Checklist for studies of HIV Drug Resistance prevalence or incidence (CEDRIC-HIV): rationale and recommended use

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Abstract

HIV drug resistance (HIVDR) is a major challenge to the effectiveness of antiretroviral therapy (ART). Global efforts in addressing HIVDR require clear, transparent, and replicable reporting of HIVDR studies. We describe the rationale and recommended use of a checklist of items that should be included in reports of HIVDR incidence or prevalence. After preliminary consultations with experts and establishing the need for guidance, we used a sequential explanatory mixed methods approach to create the checklist. The checklist and accompanying articles were reviewed by the writing team and validated externally. The Checklist for studies of HIV Drug Resistance prevalence or incidence (CEDRIC-HIV) includes 15 recommended items that would enhance transparency and facilitate interpretation, comparability, and replicability of HIVDR studies. CEDRIC-HIV will help authors of HIVDR studies prepare research reports and help reviewers and editors to assess completeness of reporting. It will also assist statistical pooling and interpretation of HIVDR data.

Background:

Close to 37.7 million people were living with HIV in 2020, and in 2021 approximately 28.2 million people were accessing antiretroviral therapy (ART) worldwide.[1] There has been considerable scale up of ART, with new recommendations to test and treat,[2] and for the use of antiretroviral drugs for the prevention of HIV infection. While ever expanding access to ART has reduced Acquired Immune Deficiency Syndrome (AIDS)-related morbidity and mortality, the emergence of HIV drug resistance (HIVDR) over time remains a public health challenge.[3]

Broadly, for the purposes of discussion and public health policy making, HIVDR can be divided into three main categories. Acquired drug resistance (ADR) occurs when drug resistance is selected for in an individual receiving antiretroviral drugs (either as therapy or as prevention for HIV infection) with sub-optimal dosing or poor adherence. Transmitted drug resistance (TDR) occurs when a drug-naïve individual is infected with a drug-resistant virus. Pre-treatment drug resistance (PDR) is drug resistance detected at the time of ART initiation or re-initiation (i.e., detected PDR may therefore be either TDR or ADR or both).[4] In addition, natural drug resistance occurs in HIV type 2 and in HIV-1 groups N and O. This naturally occurring drug resistance is due to the existence of pre-existing polymorphisms conferring innate resistance to first-generation non-nucleoside reverse transcriptase inhibitors [NNRTI]), thymidine analogues, and/or integrase inhibitors. [5,6]

In a public health context where ART is provided in the absence of individual HIVDR testing, PDR is most concerning because it may exist in people who do not know their HIV status and therefore may continue to transmit infection. Depending on available ART, PDR may compromise the effectiveness of ART, if the resistance mutations relate to one or more of the drugs in the ART regimen. However, with the global shift to integrase inhibitor-based ART, specifically, dolutegravir-based ART, PDR may be less relevant. Naturally occurring resistance observed in HIV-2 and in HIV-1 Groups N and O is less relevant from a pubic health standpoint, due to their limited global spread. .[2]

Given the absence of individual HIV drug resistance testing in most low- and middle-income countries, national and regional genotyping surveillance are pillars in the identification and management of drug resistance. Sound surveillance of HIV drug resistance requires knowledge of the affected populations and how resistance to drugs and drug classes emerges. From a public health perspective, there is value in assessing trends in prevalence or incidence of HIVDR over time, including clustered outbreaks of drug resistance, as robust measurements are required to ensure timely and appropriate responses to HIVDR within and between populations over time, including establishment of agreed upon population-level thresholds which necessitate public health or programmatic response.[7] As newer drugs are developed and used in different case scenarios (e.g., Pre-Exposure Prophylaxis [PrEP]), HIVDR standardized surveillance takes on enhanced importance.[7]

This is particularly true for regions of the world where HIVDR testing is costly, and not performed as part of the standard of care. In these countries, decision-makers must rely on population-level HIVDR prevalence estimates to determine if a drug should be used in a first-line or subsequent drug regimen.[4] Therefore, the prevalence of HIVDR should be measured over time and across populations to understand the possible impact of resistance on the effectiveness of ART regimens.

For studies of HIV drug resistance to be optimally interpreted individually or synthesized for systematic reviews or meta-analyses, contextual information regarding how and when the data were generated are critical. For example, recent studies highlight several limitations in the reporting of studies on HIV drug resistance, [8,9] hence the need for standardized guidance.

Development of the checklist:

We used the guidance proposed for developers of reporting guidelines which outline 18 steps in five phases: an initial preparatory phase (identifying the need for guidance and literature review); pre-meeting planning; a face-to-face (or virtual) consensus meeting; post meeting activities; and post-publication activities.[10] In brief, we established the need for guidelines based on a systematic review of the prevalence of HIV drug resistance in key populations,[8] and a subsequent methodological study highlighting important gaps in reporting.[9] We used a mixed methods sequential explanatory approach with two phases. The protocol for this mixed methods study is published elsewhere.[11] This checklist was registered on the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network website on the 22 September 2020.

In the first phase, we generated a list of participants from the authorship lists of articles included in the methodological review and collected data from 51 authors. In this survey, twenty-three (23) items were proposed, and participants were allowed to propose additional items. We asked responders to declare if an item was 'essential', 'useful but not essential', or 'not necessary'. A validity ratio was computed to determine the items that at least 50% of the participants thought were essential.[12] The "essential" items and the newly proposed items were compiled into a list for discussion.

In the second phase we conducted two focus group discussions. Participants were presented with the lists of items and requested to discuss the importance of reporting these items, whether they should be reported and why. The results of these discussions were compiled into a reporting checklist and rationale which is reported here. Full details of the mixed methods study will be reported separately and are under review.

The items on the checklist were reviewed and refined for clarity by the writing team which includes the participants of the focus group and invited content experts. This document and the checklist were also reviewed by external parties including patient representatives.

Scope of intended use:

The archetypical study design for prevalence or incidence would be a cross-sectional observational study.[13] However, prevalence and incidence data may be generated from both observational (cross sectional or longitudinal) and experimental studies.[13] This reporting checklist is meant to support transparent and replicable reporting of HIV drug resistance data from any study design. As such it was not developed as an extension to any of the popular design-based reporting guidelines like STROBE or CONSORT,[14,15] but rather as a topic-based reporting guideline, similar to STARD (Standards for Reporting of Diagnostic Accuracy Studies)[16] or REMARK (REporting recommendations for tumour MARKer prognostic studies).[17]

These guidelines are not meant to inform the design or implementation of research and are not intended to be prescriptive. The goal, as with all reporting guidelines, is that what was done is presented clearly and in a manner that can inform replication, comparisons, and pooling of data. These guidelines can be used by individual researchers or by locoregional programs alongside the WHO HIVDR surveillance guidance. [18]

While there is immense value in data sharing and collaboration across institutions and regions, there is also a potential for harm. For example, phylogenetic analyses can lead to potential identification of HIV transmission between individuals and aggravate stigma and marginalization of certain groups, if their characteristics accompany the analyses.[19] Ethical, legal and safe approaches to generating and using phylogenetic data are beyond the scope of this paper, but we advise that authors should carefully consider the wording used and level of granularity reported on transmission clusters.[19]

How to use this paper:

Below we provide a list of recommended reporting items. A brief explanation is followed by an example drawn from a paper in which the item was reported. In some instances, more than one example is shown.

The choice of articles from which the examples were drawn is arbitrary and does not imply that the paper reported all the items on the checklist.

CEDRIC-HIV:

The Checklist for studies of Drug Resistance in HIV (CEDRIC-HIV) prevalence or incidence includes 15 reporting items to be addressed in the title, introduction, methods, results, and discussion sections of the paper (Table 1). Additional items that could be reported where relevant are also listed. We have provided a description of the reporting items below with a rationale and examples.

Title

1) The title of the paper should identify the report as a study of HIV drug resistance if that is the primary goal, and provide details on the population, the type of drug resistance and the location of the study. This information will help to properly index and subsequently identify the study.[20]
   Example: In this study, the authors clearly outline the type of drug resistance, the population included in the study and the location of the study: "Transmitted drug resistance in recently infected HIV-positive Individuals from four urban locations across Asia (2007–2010) – TASER-S"[21]
   Example: In this study the authors outline the type of drug resistance, the population, and the location of the study: "Transmitted Antiretroviral Drug Resistance Among Drug-Naive Female Sex Workers With Recent Infection in Kampala, Uganda"[22]

Introduction

2) In the introduction, authors should provide contextual information that will facilitate interpretation of the results. For example, the ARV drug classes (or regimens) commonly used in the region the study was conducted, previous studies of HIVDR in that population and any relevant changes over time.
   Example: In this study, in the introduction section, the authors describe the type of ART used: "Following World Health Organization (WHO) guidelines, a standard regimen consisting of 2 nucleoside reverse transcriptase inhibitors (NRTIs) and a non-NRTI (NNRTI) has been rolled out as initial cART"; and other contextual information: "The prevalence of HIV in Aruba is estimated at 0.5%"; "HIV treatment is free for all individuals legally registered in Aruba."[23]

Methods

3) Study design
   Authors should report the study design, so that it is clear whether data were collected at one point in time or over a period. Authors should also report on the ethics approvals and waivers, and whether participants gave consent for their data to be used beyond the purposes of the published study.
   Example: In this study the authors described the design of the study: "This cross-sectional study formed part of a larger project aimed at understanding the complex interplay of factors associated with HIV infection for FSWs (Female Sex Workers) in Soweto"; ethics approvals: "Ethical approval was provided by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, South Africa"; and participant consent:" After screening, participants gave their consent to participate in the study."[24]
4) Setting:
   The setting of the study should be described in detail and the report should include information on whether it was a community or population-based study, as opposed to a hospital-based study or a study based on laboratory or administrative records. The locations, relevant dates including the periods of recruitment, exposure, follow-up, and data collection should be reported.
   Example: This study provided a detailed description of the setting in which the research was conducted: "The study was conducted in Soweto, a township on the outskirts of Johannesburg, South Africa. Soweto is predominantly urban and peri-urban, low-income with limited educational and

employment opportunities. It has the highest population density in South Africa, comprises more than 40 suburbs within 61 km^2, and is estimated to house over two million inhabitants".
Example: This study reported the source of the data and the dates of collection: "The Swedish InfCareHIV database includes demographic and clinical information as well as genotyping results and the viral pol sequences obtained in routine clinical care from more than 99% of Swedish residents with known HIV infection. As of March 2017, the time of the latest data extraction, 10 858 patients were registered in the database of whom 7151 were still followed up at the Swedish HIV clinics."

5) Participants:
The participants in the study should be fully characterised using eligibility and exclusion criteria. Given that drug resistance may vary across different population types it is critical to report the target population of the study and how they were defined. They should also report the source of participant data (e.g., hospital charts, registries, self report).
Example: This study reported the inclusion criteria and exclusion criteria of the included participants: "In this retrospective study, we included 1138 HIV-positive adults aged 18 years or greater who initiated cART (combination Anti Retroviral Therapy) of 2 NRTIs plus 1 nNRTI at 3 major designated hospitals (National Taiwan University Hospital, Taipei; Far Eastern Memorial Hospital, New Taipei City; and Taoyuan General Hospital, Taoyuan) with access to genotypic resistance testing in northern Taiwan between June 2012 and March 2016. Patients without genotypic resistance data and those with RAMs (resistance-associated mutations) to nNRTIs or NRTIs at baseline were excluded from analysis."[25]
Example: This study focused on men who have sex with men (MSM): "A cross-sectional study was conducted among newly diagnosed HIV-infected MSM."[26]

6) Variables:
It is of interest to readers to know the mechanism of HIV drug resistance reported because the implications differ. Readers should be able to identify if the HIVDR reported in TDR, ADR or PDR. If the authors are reporting on recent infections, they should provide information that characterises how recent HIV infection were defined in their study, especially for TDR.
Example: In this study the authors clarified the type of resistance they were interested in measuring: "To provide information about the epidemic trends of HIV and to optimize the treatment strategies in Anhui, the prevalence of surveillance/transmitted drug resistance mutations (SDRMs) was evaluated in ART-naïve MSM who were newly diagnosed as HIV-infected in 2011."[26]
Example: Here the authors were interested in pretreatment drug resistance: "In the current report, we analyzed the characteristics of participants enrolled into the surveys, and estimated the point prevalence of Pre-treatment DR (PDR)…."[27]

7) Laboratory methods.

A clear description of the laboratory methods ensures that the methods used can be replicated and compared. The type of the specimen used for drug resistance should be reported (plasma or dried blood spots [DBS]). Plasma-based samples provide information on the HIV drug resistance profile of the population of replicating viruses while DBS specimens may also include archival HIV DNA in latent cell reservoirs, potentially creating discrepancies in the estimates observed.[28] The methods used for viral load testing, particularly the lower limit of detection, especially since virus must be detected for genotyping. The methods used to characterise HIV strains and the subtyping tool (and version) should be reported. Subtyping tools do not all yield the same results, change over time, and should be updated to enhance subtype characterization.[29,30] The algorithm used to generate the predicted resistance interpretation (version and year) and mutation list (version and year) used as the basis of a given prediction algorithm. A variety of algorithms exist, and their interpretation is not always straightforward. This makes them challenging to compare, especially across versions. [31] If NGS was used, it is critical to report the mutation-detection threshold, as different thresholds would result in different estimates of prevalence.[31] The definitions used for predicted resistance to a drug or drug class should also be reported. If any approaches are implemented for quality assurance, they should be reported. For example, some laboratories have specific quality assurance procedures in place.[32,33]

8) Sampling issues:
Authors should report how they arrived at their study size and what sampling strategy was used, and the data source (e.g., registries). This will allow readers to judge the representativeness of the results.
Example: *This study described how they arrived at their sample size: "A minimum sample size of 70 was calculated with EPI Info (95% confidence level). For this calculation, the expected frequency of primary TDR in Suriname was set at 5%. This expected frequency was based on international figures, the relatively young epidemic, and the relatively short history of widespread use of ARV in Suriname."*[34]

9) Statistical methods: Detailed statistical methods as recommended for the study design should be reported. In addition, the approaches used to estimate prevalence or incidence and confidence intervals should be reported. If any analytical methods were used to account for the sampling strategy, including weighting or other adjusted analyses, these should be reported. Readers would be interested in the variables used for weighting or used in adjusted analyses.
Example: *In this study, the authors conducted a weighted analysis: "A weighted analysis was performed to correct for the number of patients enrolled in the I.Co.N.A. cohort and for those who received a genotypic test at each clinical Center during the specific time interval"*[35]

Results

10) Participants:
Authors should report the number of individuals at each stage e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, and number successfully genotyped. If any participants were not included at any stage or if data are missing for any variables of interest, these should be reported. A flow diagram may be helpful in showing participant flow through the study.
Example: *In this study, the authors used a flow chart to show the number of participants who accepted a drug resistance test, the number successfully genotyped, the number excluded due to lack of data, exposure to ART and presence or absence of drug resistance.*[36]

11) Descriptive data:
The characteristics of the study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders should be reported. These may include age, sex/gender, migration status, risk factors or transmission risk group (e.g., sex workers [SW], men who have sex with men [MSM], people who inject drugs [PWID]), timing of infection, viral load at time of infection, CD4 cell counts, and exposures to antiretroviral drugs (including ART, PrEP, Prevention of Mother-To-Child Transmission [PMTCT]), level of adherence to ART). For children, the HIV status of the mother, maternal breastfeeding, and maternal and infant treatment history, might be of interest. This can be facilitated by using a table.
Example: *The authors of this paper include a table showing the age, gender, marital status, occupation, literacy, risk factors, blood transfusions, prison record and coinfection (hepatitis B and C) of the participants.* [37]

12) Main results:
Authors should provide estimates with their precision and report the numbers and proportions with any drug resistance mutations, for each class (NNRTI, NRTI, PI, INSTI) and for each drug. They should also report the numbers with more that one resistance mutation, and clearly distinguish major/clinically relevant mutations from minor/accessory mutations. Where applicable, the main results should be reported for each subgroup. This can be facilitated by using a table.
Example: *The authors present the impact of transmitted drug resistance on the first-line regimen, "Of 11 patients harboring NNRTIs mutations, all of them were forecasted to have intermediate or high-level resistance to Efavirenz (EFV, 2.0%) and Nevirapine (NVP, 2.0%), followed by Rilpivirine (RPV, 1.1%) and Etravirine (ETR, 1.1%).*[38]
Example: *The authors present their main findings in a table showing the prevalence of mutations with 95% confidence intervals, and by drug class.* [39]

13) Other analyses:
If other analyses were conducted, such as adjusted analyses or phylogenetic analyses, they should be reported.

Example: The authors in this paper performed a phylogenetic analyses and network construction, specifying the number of people the sequences were generated from along with denominators and percentages. "Phylogenetic analysis showed that 325 (60.0%) of 542 sequences of this study grouped in 72 transmission clusters compared of 2 or more individuals..[..]..The prevalence of treatment drug resistance was not significantly different among individuals who were part of clusters and who were not [4.6% (15/325) vs. 8.3% (18/217), respectively; P =0.1] [38]

14) Discussion:
Authors should discuss the generalizability of their findings bearing in mind the study sample, the sampling strategy, and any limitations.
Example: The authors in this paper discuss the generalizability of their sample, "Although not all autonomous communities in Spain are represented in this study, we succeeded in including the areas with the higher concentration of HIV cases, representing 78% of the Spanish population, but 85% of new HIV diagnoses". [40]
15) Additional information:
The authors should specify if the nucleotide sequence data are publicly available, available upon request or not, and report the repository where they are stored, the digital object identifier (DOI;if available) and the procedures for access, where applicable. They should also report the Genbank Accession Numbers for the nucleotide sequences used. Publicly available HIV drug sequence data is useful in identifying genotypic correlates of resistance and understanding global trends. Further, shared sequence data optimises investments in research by guiding the selection of treatment regimens when personalised HIV drug resistance testing is not possible[41]

Example: The authors of this paper specify the availability of their data, "Data contain potentially identifying information and are not suitable for public sharing. Data may be obtained on request to the authors." [42]

Example: The authors of this study report sequence accession numbers, "GenBank Sequence Reads Archive (SRA) accession number of the bulk sequence dataset used in this article is SRP075904, and the accession numbers of the nucleotide sequences representing the bulk sequence of each patient are: KX247148, KX247257". [43]

Discussion:

CEDRIC-HIV was developed in response to a need to measure and synthesize evidence on HIV drug resistance. It will help authors design their research and prepare research reports; help peer reviewers and editors to assess completeness of reporting and assist in narrative and statistical pooling of data from HIV drug resistance studies. CEDRIC-HIV, this document and the upcoming website would be valuable tools to help reduce research waste and ensure transparency and replicability in research.

This article explains why the items are important and provides examples of reporting which were deemed appropriate. The use of this checklist will facilitate pooling in systematic reviews and meta-analyses and allow a full understanding of the drug resistance HIV situation in the specific location of the study, in the relevant population, at the time that specimens were collected. This granular undertaking not only advances general knowledge but facilitates translation of data from research to public health policy, thus enhancing the impact of research. Science, and reporting science is always evolving. We anticipate that there will be future updates to CEDRIC-HIV to ensure that it keeps up with changes in data science, genotyping technology, and ethics. There is also value in translating the checklist into various languages to facilitate its use by diverse audiences. Our website will be a forum where end-users can provide feedback and propose various ways in which the value, uptake and use of CEDRIC-HIV can be enhanced.

As knowledge regarding what are the primary and secondary mutations and polymorphisms implicated in drug resistance and their impact on drug susceptibility continues to evolve, the application of the CEDRIC-HIV guidelines and the information collected will assist in improving our understanding of drug resistance mutations and polymorphisms and their role in drug responses.

We encourage journals to adopt these guidelines and to include them in their instructions for authors.

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The authors declare none.

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