

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort Profile: The ATHENA (AIDS Therapy Evaluation in the Netherlands) national observational HIV cohort
AUTHORS	Boender, Tamara Sonia; Smit, Colette; Sighem, Ard I; Bezemer, Daniela; Ester, Catriona; Zaheri, Sima; Wit, FW; Reiss, Peter

VERSION 1 – REVIEW

REVIEWER	Eileen Martin, Ph.D. Professor of Psychiatry Rush University Medical Center 1645 W. Jackson Blvd., Suite 600 Chicago, IL 60612 USA
REVIEW RETURNED	17-Apr-2018

GENERAL COMMENTS	This is a broadly descriptive report of the ATHENA cohort, an observational study of HIV+ individuals receiving care in the Netherlands. This report provides a clearly written description of the overall approach to data collection, study procedures, variables extracted from medical records, advantages and limitations of the cohort, which could be very useful as an introduction to potential investigators considering further study of data drawn from this cohort. The authors do a good job acknowledging the limitations imposed by this observational cohort, such as the absence of a formal schedule of patient visits and reliance on data extracted from medical charts, and they clearly state that their data are limited to findings from HIV+ individuals in care. However, I think it might be useful to mention the limitations imposed by the difficulty of obtaining data regarding comorbid psychiatric and substance use and neurocognitive function. Additionally, a mention of the limits to generalization to the larger population of HIV+ individuals in the Netherlands and some further characterization of undiagnosed cases and populations with significant barriers to care (e.g., sex workers, transgender individuals, migrants).
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REVIEWER	Sabina A. Haberlen Assistant Scientist Department of Epidemiology Johns Hopkins Bloomberg School of Public Health U.S.A.
REVIEW RETURNED	31-May-2018

GENERAL COMMENTS	This cohort profile will be a useful source of information on the ATHENA cohort, with rich data and remarkable levels of coverage among people in HIV care in the Netherlands. The authors summarize some of the key contributions of the data to knowledge and practice that have indeed been impressive and wide-reaching, from facilitating the provision of life insurance to people with HIV to clinical quality indicators, to future focus areas on aging with HIV and comorbidities and coinfections. The enumeration of the many research collaborations in which this cohort participates highlights
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	<p>the utilization of this data and provides cross-references to many of the major HIV observational meta-cohort studies that will be handy for readers.</p> <p>The manuscript content and structure are well-conceived and executed, but a few minor revisions would further improve clarity on a few points.</p> <ol style="list-style-type: none"> 1. Is there any limitation in capturing the time of HIV diagnosis? With enrollment at entry into HIV care, it isn't clear whether diagnosis date is self-reported retrospectively upon entry to care, or whether this data is linked from the health records or done at the specialized HIV clinics 2. The scope of the original expansion of the cohort in 2000 isn't entirely clear—does the cohort size of 3,449 people in Nov 2000 (line 95) reflect retained participants from the original study, or the sample size after expansion to everyone starting HIV care at some point during that year? If the former, it would be helpful if this sentence specified that this was prior to expansion. 3. Can you provide slightly more detail on the opt-out process? When patients are informed by their treating physician about the data collection, do they see any written material, or is this done verbally? 4. Another notable strength of this data is that it follows patients even when they transfer care, which can be challenging in contexts with more fragmented health information systems. If space allows, it would be interesting to know how this is done.
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1 This is a broadly descriptive report of the ATHENA cohort, an observational study of HIV+ individuals receiving care in the Netherlands. This report provides a clearly written description of the overall approach to data collection, study procedures, variables extracted from medical records, advantages and limitations of the cohort, which could be very useful as an introduction to potential investigators considering further study of data drawn from this cohort. The authors do a good job acknowledging the limitations imposed by this observational cohort, such as the absence of a formal schedule of patient visits and reliance on data extracted from medical charts, and they clearly state that their data are limited to findings from HIV+ individuals in care.

We thank the reviewer for the positive comments.

1.1 However, I think it might be useful to mention the limitations imposed by the difficulty of obtaining data regarding comorbid psychiatric and substance use and neurocognitive function.

We have added these limitations to the manuscript, under 'Strengths and limitations': "Data collection largely depends on information captured by the medical records of HIV physicians and HIV nurse-consultants. This potentially limits obtaining more detailed data regarding less severe comorbid conditions and substance use, which may not be brought to the attention of the HIV physician."

1.2 Additionally, a mention of the limits to generalization to the larger population of HIV+ individuals in the Netherlands and some further characterization of undiagnosed cases and populations with significant barriers to care (e.g., sex workers, transgender individuals, migrants).

The cohort captures 98% of all people in HIV care in the Netherlands, and is therefore highly representative of the total population in HIV care. More information on the estimated population of still undiagnosed individuals with HIV is provided in the section 'The HIV epidemic in the Netherlands'. In addition, we have added this limitation to the manuscript, under 'Strengths and limitations':

“Furthermore, while the cohort captures 98% of all people in HIV care, we do not know well which (e.g. migrants) and how many people do not enter HIV care.”

Reviewer 2 This cohort profile will be a useful source of information on the ATHENA cohort, with rich data and remarkable levels of coverage among people in HIV care in the Netherlands. The authors summarize some of the key contributions of the data to knowledge and practice that have indeed been impressive and wide-reaching, from facilitating the provision of life insurance to people with HIV to clinical quality indicators, to future focus areas on aging with HIV and comorbidities and coinfections. The enumeration of the many research collaborations in which this cohort participates highlights the utilization of this data and provides crossreferences to many of the major HIV observational meta-cohort studies that will be handy for readers. The manuscript content and structure are well-conceived and executed, but a few minor revisions would further improve clarity on a few points.

We thank the reviewer for the positive comments. We have addressed the suggested minor revisions in the manuscript and below.

2.1 Is there any limitation in capturing the time of HIV diagnosis? With enrolment at entry into HIV care, it isn't clear whether diagnosis date is self-reported retrospectively upon entry to care, or whether this data is linked from the health records or done at the specialized HIV clinics.

We have clarified the data capture on the time of HIV diagnosis in the section ‘Methods of data collection and follow-up’: “The date of HIV diagnosis is usually retrieved from the letter of referral from the GP or STI clinic, or from health records in the HIV treatment centre, and can be self-reported upon entry to care if there is no documentation available. All reported HIV tests, test dates and test outcomes (including the last negative HIV tests) are captured in the cohort.”

2.2 The scope of the original expansion of the cohort in 2000 isn't entirely clear—does the cohort size of 3,449 people in Nov 2000 (line 95) reflect retained participants from the original study, or the sample size after expansion to everyone starting HIV care at some point during that year? If the former, it would be helpful if this sentence specified that this was prior to expansion.

We apologise for the ambiguity – the 3,449 indeed reflects the original study, before expansion. We have revised this sentence accordingly: “On 1 November 2000, prior to expansion, the cohort comprised 3 449 HIV-positive people, of whom 554 participated in a focus group for sub-studies on antiretroviral drug resistance and therapeutic drug monitoring, adherence, quality of life, and costs of treatment.”

2.3 Can you provide slightly more detail on the opt-out process? When patients are informed by their treating physician about the data collection, do they see any written material, or is this done verbally?

We have added more detail about the opt-out process to ‘Ethical approval & Patient consent’: “People entering HIV care receive both written material about participation in the ATHENA cohort and are informed by their treating physician of the purpose of collection of data, after which they can consent verbally or elect to opt-out.” In addition, we have added a reference to the additional information on the opt-out process to ‘Eligibility criteria and recruitment’: “Subsequently, enrolment in the ATHENA cohort is based on an opt-out principle (see also: Ethical approval & Patient consent).”

2.4 Another notable strength of this data is that it follows patients even when they transfer care, which can be challenging in contexts with more fragmented health information systems. If space allows, it would be interesting to know how this is done.

We have included this additional strength to ‘Strengths and limitations’, with additional explanation, as follows: “Furthermore, follow up and data collection continues uninterrupted for children who transfer from paediatric to adult HIV care, and for people who transfer to another HIV treatment centre within the Netherlands.” And added an explanatory line to the ‘Methods of data collection and follow-up’ section: “Participant registration and data collection are organised on a national level. When transferring to a new treatment centre within the Netherlands - in case of transfer from paediatric to adult care, or transfer to another treatment centre - the participants’ study identifier is retained and data collection is continued without interruption.”

VERSION 2 – REVIEW

REVIEWER	Eileen Martin, Ph.D. Rush University Medical Center United States
REVIEW RETURNED	07-Jul-2018
GENERAL COMMENTS	The authors have addressed reviewer comments satisfactorily.
REVIEWER	Sabina Haberlen Assistant Scientist Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology USA
REVIEW RETURNED	27-Jun-2018
GENERAL COMMENTS	The revisions have addressed my suggestions and further strengthened the paper. I recommend that it be accepted for publication.