CASCADE protocol: exploring current viral and host characteristics, measuring clinical and patient-reported outcomes, and understanding the lived experiences and needs of individuals with recently acquired HIV infection through a multicentre mixed-methods observational study in Europe and Canada

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ABSTRACT

Introduction Despite the availability of pre-exposure prophylaxis (PrEP) and antiretroviral therapy (ART), 21,793 people were newly diagnosed with HIV in Europe in 2019. The Concerted action on seroconversion to AIDS and death in Europe study aims to understand current drivers of the HIV epidemic; factors associated with access to, and uptake of prevention methods and ART initiation; and the experiences, needs and outcomes of people with recently acquired HIV.

Methods and analysis This longitudinal observational study is recruiting participants aged ≥16 years with documented laboratory evidence of HIV seroconversion from clinics in Canada and six European countries. We will analyse data from medical records, self-administered questionnaires, semistructured interviews and participatory photography. We will assess temporal trends in transmitted drug resistance and viral subtype and examine outcomes following early ART initiation. We will investigate patient-reported outcomes, well-being, and experiences of knowledge of, and attitudes to HIV precautions, including PrEP. We will analyse qualitative data thematically and triangulate quantitative and qualitative findings. As patient public involvement is central to this work, we have convened a community advisory board (CAB) comprising people living with HIV.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This Vannappagari, Alain Volny Anne, Lital Young is a large study of several European HIV cohorts and a Canadian cohort of individuals with recently acquired HIV.
⇒ Few large cohorts combine quantitative and highly participatory and innovative qualitative research methods.
⇒ Strong patient and public involvement ensures that the study is informed and shaped by those with lived experience of HIV and represents their research priorities.
⇒ Recruitment of individuals close to the time of HIV acquisition reduces, but does not eliminate, recall bias and will allow for detailed investigation of circumstances around HIV acquisition and missed opportunities for prevention.

INTRODUCTION

Despite widespread availability of antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) in Western Europe and Canada, continuing HIV transmission remains a significant challenge, with an estimated 15,782 individuals being newly diagnosed in Western Europe in 2021. Unsuppressed viraemia among people with...
undiagnosed HIV likely accounts for ongoing transmission.\textsuperscript{2–4} This is of particular relevance for those with recently acquired HIV as viral load remains markedly elevated for the first year or so following seroconversion before achieving a viral set point.\textsuperscript{5,6} Studies of individuals who have recently acquired HIV are crucial for detecting and measuring the effects of any changes in circulating virus, as well as providing insights into missed prevention opportunities.

Although guidelines recommend immediate ART initiation regardless of CD4+ cell count,\textsuperscript{6–10} there is evidence of variability in ART initiation among individuals with recent HIV infection, with one study reporting ART initiation 6 months after diagnosis.\textsuperscript{11} This is concerning as ART initiated in the first 4 months following seroconversion is more likely to lead to a rapid recovery of CD4+ cell counts.\textsuperscript{12} In addition, while clinical benefits of immediate ART initiation are well recognised in terms of reducing AIDS-defining morbidity and mortality,\textsuperscript{13–14} the association of ART and of new anti-HIV drugs, as they are introduced, with longer-term outcomes is not yet known.\textsuperscript{15–17} Evidence is needed to understand, for instance, the potential association between Integrase Strand Transfer Inhibitor-based ART regimens, which are highly efficacious for viral suppression,\textsuperscript{18} with weight gain and obesity\textsuperscript{19} or incident cardiovascular disease.\textsuperscript{20} Furthermore, little is known about the outcome and experiences of people who acquire HIV at older ages who may also have to manage age-related comorbidities and polypharmacy, with most evidence to date being based on those who acquired HIV at a younger age. Similarly, individuals who acquire HIV in their teens and early twenties may experience specific challenges with the prospect of lifelong medication. Finally, the majority of the limited qualitative literature on recently acquired HIV predates PrEP and treatment as prevention, and mainly focuses on circumstances around infection and sexual behaviour following diagnosis.

In summary, there is a need for interdisciplinary work that engages with the complexities of recently acquired HIV. We present the protocol for the Concerted action on recently acquired HIV in Western Europe and Canada. Using a mixed-methods approach, we aim to explore current viral and host characteristics, measure clinical and patient-reported outcomes, and understand the lived experiences and needs of individuals with recently acquired HIV in Western Europe and Canada.

Our specific research objectives are to:

- Describe current epidemic trends and examine the relationship between HIV incidence and use of prevention, including PrEP, and early ART initiation in the population.
- Gain insights into new infections occurring each year and reasons for continuing HIV transmission.
- Explore determinants of ART initiation, choice of regimen and outcome.
- Investigate how clinical, social and structural determinants (including stigma) impact on health outcomes and self-perception of well-being.
- Understand contextual factors that shape HIV acquisition risk and lived experiences of recently acquired HIV.

### METHODS AND ANALYSIS

#### The CASCADE collaboration

The CASCADE collaboration was established in 1997 with European Commission funding and subsequent renewal to pool data from cohorts of individuals with recently acquired HIV.\textsuperscript{22–24} The current study will create a new UK-based cohort of individuals with recently acquired HIV at the time of HIV diagnosis recruited directly from National Health Service clinics with clinical data entered into a REDCap database, and bring together eight long-established HIV cohorts (table 1).

#### Study design

Mixed-methods research ‘focuses on collecting, analysing, and mixing both quantitative and qualitative data in a single study or a series of studies’.\textsuperscript{25} The underlying assumption is that it has the potential to address research questions more comprehensively than by using either quantitative or qualitative methods alone.

Our study will use a mixed-methods convergent parallel design approach, with quantitative (comprising secondary analysis of existing data and primary data collection via questionnaires) and qualitative work (comprising semistructured interviews (SSIs) and participatory photography) undertaken concurrently. The study is organised into four inter-related work packages (WPs) detailed below:

**WP1: epidemic trends**

Clinical data on individuals from participating cohorts will be extracted and linked to HIV nucleotide sequences using the HIV Cohorts Data Exchange Protocol, a well-established protocol, which we had collaboratively
established, releasing the first version in September 2011. We will describe current epidemic trends and host (eg, age, sex, ethnicity, mode of infection) and viral (subtype, rate of transmitted drug resistance) characteristics, as well as viral/host interactions, CD4+ cell count and HIV RNA value at or close to the time of seroconversion. Likewise, we will determine whether the CD4+ cell count at seroconversion has changed over the past decade, or whether there are differences by person characteristics, including any prior exposure to PrEP. Pooling data from the CASCADE constituent cohorts will allow us to examine effects with greater precision and to compare across countries.

WP2: HIV acquisition risk and patient well-being
Through questionnaires completed by individuals with recently acquired HIV attending participating clinics, we will collect information about behaviour, knowledge and attitudes to HIV prevention prior and leading up to their HIV diagnosis; factors influencing ART initiation; experiences of taking early ART; self-perceptions of health and well-being over time; and experiences of living with

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Type of study</th>
<th>Participant demographics</th>
<th>Total study size/ number eligible for inclusion in CASCADE*</th>
<th>Study website</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQUIVIH Nouvelle Aquitaine Cohorte ANRS CO3, France3738</td>
<td>A prospective hospital-based cohort in South-Western France initiated 1987</td>
<td>Age ≥18 years with signed informed consent and affiliated to social security. 25% women, 42% MSM 19% PWID Median age 37 years</td>
<td>11 092/1548</td>
<td><a href="https://aquivih-na.fr">https://aquivih-na.fr</a></td>
</tr>
<tr>
<td>ANRS CO4 French Hospital Database on HIV, France3940</td>
<td>A nationwide prospective hospital-based cohort launched 1992</td>
<td>Aged &gt;18 years, HIV-1 or HIV-2 infection 34% women, 58% MSM, 10% PWID, 39% migrants Mean age 36 years</td>
<td>201 243/20 385 (Duplicates with PRIMO cohort will be removed)</td>
<td><a href="http://www.ANRS-CO4.FHDH.fr">www.ANRS-CO4.FHDH.fr</a></td>
</tr>
<tr>
<td>ANRS CO06 PRIMO Cohort, France4142</td>
<td>A multicentre cohort of seroconverters initiated 1996</td>
<td>Age ≥15 years, 12% women, 85% MSM, 5.6% born in Sub-Saharan Africa Median age 35 years</td>
<td>2578/2578</td>
<td></td>
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<tr>
<td>CoRIS cohort, Spain4344</td>
<td>A national multicentre prospective hospital-based cohort established 2004</td>
<td>Aged ≥18 years and naïve to ART at enrolment 15% women, 65% MSM, 7% PWID, 45% migrants</td>
<td>18 573/1044</td>
<td><a href="https://coris.iscii.es/en">https://coris.iscii.es/en</a></td>
</tr>
<tr>
<td>Athens Multicentre AIDS Cohort Study, Greece45</td>
<td>A collaborative population-based cohort initiated 1996</td>
<td>All HIV+under follow-up ≥1996 in one of the collaborating clinics 16% female, 52% MSM, 23% MSW, 11% PWID Median age 33.9 years</td>
<td>12 908/513</td>
<td></td>
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<tr>
<td>AIDS Therapy Evaluation in the Netherlands/ Stichting hiv monitoring, Netherlands46</td>
<td>A national observational HIV cohort established 1998</td>
<td>All individuals with HIV in care in the Netherlands 6% female, 86% MSM Median age 34.8 years</td>
<td>30 850/4341</td>
<td><a href="https://www.hiv-monitoring.nl/en">https://www.hiv-monitoring.nl/en</a></td>
</tr>
<tr>
<td>InfCareHIV, Sweden4748</td>
<td>A national hospital-based HIV cohort of retrospective and prospective data established 2003</td>
<td>39% women at birth, 64% migrants, 51% MSW</td>
<td>13 029/949</td>
<td><a href="https://infcarehiv.se">https://infcarehiv.se</a></td>
</tr>
<tr>
<td>Southern Alberta Clinic Canada4950</td>
<td>A prospective and retrospective HIV cohort of individuals attending a single centre including data from 1989</td>
<td>All persons with HIV living in southern Alberta 20% female, 40% migrants Median age 53 years</td>
<td>2400/270</td>
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</table>

*At last database update.
CASCADE, Concerted action on seroconversion to AIDS and death in Europe; MSM, men who have sex with men; MSW, sex between men and women; PWID, people who inject drugs.
HIV (see online supplemental documents). PROMs data will focus on mental health, health-related quality of life, experiences of stigma and symptoms. The questionnaire is informed by the theoretical framework of COM-B, a theory of change model that understands behaviour (B) as an interaction between the necessary conditions of capability (C), opportunity (O) and motivation (M). Participants will be invited to complete a follow-up questionnaire between 12 and 18 months after completing the baseline questionnaire.

WP3: effectiveness of ART
Using clinical data and laboratory results, we will assess whether ART in individuals with recently acquired HIV has the potential to restore CD4+ cell count and CD4:CD8 ratio to normal levels and rapidly lower HIV viral load; evaluate treatment effectiveness and tolerability; investigate differences between immediate and delayed ART at seroconversion; determine treatment durability and rates and predictors of starting and switching regimens; investigate differences among drug classes in terms of virological and immunological response, especially in persons with very high initial viraemia or seroconversion illness; and evaluate the burden of concomitant medications, particularly in those aged over 50, under 25 and those experiencing symptomatic seroconversion. This WP will combine individual characteristics, clinical data and laboratory test results from participants’ medical records and data from questionnaires.

WP4: qualitative investigation of experiences
We will prospectively recruit 20–30 participants in total from three countries in Europe (UK, Greece and Spain) for SSI covering the following themes:

► Experiences of HIV testing.
► Attitudes to and experiences of combination prevention.
► Access to combination prevention.
► Barriers to and facilitators of combination prevention uptake and adherence.
► Access to immediate ART.
► Barriers to and facilitators of immediate ART adherence.
► Impact of recently acquired HIV on sexual behaviour.
► Lived experiences of recently acquired HIV, including stigma.

Qualitative approaches will allow us to capture lived experiences, the context within which decisions are made and outcomes are reached, and the motivations underlying particular health behaviours. They can, therefore, provide a deeper insight into, for example, the reasons why PrEP and other methods of prevention were not used, barriers to ART adherence and why individuals choose to delay or stop ART. SSIs will be conducted either face to face, by telephone or via online video. Participants will be invited to a baseline SSI of approximately 1 hour, and an exit SSI of the same length around 12–18 months later. In the intervening period, participants will be asked to submit between one and five photographs (with a written or voice-recorded explanation), or complete and submit a short writing task at 3, 6, 9 and 12 months (depending on participant preference). Photographs and writing exercises will be elicited through prompts sent by short message service text message or email. Towards the end of the study, we will invite participatory photography participants to two 2-hour online workshops, during which they will be invited to share and discuss their photographs with each other and reflect on their experiences.

We have developed a modified version of the photovoice method, a method which has been widely deployed in health research, including HIV, as photovoice is traditionally conducted face to face over a short period of time. The adaptation allows us to conduct the research remotely and to collect data over a longer period of time at predefined time points. The exit interview will use photo elicitation, meaning that participants will be asked to reflect on their photographs (or writing tasks) as a focus of discussion. The longitudinal qualitative design will allow us to build rapport and explore how experiences change over time.

Recruitment of participants
Pooled clinical data for WPs 1 and 3 will include all those eligible and already enrolled into a participating cohort, or recruited through UK clinics, as well as individuals acquiring HIV in the 12-month period preceding recruitment prospectively. Pooled clinical data will thus potentially include individuals acquiring HIV from the 1980s to 2024. For WPs 2 and 4, only individuals with recently acquired HIV in the 12-month period preceding recruitment are eligible. Due to the relatively small number of participants recruited to WP4 (20–30 across all sites), we will not be quota sampling by selected characteristics.

Consent is already in place for pooling clinical data (WPs 1 and 3). Cohort leads of existing cohorts will identify individuals who meet the inclusion criteria from databases: aged 16 years or over, with confirmed evidence of recently acquired HIV at the time of diagnosis (see table 2). In the UK, clinical research staff will approach potential participants to invite them to take part, and those interested will receive participant information sheets and sign a consent form. Identified eligible participants across all cohorts will need separate consent to take part in WP2 (questionnaire) and WP4 (interviews and participatory photography), which will be initiated through their respective clinical centres (in UK) or cohort leads (elsewhere). Cohort leads may recompense participants for their time with a gift voucher for £10 (or equivalent) for completing each baseline and follow-up questionnaire, and £20 (or equivalent) for participating in interviews or photography workshops.
Analysis plan

We will analyse quantitative and qualitative data separately, and where possible, conduct integrated mixed-methods analyses to triangulate and contextualise the findings.35

Quantitative analysis will combine data pooled for WPs 1–3. As well as descriptive analyses, we will use regression analysis to examine changes in person characteristics and trends over calendar time. We will use software previously developed by the group to create analysis files of the interpretations from HIV sequences, for example, viral subtype, position of mutations and drug susceptibility scores. We will use logistic regression to examine the association between transmitted drug resistance mutations and year of seroconversion, adjusting for confounders. To examine changes in initial CD4+ cell count and HIV RNA values, all longitudinal measurements before the initiation of ART will be analysed using linear or fractional polynomial mixed models adjusting for all available potential confounders. The variance of the responses and the within-subjects correlation will be modelled through the inclusion of a random intercept term and a number of random functions of time since seroconversion (eg, natural cubic splines) on top of the level 1 errors. Calendar time effects will be modelled through natural cubic splines.

We will analyse questionnaire data using regression analysis to examine the association between several factors (demographic characteristics, knowledge, attitudes and experience) and outcomes, including PROMs. Qualitative data will be synthesised during data collection using a modified rapid assessment procedure (RAP) sheet.36 A separate RAP sheet will be created for baseline SSI, participatory photography and exit SSI. This will allow us to identify emerging findings (including highlighting gaps in data collection that need to be addressed or topics to be further explored) and facilitate consistency across settings. Thematic analysis of SSI data using NVivo will be conducted. The analysis will include the interpretation of visual materials, writing tasks and workshops.

To achieve the mixed-methods data integration, we will analyse the qualitative data thematically using a deductive organising framework derived from results from the quantitative analyses.35 This will facilitate integration of quantitative and qualitative data. For instance, if quantitative analyses reveal reduced access to immediate ART among older people, we will interrogate the qualitative dataset to explore barriers and facilitators to immediate ART in this group. To aid this process, we will use coding matrices.

ETHICS AND DISSEMINATION

Research ethics approval

CASCADE constituent cohort leads obtained ethics approval to pool clinical data following informed signed consent. The following committees revised and approved the protocols: The Research Ethics Committee H. General Universitario Gregorio Marañon on 20 April 2012 (CoRIS Cohort), the Commision Nationale de l’informatique et des Libertés on 27 November 1991, renewed authorisations were obtained in 2021 (19 February 2021 and 30 March 2021) (French Hospital database on HIV, the avis initial du CPP on 2 July 1996 (PRIMO cohort), the Comité de protection des personnes Sud-ouest et outre-mer III on 25 May 2016 (Cohort Aquitaine), the institutional review board (ATHENA cohort), the Bioethics and Deontology Committee of the Medical School of the National and Kapodistrian University of Athens on 18 October 2005, and the National Organisation of Medicines on 5

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### Table 2 Inclusion and exclusion criteria

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<thead>
<tr>
<th>Inclusion criteria</th>
<th>Confirmed laboratory evidence of seroconversion in previous 12 months that requires fulfilling at least one of the following:</th>
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<tr>
<td></td>
<td>HIV positive antibody test within 12 months of an HIV-negative antibody test.</td>
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<td></td>
<td>HIV antibody negative with positive RT-PCR.</td>
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<td></td>
<td>Test ‘incident’ using a recent incident testing algorithm assay.</td>
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<td></td>
<td>Equivocal HIV antibody test supported by a repeat test within a 2-week period showing a rising optical density.</td>
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<td></td>
<td>Have clinical manifestations of symptomatic HIV seroconversion illness supported by antigen positivity and &lt;4 bands positive on Western Blot.</td>
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<td></td>
<td>Aged 16 or over at the time of confirmed HIV infection.</td>
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<td></td>
<td>Attending HIV services in participating clinics.</td>
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<td></td>
<td>Able to complete the consent process.</td>
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<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th>No confirmed laboratory evidence of HIV seroconversion.</th>
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<tr>
<td></td>
<td>Younger than 16 years of age.</td>
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<td></td>
<td>Not attending HIV services at one of the clinical study sites.</td>
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<td></td>
<td>Unable to consent to participate.</td>
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June 2006 (AMACS cohort), and the Conjoint Health Research Ethics Board (CHREB), University of Calgary on 2 July 2020 (Southern Alberta cohort). Approval for self-completed questionnaires and qualitative work is currently in progress. This study has been revised and approved in the UK by the Yorkshire and the Humber—South Yorkshire Research Ethics Committee (22/YH/0114) on 20 June 2022, in Sweden by the Ethics Review Authority 23 May 2022 (Dnr 2022-00543-01), and in Spain by the Research Ethics Committee of the Institute of Health Carlos III (CEI PI 66_2022) on 21 September 2022. Signed consent will be obtained by all the participants. Participants have the right to enrol in any or none of the WPs. While they may not personally benefit from taking part in CASCADE, the knowledge gained through this research will help to inform policy and improve health services.

Data storage and security
Patient privacy and confidentiality will be central to the study. A dataset, with all personal identifiers removed, will be generated for analyses. Care providers will not have access to questionnaire responses or to information shared through SSIs. Pooled clinical data will be deidentified and a linking log with identifiers will be kept and stored securely by the participating cohort sites. Questionnaires will be submitted by participants directly into a REDCap database within University College London’s (UCL) Data Safe Haven (DSH). Qualitative data will be transcribed and pseudo-anonymised before being sent to the UCL DSH via managed file transfer. This study has been registered in the UCL Data Protection Office (Z6364106/2022/03/83). CASCADE data will be archived in UCL archive facilities for a minimum of 10 years after publication in accordance with UCL Research Data Policy.

Patient and public involvement
The involvement of people living with HIV is central to this study and takes place at several points during the project. Since its inception in 1997, CASCADE has included representatives from the community of people living with HIV as advisory group members. With the launch of this new study, some of the original community representatives remain closely involved as members of the CASCADE Executive Committee, and the social-science subcommittee for WPs 2 and 4. Community representatives are included in the latter subcommittee, ensuring a range of perspectives. We aim to ensure that community representatives are diverse in terms of gender, ethnicity, age and HIV acquisition risk. Community representatives attend steering group meetings, review documents, and contribute to analyses and papers as coauthors. So far, CASCADE community representatives have guided design and conduct of the study including questionnaire design and interview topic guide.

In Autumn 2021, we held a series of patient public involvement (PPI) meetings in France, Greece and the UK. These comprised people living with HIV, recruited by CASCADE community representatives, who also cofacilitated these meetings. These meetings further shaped the design and conduct of our work, helping us to develop an approach and tools that are sensitive to the needs of people who have recently acquired HIV. All our PPI work has been costed and we reimburse our community representatives at rates recommended by the UK’s National Institute for Health and Care Research, in recognition of their time and expertise.

Dissemination plan
Findings will be communicated using a comprehensive dissemination strategy. We will use various forms of media to reach a diverse range of stakeholder groups and individuals, at the local, national and international level. This will include the use of academic media (i.e., peer-reviewed journal articles, national and international conference presentations), and social media. Finally, we will ask participants in WP4 (investigation of qualitative experiences) for consent to share images from the participatory photography project in the form of a physical or online art exhibition (subject to further funding). This exhibition will be created with CASCADE community representatives.

We have a study specific Twitter account (@study_cascade) and a study website (https://www.cascadestudy.net), allowing us to engage with people living with HIV, the academic community, clinicians and the wider public. We aim to produce accessible infographic summaries of key findings and will present an overview of the study and findings through a series of webinars.

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Contributors CASCADE Collaboration: CASCADE Executive Committee: Santiago Moreno (Chair), Fionn Burns, Rafael Eduardo Campo, Harmony Garges, Cristina Mussini, Nikos Pantazis, Barbara Pinto, Kholoud Porter, Caroline Sabin, Shema Tarqi, Giota Touloumi, Vani Vannappagari, Alain Volny Anne, Lital Young. CASCADE Scientific Steering Committee: John Gill (co-chair), Kholoud Porter (co-chair), Christina Carlander, Rafael Eduardo Campo, Harmony Garges, Sophie Grabar, Inna Jarrin, Laurence Meyer, Barbara Pinto, Giota Touloumi, Marc van der Valk, Vani Vannappagari, Alain Volny Anne, Linda Wittkop, Lital Young. CASCADE Social Science subcommittee: Shema Tarqi (Chair), Aigis Alesan, Diana Barger, Udi Davidovich, Marie Dos Santos, Lars Eriksson, Eli Fitzgerald, John, MG Sophie Grabar, Inna Jarrin, Argyro Karakosta, Hartmut Krentz, Cristina Mussini, Emily Jay Nicholls, Nicoletta Policek, Elisa Ruiz-Burga, Chris Sandford, Bruno Spire, Inês Suarez-Garcia, Giota Touloumi, Alain Volny Anne.

The study protocol was conceptualised by KP, GT, MJG, CS, CM and LM. ST, EJN and FMB contributed to study design and developed the rationale and methodology for WPs 2 and 4. ER-B wrote the first draft of the manuscript. AWA, CC, SG, LJ, MVoV, LW, BS and NP provided critical feedback on overall study design and manuscript. All authors read, revised and approved the final manuscript.

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Competing interests The funders did not participate in the study design and will not intervene in its process, analysis or publication of the findings. ST has received speaker honoraria and consultancy fees from Gilead Sciences. CC has received speaker/moderator honoraria and advisory board fees from Gilead Sciences, GSK/ViV and MSD as well as an unrestricted Gilead Sciences Nordic Fellowship Research Grant. CS has received funding from Gilead Sciences, ViV Healthcare and Janssen-Cilag for participation in Advisory Boards, speaker panels and for preparation of educational materials. MVoV has received consultancy fees for participation in advisory boards and research grants from Gilead, MSD and ViV all paid to his institution. FMB has received funding from Gilead Sciences Ltd for preparation and delivery of educational materials. LJ has received teaching fees from ViV Healthcare and advisory fees from Gilead Sciences. GT has received research grants and advisory board fees from Gilead, all paid to her institution, and MJG has received honoraria for ad hoc participation in national Advisory boards of Gilead Merck and ViV.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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