV-infected subjects up to now.

Proposed causes of myocardial diseases in HIV-infected subjects are manifold. Myocardial disorders, such as cardiomyopathy, could result of a direct infection of the heart by HIV, effects of circulating or systemic toxins, infection of the heart by opportunistic pathogens, toxicity of illicit, self-prescribed pharmaceuticals 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 myocardial 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 antiretroviral therapy, it could be assumed, that the better control 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 cardiomyopathy is, in particular, associated with antiretroviral 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-negative people for coronary heart disease and heart failure are evaluated, such as smoking or arterial hypertension. For further characterization, the type of cardiomyopathy due to the common classification of the WHO will be defined by echocardiography and magnetic resonance tomography, which provides further information for the etiology of HIV-associated myocardial function.³⁴

Even a variety of non-invasive techniques are performed, 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 population 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 disorders, not only due to common established methods for non-HIV infected persons, but also for HIV-specific parameters, such as state and duration of HIV-infection as well as duration and type of antiretroviral therapy.

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Address for correspondence:

Till Neumann, MD, MBA
Department of Cardiology
University of Duisburg-Essen, Medical School
Hufelandstr. 55