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Understanding and avoiding late presentation for HIV diagnosis – study protocol of a trial using mixed methods (FindHIV)

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ABSTRACT

Many patients infected with HIV are diagnosed at an advanced stage of illness. These late presenters are individuals with a CD4 cell count of less than 350 cells/µL and/or an AIDS defining disease at initial HIV diagnosis. Purpose of FindHIV is to develop and distribute a questionnaire/scoring system aimed at a reduction in late presentation. FindHIV uses a mixed methods approach. In a first step, primary data of patients were collected. Inclusion criteria were: age ≥ 18 years, cognitive ability and language skills to participate in the study, initial HIV diagnosis within the past 6 months, and patient informed consent. Descriptive methods and regression models are used to identify: (1) patient characteristics associated with late presentation and (2) contacts to the healthcare system with indicator diseases that did not lead to HIV testing. Secondly, a questionnaire/scoring system is created by an expert panel. Afterwards the questionnaire/scoring system is to be disseminated. The greatest challenge was in reaching an adequate sample size. Another risk may be a recall bias. Nevertheless, FindHIV is devised as an in-depth study of the phenomenon of late presentation with potential to significantly improve HIV detection.

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; BFI-S, Big Five Inventory-Socio-Economic Panel; DRKS, German Clinical Trials Register; HIV, human immunodeficiency virus; LP/LPs, late presentation or late presenter/s

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HIV; late presentation; AIDS; mixed methods; scoring system; Germany

Introduction

Human immunodeficiency virus infection (HIV) is a chronic illness with global relevance. Its prevalence in Germany was estimated at 90,700 at the end of 2019. With 2,600 new cases, the incidence in Germany in 2019 was slightly higher than in 2018 (Robert Koch-Institut, 2020).

Current antiretroviral therapy (ART) allows disease control in many cases, not only preventing disease progression, but also allowing the reconstitution of the immune system and preventing further transmission of the virus (A Working Group of the Office of AIDS Research Advisory Council (OARAC), 2017; Cohen et al., 2016; Rodger et al., 2016). Starting therapy as early as possible is ideal for optimal therapy success. However, many cases with HIV infection are diagnosed in later stages of the illness. Late presenters (LPs) have been defined as individuals that have a CD4 cell count of less than 350 cells/µL and/or the acquired immunodeficiency syndrome (AIDS) at the time of HIV diagnosis (Antinori et al., 2010). Late presentation (LP) is associated with increased morbidity, mortality, and healthcare costs. The rate of LP for Germany is estimated at 44.0–63.5%; estimates for Europe are similar (Bickel et al., 2020; Kittner et al., 2015; Mocroft et al., 2015; Schäfer et al., 2016; Valbert et al., 2020; Zoufaly et al., 2011).

The United Nations have issued its 90-90-90 goal, aiming that 90% of HIV-positive people know about their infection, that 90% of people with a diagnosed HIV infection receive an ART, and that 90% of the people receiving ART have viral suppression (undetectable viral load). In order to meet the United Nations 90-90-90 goal for Germany, more HIV-infected individuals

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Trial registration: German Clinical Trials Register (DRKS00016351)

need to be diagnosed. At the end of 2019, this rate was estimated at maximum 88% (Robert Koch-Institut, 2020; The Joint United Nations Programme on HIV/AIDS (UNAIDS, 2014)) in Germany, about 12% of HIV-infected individuals still being undiagnosed.

Despite the relevance of LP, there is still little scientific evidence regarding the reasons for LP in Germany. In addition, evidence from international literature can only be applied to a limited extent to Germany, since factors for LP could be associated with socio-cultural aspects and healthcare systems.

In a first step, FindHIV aims to identify predictive variables of patient characteristics and facets of the healthcare system, which are significantly linked to LP. In a second step, a scoring system or questionnaire is to be developed by an expert panel based on the findings in the first step and those found in other published data. The scoring system/questionnaire is intended to serve as an instrument to direct HIV-infected persons to HIV testing and thus ultimately to decrease the rate of LP.

Materials and methods

Purpose and design

The primary research questions to be investigated within FindHIV are: (1) Which structural and patient-related factors characterize HIV LPs compared to other newly diagnosed cases? (2) Which of these characteristics influence/delay the diagnosis? Secondary research questions are: (3) How high is the proportion of LPs with an AIDS-defining disease in this cohort? (4) What are the typical symptoms/diseases causing patients to seek healthcare prior to HIV diagnosis? (5) Which specific areas of the healthcare system were contacted (specialist group, outpatient vs. inpatient care) before HIV diagnosis? (6) Which variables and questions are suitable for an instrument that focuses on early diagnosis of HIV infection? (7) Which recommendations for using the developed scoring system/questionnaire can lead to a reduction in late presentation in Germany?

A mixed methods approach is used to answer these questions. This approach combines qualitative and quantitative methods.

Primary data collection and analysis

Primary data of 800 newly diagnosed patients should be collected between January 2019 and March 2020 in 47 specialized practices, ambulatory care centers and hospitals throughout Germany. This setting reflects routine care of patients with HIV in Germany. Patients were eligible for inclusion if they met the following criteria: (1) age $\geq$ 18 years, (2) cognitive ability and language skills to participate in the study, (3) initial HIV diagnosis in the past six months, and (4) patient informed consent.

The data were collected by physicians via standardized reporting forms, which gather information on personality structure, socio-demographics, sexual contacts, partnership, knowledge of HIV transmission routes, circumstances of HIV testing, disease stage, symptoms and diseases prior to HIV diagnosis, as well as contacts to the healthcare system prior to HIV diagnosis with reason and the type of contact (inpatient versus outpatient; specialty if applicable). Relevant laboratory parameters were also documented. In addition, the attending physician assessed any missed diagnosing opportunities and possible reasons from both the patient- and care system side.

The standardized questionnaire was tested in a pretest using methods like think-aloud and probing (Häder, 2006). In addition to the FindHIV questionnaire, the already established Big Five Inventory-Socio-Economic Panel (BFI-S) was used to describe the patients' personality structures (Schupp & Gerlitz, 2014.).

Sample size calculation was performed. In order to guarantee a valid estimate in the logistic regression analysis, the data set should contain 10 events per variable (for example LP) per potential predictor (Hendriksen et al., 2013; Peduzzi et al., 1996). Using a conservative assumption of only 25% LP in the study population and 20 potential predictor variables, the number of required cases was calculated to be 800. The sample size has to be adjusted if there is a significantly different LP rate.

Various statistical methods will be used to analyze the data obtained according to the research questions. Methods include descriptive statistics, such as means, medians and ranges, as well as uni- and multivariate logistic (or other, if appropriate) regression models to identify predictors for late presentation. Depending on the scaling and the distribution of the variables, suitable tests for statistically significance of group differences/effects will be carried out, for example, the paired t-, the chi-squared or the Mann–Whitney *U* tests for univariate comparisons and likelihood ratio or Wald tests for multivariate testing.

The data collected will be stored for 10 years.

Development, discussion, and dissemination of an instrument to prevent delayed diagnosis

Parallel to the primary data collection, a systematic literature and internet search was carried out to identify any international scoring systems or questionnaires for the diagnosis of HIV/AIDS. Based on these findings and the results of the primary data collection, a scoring

system/questionnaire will be developed to enable earlier diagnosis through more specific testing offers. In addition to the instrument, recommendations on its application and dissemination will be developed.

This preliminary instrument will be discussed and revised by an expert panel consisting of representatives of self-help organizations, HIV practitioners, specialists from areas with a particularly large number of missed diagnosing opportunities, and representatives from health insurance companies.

At the end of this two-stage process a consented instrument and recommendations on its use will be made available. Dissemination will be aspired by publishing the questionnaire/scoring system in a peer reviewed journal. Additionally, it will be disseminated through medical associations, self-help organizations and the public health service. Institutions and specialist groups are specifically addressed to increase their awareness, if the primary data should indicate a relevant number of contacts to those specialists without subsequent testing for HIV.

Ethics and transparency

FindHIV is funded by the innovation fund of the 'Gemeinsamer Bundesausschuss' (Federal Joint Committee) (project number: VSF1_2017-174). Before starting the primary data collection, an ethics approval was obtained from the medical faculty of the University of Duisburg-Essen (application number: 18-8263-BO). Where necessary, local and regional ethic approvals from the medical chambers and medical faculties of participating university clinics were obtained. In addition, written informed consent for participation was obtained from every patient included in the primary data collection. FindHIV is registered in the German Clinical Trials Register (DRKS) (DRKS-identifier: DRKS00016351). The aim is to publish the results in a peer reviewed scientific journal.

Discussion

A decisive factor for FindHIV study success lies in an adequate sample size. To ensure sufficient recruitment and regional representation, a large number of centers were participating. Prior to the collection of data, numbers of previous new HIV diagnoses were queried at most centers to serve as an indicator for feasible sample size. In addition, the assumptions made in planning the number of cases are extremely cautious. This applies particularly the rate of LP, which is assumed to be 25%, while recent publications show a much higher LP rate in Germany.

The risk of recruiting a study population that is not representative of the German HIV care situation is countered by the large sample size. The estimated number of new diagnoses in Germany is 3300 in 2019. Assuming that the estimated incidence and number of new HIV diagnoses in the first quarter of 2020 is equal to a quarter of the incidence / number of new diagnoses in 2019, FindHIV will include approximately 25% of all newly HIV-infected and 19% of all first HIV diagnosis patients in Germany (Robert Koch-Institut, 2020). Also, the study centers cover all geographical regions of Germany, both urban and rural, and provide both in- and outpatient care.

The large number of centers is challenging and requires a high level of organization. All partners of the consortium have longstanding experience in the conduction of nationwide clinical and health economic studies in the field of HIV and can build on an existing well developed trial infrastructure (Valbert et al., 2020).

The recall bias must be taken into account when querying, for example, past contacts to the healthcare system. Considering the relatively young age of the expected study population, the effect size of recall bias associated with age is expected to be low. However, especially in late presenters with a longer period between acquiring HIV infection and HIV diagnosis, a recall bias cannot be ruled out.

The acceptance of the instrument to be developed is ensured by the broad involvement of various actors in the creation process. For example, physicians from specialist areas with a high number of missed diagnosing opportunities and representatives of self-help organizations are invited to participate.

Conclusion

With regard to the diagnosis of HIV, there are still many delays in Germany. A better understanding of the phenomenon of late presentation and the questionnaire/scoring system developed in the FindHIV study can lead to a more adequate HIV test offering. This significant improvement in the care of HIV is suitable to make severe disease progressions less frequent and to avoid transmissions of this infection.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Ethics approval and consent to participate

Before starting the primary data collection, an ethics approval was obtained from the medical faculty of the University of Duisburg-Essen (application number: 18-8263-BO). Where necessary, local and regional ethic approvals from the medical chambers and medical faculties of participating university clinics were obtained. In addition, written informed consent for participation is obtained from every patient included in the primary data collection.

Availability of data and materials

Case Report Form (available only in German).

BFI-S (available in English).

Competing interests

Frederik Valbert: Frederik Valbert has no competing interests to disclose.

Eva Wolf: Eva Wolf has no competing interests to disclose.

Stefan Preis: Stefan Preis has no competing interests to disclose.

Sven Schellberg: During the last 5 years Sven Schellberg has received: Honoraria for lectures or advise from: Gilead Sciences, ViiV Healthcare, Janssen Pharmaceuticals, Merck, Sharp & Dohme, Thera Therapeuticals, Abbvie, Hexal, GfK, IQVIA, Atheneum Partners, Guidepoint, Medothics, DAGNÄ; Study Support from: Gilead Sciences, ViiV Healthcare.

Knud Schewe: Knud Schewe has no competing interests to disclose.

Nikola Hanhoff: Nikola Hanhoff has no competing interests to disclose.

Birgit Mück: Birgit Mück has no competing interests to disclose.

Christine Kögl: Christine Kögl has no competing interests to disclose.

Paul Lauscher: Paul Lauscher has no competing interests to disclose.

Jürgen Wasem: Jürgen Wasem has no competing interests to disclose.

Silke Neusser: Silke Neusser has no competing interests to disclose.

Anja Neumann: Anja Neumann has no competing interests to disclose.

Authors' contributions

Author	Drafting of the manuscript	Critical revision of paper for important intellectual content	Concept and design	Obtaining funding	Supervision
Valbert	✓		✓		
Wolf		✓	✓	✓	✓
Preis		✓	✓	✓	✓
Schellberg		✓	✓	✓	✓
Schewe		✓	✓	✓	✓
Hanhoff		✓	✓		
Mück		✓	✓		
Kögl		✓	✓		
Lauscher		✓	✓		
Wasem		✓	✓	✓	✓
Neusser		✓	✓	✓	
Neumann		✓	✓	✓	✓

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References

Antinori, A., Coenen, T., Costagiola, C., Dedes, N., Ellefson, M., Gatell, J., Girardi, E., Johnson, M., Kirk, O., Lundgren, J., Mocroft, A., Monforte, A. D. A., Phillips, A., Raben, D., Rockstroh, J., & Sabin, C. (2010). Late presentation of HIV infection: A consensus definition. *HIV Medicine*, *12*(1), 61–64. https://doi.org/10.1111/j.1468-1293.2010.00857.x

Bickel, M., Hoffmann, C., Wolf, E., Baumgarten, A., Wyen, C., Christoph, D., Spinner, J., Postel, H., Esser, N., Mueller, S., Stoehr, M., Preis, A., Klauke, S., & Schewe, S., & K, C. (2020). High Effectiveness of Recommended first-line antiretroviral Therapies in Germany: A nationwide, Prospective cohort study. *Infection*, *48*(3), 453–461. https://doi.org/10.1007/s15010-020-01428-1

Cohen, M. S., Chen, Y. Q., McCauley, M., Gamble, T., Hosseinipour, M. C., Kumarasamy, N., Hakim, J. G., Kumwenda, J., Grinsztejn, B., Pilotto, J. H. S., Godbole, S. V., Chariyalertsak, S., Santos, B. R., Mayer, K. H., Hoffman, I. F., Eshleman, S. H., Piwowar-Manning, E., Cottle, L., Zhang, X. C., … Fleming, T. R. (2016). Antiretroviral therapy for the Prevention of HIV-1 transmission. *New England Journal of Medicine*, *375*(9), 830–839. https://doi.org/10.1056/NEJMoa1600693

Häder, M. (2006). *Empirische Sozialforschung: Eine Einführung*. Springer Fachmedien Wiesbaden.

Hendriksen, M., Geers, G., Moons, K., & Groot, J. D. (2013). Diagnostic and prognostic prediction models. *Journal of Thrombosis and Haemostasis*, *11*, 129–141. https://doi.org/10.1111/jth.12262

The Joint United Nations Programme on HIV/AIDS (UNAIDS). (2014). 90-90-90 An ambitious treatment target to help end the AIDS epidemic. Retrieved 30.04.2020 from https://www.unaids.org/en/resources/documents/2017/90-90-90

Kittner, J., Bialy, L. V., Wiltink, J., Thomaidis, T., Gospodinov, B., Rieke, A., Katz, F., Discher, T., Rath, K., Claus, B., Held, G., Friese, G., Schappert, B., Schuchmann, M., & Galle, P. (2015). Lack of awareness in both patients and physicians

contributes to a high rate of late presentation in a South West German HIV patient cohort. *Infection*, *43*(3), 299–305. https://doi.org/10.1007/s15010-014-0719-9

Mocroft, A., Lundgren, J., Antinori, A., Monforte, A. D. A., Brännström, J., Bonnet, F., Brockmeyer, N., Casabona, J., Castagna, A., Costagliola, D., Wit, S. D., & Fätkenheuer, G. (2015). Late presentation for HIV care across Europe: Update from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study, 2010 to 2013. *Eurosurveillance*, *20*(47), 7–18. https://doi.org/10.2807/1560-7917.ES.2015.20.47.30070

Peduzzi, P., Concato, J., Kemper, E., Holford, T., & Feinstein, A. (1996). A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology*, *49*(12), 1373–1379. https://doi.org/10.1016/S0895-4356(96)00236-3

Robert Koch-Institut. (2020). Epidemiologisches Bulletin Nr. 48.

Rodger, A., Cambiano, V., Bruun, T., Vernazza, P., Collins, S., Lunzen, J. V., Corbelli, G., Estrada, V., Geretti, A., Beloukas, A., Asboe, D., Viciana, P., & Gutiérrez, F. (2016). Sexual Activity without Condoms and risk of HIV transmission in Serodifferent Couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA*, *316*(2), 171–181. https://doi.org/10.1001/jama.2016.5148

Schäfer, G., Kreuels, B., Schmiedel, S., Hertling, S., Hüfner, A., Degen, O., Lunzen, J. V., & Wiesch, J. S. Z. (2016). High proportion of HIV late presenters at an academic tertiary care center in northern Germany confirms the results of several cohorts in Germany: Time to put better HIV screening efforts on the national agenda? *Infection*, *44*(3), 347–352. https://doi.org/10.1007/s15010-016-0880-4

Schupp, J., & Gerlitz, J. (2014). Big Five Inventory-SOEP (BFI-S) [Internet]. https://doi.org/10.6102/zis54

Valbert, F., Wolf, E., Schewe, C. K., Klauke, S., Hanhoff, N., Hoffmann, C., Preis, S., Pahmeier, K., Wasem, J., & Neumann, A. (2020).). Cost of human immunodeficiency virus (HIV) and determinants of healthcare Costs in HIV-infected treatment-Naive patients initiated on antiretroviral therapy in Germany: Experiences of the PROPHET study. *Value in Health*, *23*(10), 1324–1331. https://doi.org/10.1016/j.jval.2020.04.1836

A Working Group of the Office of AIDS Research Advisory Council (OARAC). (2017). Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. https://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL003510.pdf

Zoufaly, A., Heiden, M. A. D., Marcus, U., Hoffmann, C., Stellbrink, H., Voss, L., Lunzen, J. V., & Hamouda, O. (2011). Late presentation for HIV diagnosis and care in Germany. *HIV Medicine*, *13*(3), 172–181. https://doi.org/10.1111/j.1468-1293.2011.00958.x