CHECKLIST FOR STUDIES OF HIV DRUG RESISTANCE PREVALENCE

DEVELOPING A REPORTING ITEM CHECKLIST FOR STUDIES ON THE PREVALENCE OF HIV DRUG RESISTANCE: A MIXED METHODS STUDY

BY MICHAEL CRISTIAN GARCIA, BSc (Honours)

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AUTHOR: Michael Cristian Garcia, BSc
SUPERVISOR: Dr. Lawrence Mbuagbaw, MD, MPH, PhD
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Lay Abstract (145/150 words)

Background and Methods: Drug resistant HIV is very challenging to treat and is an important global health problem. It is difficult to know how common HIV drug resistance is around the world because the studies on HIV drug resistance are not reported similarly. This is because there are no standard guidelines for these studies. In this study, we asked HIV drug resistance researchers to complete a survey on what they thought should be reported is studies measuring HIV drug resistance. Then, we had group conversations where we asked them to explain why they believed the items were important.

Results and Conclusions We identified 38 potential reporting items, most of which would require authors of HIV drug resistance studies to clarify the settings, participants and methods used in their research. These items will make up a reporting checklist for authors of HIV drug resistance studies and make research in this area more comparable.

Abstract (261 words)

Abstract

Background: HIV drug resistance limits the effectiveness of antiretroviral therapy. Adequate surveillance of HIV drug resistance prevalence is challenged by heterogenous and inadequate data reporting. In this study, we sought to identify a list of reporting items for studies of HIV drug resistance prevalence and an understanding of why these items are important to report.

Methods: We used a mixed-methods sequential explanatory design involving authors and users of studies of HIV drug resistance prevalence. In the quantitative phase we conducted a cross-sectional electronic survey (n=51). Survey participants rated various reporting items on whether they are essential to report, producing validity ratios which were used to produce a draft reporting item checklist. In the qualitative phase, two focus group discussions (n=9 in total) discussed this draft item checklist and which of the items should be reported and why. We also conducted a thematic analysis of the group discussions to identify emergent themes regarding items to be considered for the reporting guideline.

Results: We identified 38 potential reporting items including participant characteristics, sampling methods, and resistance testing methods. The strongest themes that emerged from the discussions were agreement over the importance of reporting certain items, concerns over the availability and ethics of reporting certain participant data, the importance of interpretability and comparability, and the necessity for reporting guidelines to appreciate context-specific prevalence research.

Conclusions: We have identified a list of reporting items for studies of the prevalence of HIV drug resistance along with an explanation of why researchers believe these items are important. The next steps involve further elaborating upon these findings in the reporting guidelines.

Keywords: HIV, drug resistance, reporting guidelines, prevalence, surveillance antiretroviral therapy

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List of Key Acronyms

ART	Antiretroviral therapy
ARV	Antiretrovirals
CEDRIC-HIV	ChEcklist for studies of Drug ResIstanCe in HIV
CVR	Content validity ratio
HIV	Human immunodeficiency virus

Declaration of Academic Achievement

The idea for this research and first draft of the study protocol was conceptualized by Dr. Lawrence Mbuagbaw. I, Michael Cristian Garcia, along with Dr. Mbuagbaw, further designed and developed this work. I completed this work between September 2020 and April 2022, creating the electronic survey, writing study procedure documents, taking part in focus groups as a note-taker, and performing the primary statistical and qualitative analyses based on Dr. Mbuagbaw's guidance. I am the sole author of this thesis document. The protocol of the study that comprises Chapter 2 has received peer review at the Journal of Medical Internet Research Protocols and was accepted for publication on April 26, 2022.

To the best of my knowledge, the contents of this thesis do not infringe upon any copyrights.

My supervisor, Dr. Lawrence Mbuagbaw, and my supervisory committee, which comprises of Dr. Holbrook, Dr. Djiadeu, and Dr. Mbuagbaw have provided their guidance and support throughout my graduate studies.

Chapter 1: General Introduction

Health research reporting guideline development is a cumulative process that builds upon prior research in the area.(1) As part of a larger project that seeks to develop reporting guidelines for HIV drug resistance research, the objective of this thesis work is to identify a list of potential reporting items for studies of HIV drug resistance prevalence and an understanding of why these items are important in this research. Future work immediately following this mixed-methods study (beyond the scope of this thesis) will use this item list and qualitative findings to develop reporting guidelines and accompanying elaboration documents. The thesis objective will be explored in the following chapters as follows:

Chapter 1: General introductory chapter. This chapter establishes the context of this thesis work, introduces the concepts of HIV drug resistance, the current problem and need for reporting guidelines, and the rationale behind selection of mixed-methods to address the research questions.

Chapter 2: A protocol for a mixed methods study. This chapter contains the mixed-methods study protocol verbatim as accepted for publication at the Journal of Medical Internet Research Protocols.

Chapter 3: Results. This chapter contains the results of the mixed-methods study, structured for readability as a thesis chapter. The content of this chapter will be later re-structured and revised for publication as per a target journal's format specifications.

Chapter 4: Concluding chapter. This chapter summarizes the key take-aways of the thesis, potential alternative methodologies, and discusses future work.

1.0 Drug Resistance in HIV

In 2020 approximately 680,000 people worldwide died from HIV-related causes.(2) While there is no effective cure for HIV, the use of antiretroviral therapy (ART) helps suppress the infection and has saved the lives of millions of individuals living with HIV/AIDS.(2, 3) Approximately 73% of the 37.7 million people living with HIV in 2020 received ART,(4) however suboptimal adherence to treatment and low retention in care remain serious challenges.(5)

An undesired consequence of expanded access to ART and pre-exposure prophylaxis is the increase in HIV drug resistance.(6) This resistance often develops when individuals are not fully adherent to their HIV medications, resulting in viral replication under pharmacologic selective pressure favoring viral mutations that confer protective effects against the active antiretroviral medications (ARVs).(3, 7) HIV drug resistance is thus particularly of concern in populations where optimal adherence to antiretroviral therapy (ART) is difficult to achieve due to systematic program barriers such as gaps in ART service delivery, limited stock of ARVs, and poor retention in HIV care.(6)

The World Health Organization (WHO) distinguishes between three types of HIV drug resistance: pre-treatment drug resistance, acquired drug resistance, and transmitted drug resistance.(2, 8) Pre-treatment drug resistance involves drug resistance in individuals before they initiate or reinitiate ART, which occurs either from infection with a drug-resistant virus (transmitted), from previous exposure to ARVs including for prophylactic use, or from reinitiating treatment after previous disengagement from HIV care (acquired).(9) Acquired drug resistance emerges from viral mutations induced in patients actively on ART.(7, 8) When resistance is detected in drug-naïve patients with no previous exposure to antiretroviral medications this is known as transmitted drug resistance, i.e. a resistant strain was transmitted to the individual.(7, 8) This thesis work focuses on all HIV drug resistance types, including pre-treatment, acquired, and transmitted drug resistance.

HIV drug resistance impacts clinical outcomes. An analysis of electronic health records (N=2,257) from four HIV programs in Malawi, Kenya, Uganda, Cambodia found that mortality was two-times greater in patients with resistance than those without (hazard ratio 2.08. 95% confidence interval(CI): 1.07 to 4.07).(10) Additionally, a meta-analysis of 32 studies (N=31,441) assessing the impact of HIV drug resistance on treatment outcomes among individuals initiating non-nucleoside reverse transcriptase inhibitors (NNRTIs), a drug class most used in first-line regimens, found the risk of virological failure three times higher in patients with drug resistance (odds ratio(OR): 3.07, 95%CI: 2.40-3.94) compared to those without drug resistance.(11) This analysis also noted that new resistance mutations were more than twice as frequent in people with HIV drug resistance taking first-line NNRTI regimens (OR: 2.5: 95%CI: 1.70-3.52) compared to those without HIV drug resistance.(11)

The prevalence of HIV drug resistance is as high as 25% in some countries.(8) Resistance to an NNRTI is up to three times more common in people with previous exposure to antiviral drugs, and nearly half of infants born to mothers with HIV exhibit drug resistance to one or more NNRTIs.(2) HIV drug resistance has direct implications for prevention and treatment regimens given its potential to jeopardize the long-term success of the treatment.(9, 12) HIV drug resistance also threatens the efficacy of antiretroviral drugs (ARVs), many of which risk becoming partly or fully inactive due to resistant strains.(2) To address the concern over increasing HIV drug resistance levels, the WHO recommends surveillance of ARV-naïve individuals for drug resistance, and if rates reach ≥10% then ART programs are instructed to implement either routine drug resistance testing prior to treatment initiation, or programmatic switches off NNRTIs to non-NNRTIs in first-line regimens.(13, 14) In 2020, twenty-one of the thirty WHO drug resistance surveys reported drug resistance to nevirapine or efavirenz in populations initiating first-line ART above 10%.(2) Many African countries experience delays in switching ART regimens, which promotes the development of further resistance.(15, 16) In June 2021 the WHO released an update to its HIV drug resistance strategy, highlighting the importance of monitoring and surveillance efforts and in obtaining high quality data on HIV drug resistance prevalence estimates.(17) However, adequate monitoring of HIV

drug resistance prevalence worldwide is challenged by heterogenous and inadequate data reporting.(18)

1.1 What is the problem and why are guidelines needed?

Inadequate reporting makes it challenging for readers to assess the reliability and interpretability of research findings.(19-21) Studies that collect information on HIV drug resistance prevalence should be reported comprehensively and consistently to allow for the ability to combine studies for better precision. Relatedly, meta-analyses seek to generate pooled estimates by compiling evidence to address a research question.(22) However, meta-analyses are only useful when pooling similarly designed studies and remain susceptible to imprecision due to small study sizes.(23) Additionally, when meta-analyses assess statistical heterogeneity based on study results rather than study methods this obscures informative heterogeneity on varying methods and resulting in problems with interpretability and the illusion of certainty in the pooled estimates.(23) These issues highlight the importance of capturing study methods when generating pooled estimates, particularly in observational epidemiology. In the area of HIV drug resistance prevalence research, such efforts for more comprehensive reporting on study methods improve interpretability and consideration of the representativeness of the participant sample and techniques used to measure resistance. In many instances HIV drug resistance prevalence is reported without disaggregation by the drug class and without distinction between major and minor resistance mutations. Such distinction is important because different resistance mutations result in differing degrees of resistance.(24) Mutations defined as major tend to occur earlier during treatment failure and generally confer larger reductions in treatment susceptibility, while those defined as minor tend to confer incremental resistance.(24) A 2020 systematic review and meta-analysis (N=63,111) sought to estimate the prevalence of HIV drug resistance in key populations i.e. sex worker, men who have sex with men, incarcerated people, transgender people and people who inject drugs.(25) The authors observed considerable unexplainable heterogeneity between studies and ultimately cautioned the interpretation of their prevalence estimates given this heterogeneity.

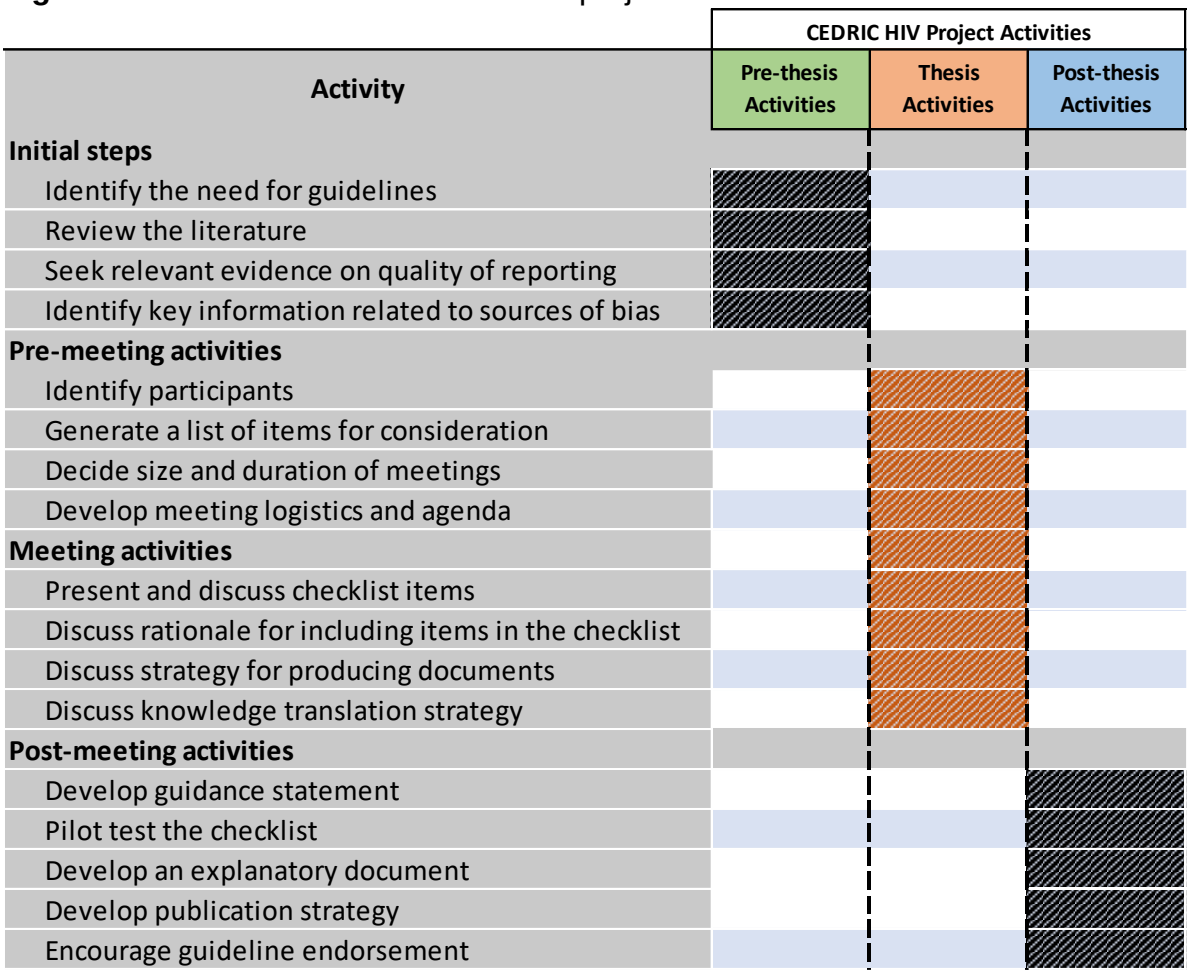
Following this meta-analysis, the authors conducted a separate methodological study focused on reporting completeness (N=234 studies) and found that many key features were not reported.(18) For example only 56.2% of studies reported their study setting (hospital, community, prison, etc.), 44.0% the study design (cross-sectional, retrospective etc.), 35.5% on participant ethnicity, 14.1% on place of residence (urban, rural), and 22.2% on the clinical relevance of observed mutations. The authors recommended the need for agreement on a list of key reporting items for studies reporting the prevalence of HIV drug resistance.(18)

1.2 Guideline development framework

In 2010 Moher et al. published a guidance framework for researchers seeking to develop health research reporting guidelines. No specific research methodologies were specified in the framework, rather the authors outlined the importance of using “robust and widely accepted methodologies”.(1) The proposed strategy involves 18 steps over five phases. The first phase involves identifying the need for reporting guidelines and appraisal of relevant evidence on the quality of reporting.(1) A progress checklist of this thesis work along the steps outlined by Moher et al. is available in Appendix 1. In accordance with this strategy and to initiate the process of developing reporting guidelines for studies of HIV drug resistance prevalence, our prior work evaluated the completeness of reporting of HIV drug resistance prevalence literature, the results of which support the need for reporting guidelines.(18, 26)

We have registered the guideline project on the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network as CEDRIC-HIV (ChEcklist for studies of Drug ResIstanCe in HIV).(27) The EQUATOR network is an international initiative where projects that seek to develop reporting guidelines can be registered.(27) The CEDRIC-HIV project seeks to develop complete reporting guidelines by following Moher’s guiding framework. This thesis work is one component of the CEDRIC-HIV project (see Figure 1). At the time of writing, there are no formal guidelines on how to structure a mixed-methods paper with regards to specific headings/sub-headings, however, there exists content guidance in the form of the Good Reporting of A Mixed Methods Study (GRAMMS) checklist (more detail on how we adhered to this checklist is provided in Chapter 3). (28)

Figure 1: Timetable of the CEDRIC HIV project activities



1.3 Research questions

In mixed-methods research it is good practice to create research questions for each phase of the project, in this case for both the quantitative and qualitative phase. (29, 30) Additionally, a mixed-methods research question is expected to illustrate how both methods are mixed (or 'integrated'). (29, 30)

1. Using cross-sectional survey methods, among HIV drug resistance researchers, which reporting items are essential in a checklist of reporting items for studies reporting the prevalence of HIV drug resistance?

2. Using focus group methods, what are the perceptions of HIV drug resistance researchers when assessing whether a reporting item is essential to HIV drug resistance prevalence research?

3. Using mixed-methods integration methodologies, how do the focus group discussions with HIV drug resistance researchers help explain the findings of the cross-sectional survey?

1.4 Methodology

Mixed-methods refers to a methodology of research that combines quantitative and qualitative approaches within different phases of the research process.(31, 32) This methodology is ideal to address complex problems that cannot be addressed by one methodology alone.(33, 34) There are two major categories of mixed methods designs: sequential and concurrent.(33) In a sequential design data collection and analysis occur in two distinct phases where the second phase only occurs after the first is complete. The first phase involves either qualitative or quantitative data collection and analysis; the second phase involves the other type of data collection and analysis. When quantitative data is collected and analyzed before the qualitative data, this is known as an explanatory design, and in the reverse order it is known as an exploratory design. There are various benefits for using mixed methods (see Table 1, below).

Table 1: Methodological strengths and weaknesses of mixed-methods studies

Strengths	Weaknesses
• Allows for deep and accurate understanding of complex phenomena	• Challenges integrating quantitative and qualitative data
• The strengths of one research method can compensate for the weakness of another	• High time and costs for data collection, analysis, and interpretation

Mixed methods are not merely the combination of separate distinct methods into a single study, but leverages insight from the integration of different methods to answer complex research questions.(30, 35) An important strength of mixed-methods is that the design allows for the compensation of methodological weaknesses.(33, 36) For example, a common limitation of focus group methods is that the results cannot be generalized to a wider population as the small group sizes used are not representative.(37) However when coupled with a cross-sectional survey as was done in this mixed-methods study, this limitation is reduced given the breadth of data from the survey participants. The result of this methodological design is the possibility to produce data richer and more comprehensive than either method could produce alone.(32)

The purpose of this study is to inform a reporting checklist which will be accompanied by an elaboration document. For this reason, an explanation is required for why any proposed reporting item is important. Given these objectives, an explanatory sequential design was selected for this thesis work to allow for the use of qualitative data to directly explore results from the quantitative findings, creating contextual understanding.(31, 38) For example, Wariri et al. used an explanatory sequential mixed methods study to determine the prevalence and predictors of disclosure and explore barriers caregivers face in disclosing their HIV-positive status to children living with HIV in Nigeria.(39) The

quantitative phase involved cross-sectional questionnaires with 120 eligible caregivers, followed by qualitative in-depth one-on-one interviews with 17 primary caregivers. The authors note that their quantitative findings were explained by evidence from the qualitative component, indicating that feelings of shame, guilt, self-blame, and self-recrimination strongly influenced disclosure practices.(39)

A strength of the sequential explanatory approach includes the ability to identify discrepancies and contradictions between quantitative results and qualitative findings, and sequential explanatory designs better reflect participants' point of view by allowing participants to verbalize their opinions grounded in their expertise and experience.(32) Additionally a sequential explanatory mixed methods approach naturally suits the order of steps proposed in Moher's guidance for developing reporting checklists,(1) allowing for the identification of a list of potential reporting items followed by group discussion on these items (Figure 1, Appendix 1). This order suits a sequential design as opposed to concurrent.

The quantitative phase of this thesis project involved disseminating an electronic survey to HIV drug resistance researchers to rate the relative importance of possible checklist items. A similar web-based survey approach was used by the CONSORT group to develop reporting guidelines for randomized control trial abstracts.(40) The results of this survey were used to generate an initial list of potential reporting items. There is no best way to generate a list of reporting items for consideration,(1) however Moher's guidance framework suggests that these checklist items be discussed in a subsequent agreement meeting, which for this thesis work was conducted through focus group discussions. A limitation of the sequential explanatory approach is given that both quantitative and qualitative phases are given equal priority; it is considerably more time-consuming and requires broader expertise to interpret both types of data.(31) Mixed-method approaches are not inherently more or less valid than other methodological approaches, but rather carry the strengths and weaknesses of the approaches used in each phase (see Table 2, below).(41)

Table 2: Methodological strengths and weaknesses of the methods selected for this mixed-methods study

Mixed-methods phase	Strengths	Weaknesses
Quantitative: Cross-sectional survey	• Inexpensive • Efficient to acquire representative summary on a topic	• Reliant on sufficient sample size to minimize non-response bias

Qualitative: Focus group discussions	• Useful to explore perspectives on opinions and rationale for decisions • Efficient for problem-solving, clarification-seeking and consensus taking	• Agreement conflicts may arise and remain unresolved in the discussion • Susceptible to group-think • Groups may arrive at premature conclusions

The quantitative and qualitative phases of this mixed-methods study are based in cross-sectional methods through the distribution of an electronic survey and focus group discussions, respectively. The primary advantage of cross-sectional studies is their inexpensive costs and efficiency to conduct, as well as the ability to acquire a representative summary or opinion on a topic if the sample size is adequate.(42) However, a major limitation of using surveys includes the potential for low response rates and consequently nonresponse bias, and reliance on sampling from a large and heterogenous population to minimize sampling bias.(42) The focus groups that comprise the qualitative phase of this study have several advantages suited for developing contextual understanding. This qualitative methodology is useful to understand why participants answer the way they do, such as the rationale behind what makes a reporting item essential to HIV drug resistance research. The focus group approach is also an efficient technique for qualitative data collection since data is collected from several people simultaneously. Additionally, focus groups work well for problem-solving purposes,(43) such as reviewing the reporting item checklist and discussing whether items should be included in the checklist. As these discussions use an interviewing technique the facilitator can seek clarification in the case of ambiguity generated in the quantitative survey data.(37)

In contrast, a limitation of the focus group approach is that agreement conflicts may arise between participants.(37) However for the purposes of this thesis work, such conflict provides valuable data and the space for participants to articulate their perspectives. The group interaction is an important source of data in the focus group process and such disagreement provides further insight on complex issues and which reporting items require additional attention and elaboration when constructing the finalized reporting guidelines.(44, 45) Importantly, agreement conflicts also help avoid another potential focus group limitation called group-think – the process where participants adjust their own behaviour in response to the impression of other group members – as participants all take the role of devil's advocate.(46) These reasons informed our decision to opt for open discussions as opposed to those traditionally used in Delphi studies (more on Delphi techniques in Chapter 4). As the focus groups in this thesis work are structured to discuss pre-specified reporting items from the quantitative phase, the focus groups function as a "working group" of sorts where empirical material is discussed and revised, forging new

kinds of understanding and avoiding premature agreement.(47) Ultimately, the robust nature of the mixed-methods approach and alignment with the existing guidance framework support the use of this methodological design to complete this thesis.

1.5 Validity

Validity is the ability of an instrument to measure the properties of the construct being measured.(48) Content validity is integral to instrument development and in this case reflects how well items reflect clarity, transparency and useful reporting. While the objectives of this study differ from those of a content validity study, there are notable similarities between the methodologies and outputs. Content validity studies are also two-stage processes that design an instrument and then judge/quantify the items among content experts.(49) Similarly, we first used quantitative content validity methods, content validity ratios, to assess agreement among researchers on the essentiality of the reporting items. This approach operationalized the item constructs being measured. We then evaluated our reporting item checklist using the focus group discussions to assess the grammar, wording, and grouping of the items. More details on content validity are provided in Chapter 4.

In the next chapter, the protocol for the mixed-methods study conducted as part of the thesis work is presented. This protocol received peer review and was accepted for publication with the Journal of Medical Internet Research Protocols on April 26, 2022. It is presented as published, including a results section as per the journal's content requirements.

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Chapter 2: Developing a Reporting Item Checklist for Studies on the Prevalence of HIV Drug Resistance: Protocol of a Mixed Methods Study

2.0 Abstract

Background

HIV drug resistance is a global health problem which limits the effectiveness of antiretroviral therapy. Adequate surveillance of HIV drug resistance is challenged by heterogenous and inadequate data reporting, which compromises the accuracy, interpretation, and usability of prevalence estimates. Previous research has found that the quality of reporting in studies of HIV drug resistance prevalence is low, and thus better guidance is needed to ensure complete and uniform reporting.

Objective

This paper contributes to the process of developing reporting guidelines for prevalence studies of HIV drug resistance by reporting the methodology used in creating a reporting item checklist and generating key insights on items that are important to report.

Methods

We will conduct a sequential explanatory mixed methods study among authors and users of studies of HIV drug resistance. The two-phase design will include a cross-sectional electronic survey (quantitative phase) followed by a focus group discussion (qualitative phase). Survey participants will rate the essentiality of various reporting items. This data will be analyzed using content validity ratios to determine the items that will be retained for focus group discussions. Participants in these discussions will revise the items and any additionally suggested items and settle on a complete reporting item checklist. We will also conduct a thematic analysis of the group discussions to identify emergent themes regarding the agreement process.

Results

As of November 2021, data collection for both phases of the study is complete. In July 2021, 51 participants had provided informed consent and completed the electronic survey. In October 2021 focus group discussions were held. Nine participants in total participated in two virtual focus group discussions. Data are currently being analysed.

Conclusions

This study supports the development of a reporting checklist for studies of HIV drug resistance by achieving agreement among experts on what items should be reported in these studies. The results of this work will be refined and elaborated on by a writing committee of HIV drug resistance experts and external reviewers to develop finalized reporting guidelines.

2.1 Introduction

An estimated 38 million people were living with HIV worldwide in 2019.(1) These large numbers reflect higher longevity in people with HIV due in part to improvements in the management of HIV infection by early detection and early treatment with antiretroviral

therapy. One obstacle to the effectiveness of antiretroviral therapy is drug resistance, as it limits the number of effective drugs, increases the potential for onward transmission, and compromises survival.(2, 3)

Drug resistance to antiretroviral therapy may be acquired when there is viral replication in the presence of a drug.(4) In some individuals, drug resistant viral strains are already present prior to the start of antiretroviral therapy referred to as pre-treatment drug resistance.(5) This type of resistance can arise due to infection with a drug resistant viral strain, also referred to as 'transmitted drug resistance', or due to prior exposure to antiretroviral treatment (e.g. women and children exposed to treatment as part of prevention programs and people who abandoned prior treatments).(6)

HIV drug resistance is a recognized global health problem.(7) People with drug resistance are more likely to experience treatment failure, discontinue treatment, and develop new drug resistant strains.(5) The rise in drug resistance is one of the greatest threats to global health, and without urgent attention can result in millions of deaths, an increase in new harder-to-treat strains of HIV and higher healthcare costs.(8) The prevalence of HIV drug resistance varies worldwide, and it can be as high as 25% in some countries,(9) likely due to the efforts to expand widespread availability of antiretroviral therapy in these settings. Understanding the levels of HIV drug resistance is important to researchers, clinicians, and policymakers because this information can inform guidelines on how treatment should be tailored and what drugs should be used as first-line treatments. For example, in 2020, twenty-one of the thirty World Health Organization (WHO) drug resistance surveys reported drug resistance to nevirapine or efavirenz in populations initiating first-line antiretroviral therapy above 10%.(10)

The prevalence of drug resistance varies among people living with HIV, but is higher in certain high-risk populations such as men who have sex with men, sex workers, transgender people, people who inject drugs, people in prisons, pregnant women, and adolescents and children; resistance prevalence also varies by sex, ethnicity, and HIV subtype due to differences antiretroviral exposures.(11-14) The pooled prevalence estimate of HIV drug resistance is high among men who have sex with men (13.0%, 95% confidence interval (CI): 11.0 to 14.0%), sex workers (17.0%, 95% CI 6.0–32.0) and people in prisons (18.0%, 95% CI 11.0 to 25.0). (15) Overall, men who have sex with men are more likely to carry any drug resistance compared to the "general population", (odds ratio (OR) 1.28, 95% CI 1.13–1.46).(15)

Adequate monitoring of HIV drug resistance across countries and populations is often challenged by heterogenous and inadequate data reporting. In our previous systematic review of pre-treatment drug resistance in key populations, we found that the quality of reporting in studies of HIV drug resistance prevalence is low. (16) This compromises the accuracy, interpretation and usability of prevalence estimates, especially if key data is not reported including: precision of the estimates, representativeness and diversity of the participants included, techniques used to measure resistance, participants' transmission risk group, prior exposure to treatments and class of drug for which resistance was tested.(15) Our recent methodological study concluded that while reporting has improved

over time,(8) guidance is needed to ensure complete and uniform reporting, to improve the interpretation of study findings, generalizability, and comparability of prevalence estimates, while accounting for differences in geographical settings and populations.(17) In 2010 Moher et al. published guidance for researchers seeking to develop health research reporting guidelines, outlining a strategy emphasizing the importance of using robust and widely accepted methodologies.(18) In accordance with this strategy and to initiate the process of developing reporting guidelines for studies of HIV drug resistance prevalence, our prior work evaluated the completeness of reporting of HIV drug resistance prevalence literature, the results of which supported the need for reporting guidelines.(15, 17) We have registered this guideline project on the EQUATOR network as: CEDRIC-HIV (ChEcklist for studies of Drug ResIstanCe in HIV).(19)

Research Objectives

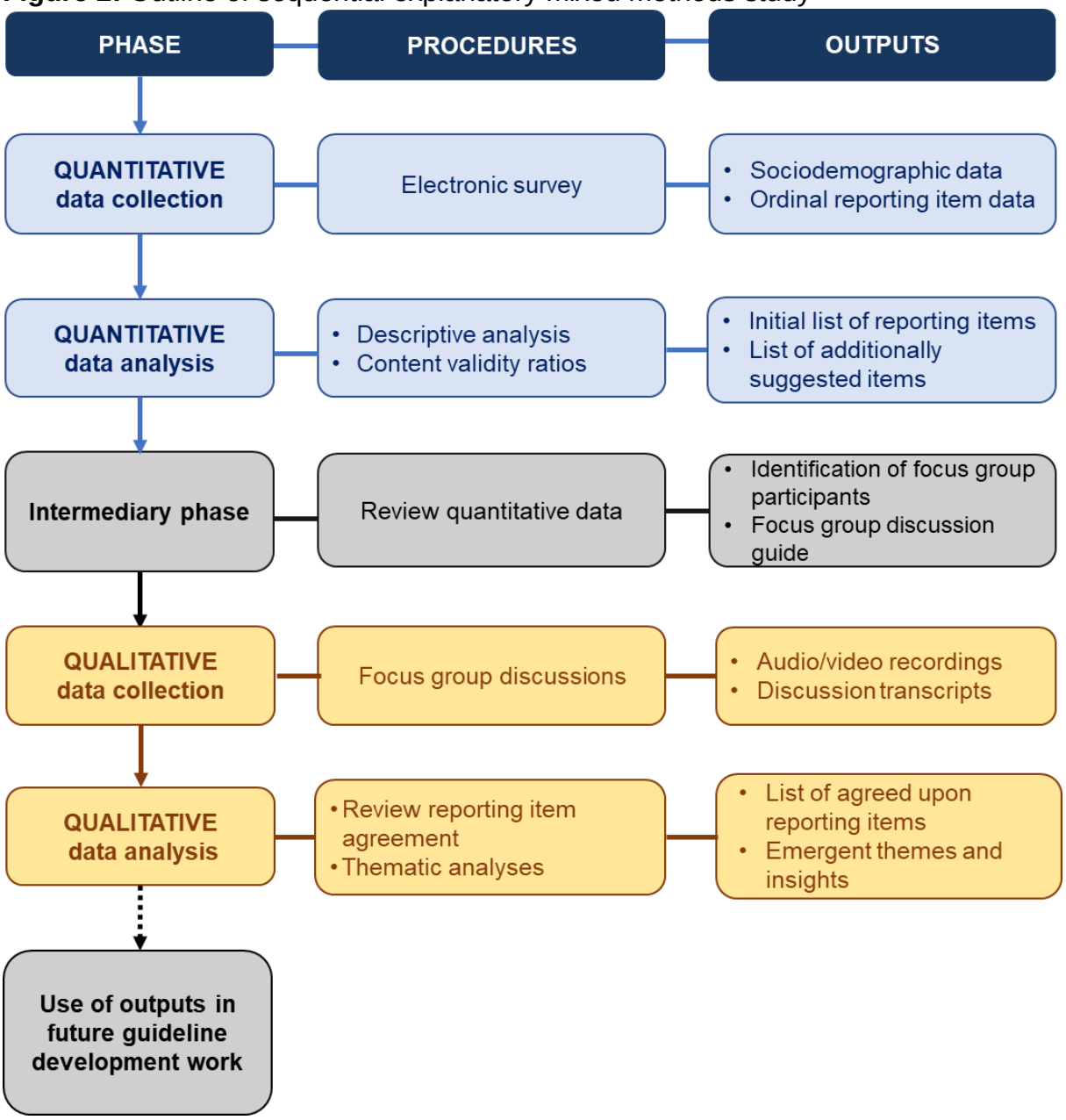
The objective of this study is to develop a reporting item checklist for prevalence studies of HIV drug resistance by achieving agreement among experts on items that should be reported in studies of HIV drug resistance prevalence. This mixed-methods study includes a) a quantitative phase with survey methodology to identify a list of reporting items considered by participants to be essential for studies on the prevalence of HIV drug resistance, b) focus group methods to identify emergent themes elucidated during discussions over whether reporting items are essential to HIV drug resistance prevalence research, and c) data integration methods to explain the findings of the cross-sectional survey

2.2 Methods and Analysis

Design

We will conduct a sequential explanatory mixed methods study (QUAN →qual) among authors of studies of HIV drug resistance. This design comprises two phases: a cross-sectional electronic survey (quantitative phase) followed by focus group discussions (qualitative phase). The results of the survey will be used to develop an initial list of potential reporting items and additionally suggested reporting items, which will be evaluated, revised, and expanded upon in the qualitative phase. Transcripts from the focus group discussions will provide key qualitative insights on why these items are important to report. Figure 2 below outlines the study design.

Figure 2: Outline of sequential explanatory mixed methods study



Rationale for Design

Mixed methods suit research objectives that cannot met by either qualitative or quantitative methodologies alone.(20, 21) The sequential explanatory design is well suited for this research as the quantitative phase provides the recommended reporting items and the qualitative phase provides the rationale for reporting these items. Each of these will inform the guidance and elaboration document that will accompany the checklist.

Sampling

We will employ a two-stage non-probability sampling procedure using purposive, convenience and snowball sampling techniques to capitalize on the small target population to achieve our study outcomes. These sampling methods allow for the targeted and efficient collection of quantitative and qualitative data, resulting in more precise results and richer insights.(22, 23)

Quantitative phase

The quantitative phase will include a convenience purposeful sample of corresponding authors of studies of HIV drug resistance. In our 2020 systematic review,(16) we searched 10 databases and identified 650 studies of HIV drug resistance. The WHO European region contributed most studies (34.4%) followed by the Americas (31.7%), Western Pacific (22.0%), and Southeast Asia (6.0%). Africa (2.8%) and Eastern Mediterranean regions (1.4%). We automatically extracted all email addresses (n=160 after deduplication) of the corresponding authors of the included studies. These authors will be contacted by email to participate in the electronic survey. Assuming this is our population of interest, with a 95% confidence level and a margin of error of 10% and an anticipated survey response proportion of 50%, 61 participants are required. These computations were done with WINPEPI.(24) A sample of n=21 participants will represent ~13% of the target population (N=160), which is sufficiently large to be representative. We intend to recruit as many participants as possible but will use this value to know the minimum required. Study invitations will be sent to all 160 e-mail addresses. If response rates are lower than anticipated, we will use a snow-balling approach and invite authors to share the link to the survey with their co-authors. In addition to using social media platforms to disseminate the survey link, HIV journals will also be contacted to share the survey link to authors who have published research on HIV drug resistance in their respective journal.

Qualitative phase

All survey participants will be asked to indicate if they are interested in the focus group discussions. In the qualitative phase, we intend to include a sample of 20 survey respondents who agreed to participate in the focus group discussion (two groups of 10 participants). We will select these participants with considerations of sex and geographical diversity, such that we have at least one male and one female participant from as many of the six WHO regions as possible: African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region.(25) We choose to divide participants into two groups of 10 to maximize spontaneity and interaction among participants,(18) and based on research indicating that groups of at least six participants is more reliable while groups greater than 12 are logistically more difficult to coordinate.(26, 27)

Data collection

Quantitative phase

Authors of drug resistance prevalence studies will be invited to take an electronic survey on the Research Electronic Data Capture (REDCap) tool hosted at St Joseph's Healthcare Hamilton open from November 2020 to June 2021. REDCap is a secure, web-based application designed for data capture in research.(28) The survey will be pilot tested by the research team prior to launching. Participants will be presented with an overview of the study, its purpose, the investigators, the privacy and confidentiality of their data and their rights as research participants. They will also be informed on how long the survey will take. Participants will be given the opportunity to provide or refuse consent to participate and the opportunity to withdraw at any time.

The survey includes 23 three-scale ordinal questions, one for each potential reporting item. These 23 items were selected in our previous methodological assessment of reporting completeness of HIV drug resistance prevalence research.(17) This list is not exhaustive, and participants are invited to add more items. Participants will rate whether each item is 'essential', 'useful but not essential', or 'not necessary. Survey items are grouped into four sections in the following order: study-level items, participant items, HIV resistance testing items, and other items. A copy of the electronic survey is provided in Appendix 2. This list was generated from a previous systematic review on the global prevalence of HIV in key populations.(16) At the end of each section participants will be prompted to enter any additional items they believe should be reported, if applicable, into a free text field. We will also collect basic sociodemographic data such as age, sex, country of residence, profession, number of years as a researcher and interest in participating in the focus group discussion. Response rates in electronic surveys are often low,(29) and thus to maximise responses we will ensure that the email addresses used are up to date, keep the survey as short as possible, declare the estimated time required to complete the survey, and send at least two reminder messages.(30)

Qualitative phase

Selected individuals who expressed interest in participating in the survey and who consent to being contacted will be approached to set up a convenient time for a group discussion in October 2021. Participants will be given the opportunity to provide consent prior to discussions and for the discussions to be recorded. Interviews will be conducted over Zoom (a video conferencing platform with real-time messaging and content sharing). The discussions will be moderated by a chair who will ensure that participants are able to contribute freely and openly. The moderator will introduce the session and initiated the discussions based on a focus group discussion guide (see Appendix 3). During the discussions, participants will review the initial list of reported items from the quantitative phase and confirmed their choice of whether the items are essential. Participants will also review all additionally suggested reporting items brought up in the survey. While the focus group discussions are not anonymous, participants will be reassured of the confidentiality of their information and that no information provided will be traced back to them. The Zoom sessions will be recorded, with the corresponding recordings/transcripts being stored on secure and password protected servers. The discussions will last about two hours. Agreement will be inferred when at least one participant verbally evaluates whether a reporting item is essential or not and there are no verbal objections with the statement.

Data analyses

Quantitative phase

Baseline data and outcomes will be summarised as counts (percentage) for categorical variables, mean (standard deviation) or median (first quartile, third quartile) for continuous or discrete variables as appropriate depending on the distribution. The ordinal data from potential reporting items will be used to compute a validity ratio. The coding of the essentiality ordinal scale is as follows: essential (3), useful but not essential (2), and not necessary (1). Data on the inclusion of additional reporting items from the open text fields will be summarised and discussed in the qualitative phase.

A validity ratio will be computed as follows: $VR = [Ne – (N/2)] / (N/2)$

where Ne is the number of participants who indicated that the item was essential (i.e., a rating of “3”) and N is the total number of participants. This ratio will indicate the items that at least half of the participants consider essential. The validity ratio will be interpreted based on a table of critical values.(31) For example, for 20 participants (N = 20), the critical value is 0.500 (i.e., at least 15 participants must deem the item to be essential). Only items based on a critical value greater than the set threshold will be considered further .(32) This approach facilitates remote and objective decision making and the estimation of content validity (the degree to which the items represent the construct of complete reporting). We will use the results of the quantitative data to create a draft list of potential reporting items. This list will only contain reporting items with validity ratios above their critical threshold and will be finalized in the focus group discussions.

Qualitative phase

The discussions will be transcribed from recordings and coded into categories by two independent coders and compared for consistency. During the discussions, participants will go over the selected set of reported items and confirm their choice of whether they are essential reporting items. They will also examine the grammar and wording of the items. Participants may propose new items (except items dropped from the survey in the quantitative phase) and these will be discussed. Qualitative data analysis will be informed by grounded theory, where open codes are generated by identifying repetitions in the text.(33) Similar codes will be grouped, with themes emerging from these groupings. Two coders will verify agreement on the generated themes. Disagreement will be resolved by discussion. Thematic analyses will continue cyclically until no new patterns or themes emerge from the data. An outline of the study is shown in Figure 2.

Validation checks

In the quantitative phase we will pilot-test our survey. In the qualitative phase, we will use member-checking, audio-video recordings, and duplicate coding to validate our data. During the focus group discussions, moderator bias will be minimized by using a discussion guide.

Consensus and agreement

Consensus will be determined statistically in the quantitative phase using item-specific validity ratios so that the items where at least 50% of participants rated essential are kept in the initial reporting item checklist at the end of the quantitative phase. In the qualitative phase, agreement was not needed on an item to proceed. Agreement is inferred when at least one participant verbally speaks on whether a reporting item was essential or not and there are no verbal objections with the statement. Therefore, agreement also involves the failure to speak up against specific items.

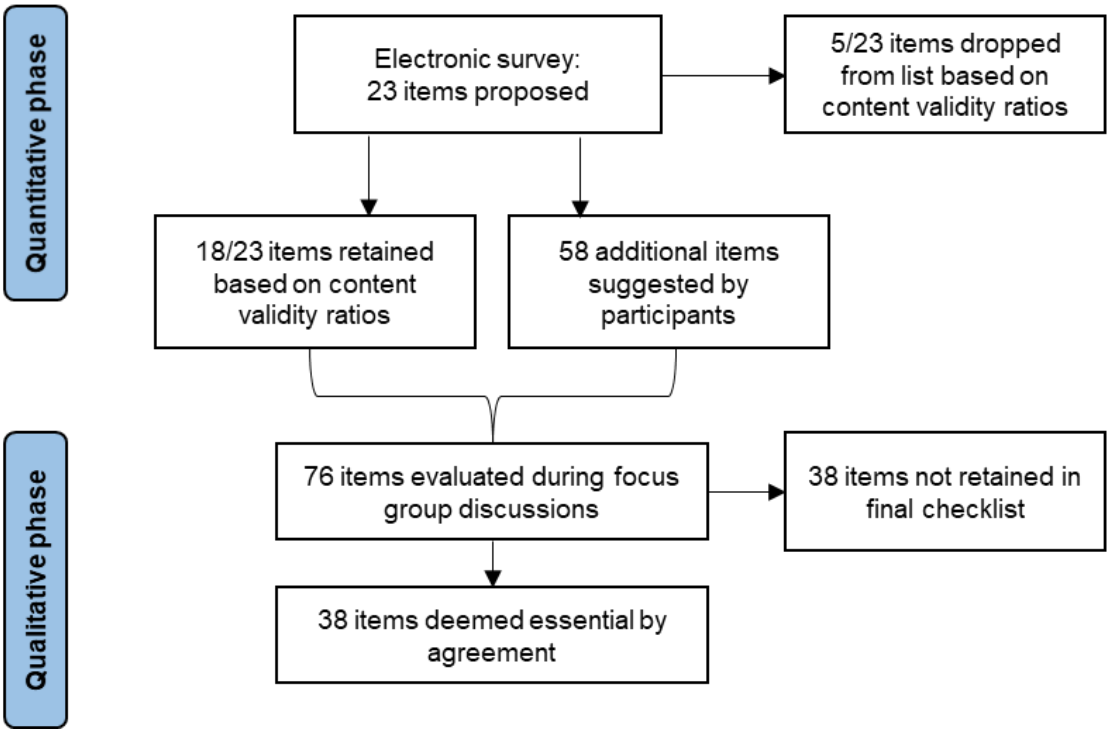
Ethics approval

This study received ethics approval from the Hamilton Integrated Research Ethics Board (project number #11558) on November 11, 2020 and received annual renewal approval on September 27, 2021. Only participants who provide informed consent will participate in the study. Participants will be able to stop the electronic survey or withdraw from the focus group discussions at any time.

2.3 Results

The electronic survey was open from November 2020 to June 2021. In total 51 participants provided informed consent and completed the electronic survey. Once the quantitative phase data collection and analysis was complete, virtual focus group discussions were held in October 2021. Two focus groups were held including nine participants in total. Results of both the electronic survey and focus group discussions are being analysed. A flowchart of items dropped and retained in the checklist is provided in Figure 3.

Figure 3: Flow diagram of reporting items dropped and kept in checklist



2.4 Discussion

In this study, we will use mixed methods to produce a reporting item checklist of items to be considered in the process of developing reporting guidelines for studies of HIV drug resistance prevalence. We will explore and highlight the insights gained from using mixed-methods to meet our study objectives. An explanatory sequential design was selected for this study to allow for the use of qualitative data to explain results from the quantitative findings, breadth and depth in the data collected .(34, 35)

We anticipate that most of the initially proposed reporting items presented in the survey will be rated as essential and go on to be evaluated in the focus group discussions. We also expect additional reporting items will be suggested by survey participants, which will also be evaluated in the focus group discussions. During the focus group discussions, we expect considerable agreement on the inclusion of most reporting items proposed in the quantitative phase, with disagreements on areas of wording, grammar, and relevance to specific types of HIV drug resistance research designs. As the purpose of this study is to develop a reporting item checklist and key insights to inform the development of reporting guidelines, we anticipate participants will discuss important considerations that the complete reporting guidelines must consider to be accessible and relevant to all authors and users of HIV drug resistance prevalence research, including any concerns over data privacy and confidentiality.

The strengths of this study include the integration of both quantitative and qualitative methodologies to elicit consensus and agreement from experts on the items that should be reported in studies of HIV drug resistance. Additionally, validation checks will be made in both phases of the study to improve data quality. Study limitations include the susceptibility to low response rates in the quantitative phase and therefore the potential for response bias. We have estimated a sample size to determine the minimum number of responses required for the quantitative phase. However, we have specifically incorporated approaches to enhancing diversity of views by reviewing the geographic coverage of the quantitative data, and purposefully selecting participants form high- and low-income settings for the focus group discussions and as external reviewers.

2.5 Dissemination and Knowledge Translation

Dissemination

The results of this work will be presented as peer-reviewed manuscripts, conference presentations, and as part of a master's thesis. Participants who express interest in the findings of the study will also be sent the results of this work.

Knowledge translation

We will incorporate several knowledge translation strategies including: engagement of opinion leaders in the agreement discussions (e.g. study authors), and through linkage and exchange mechanisms (i.e. connecting researchers and knowledge-users to

facilitate dissemination, for example via educational workshops and project summary briefings to stakeholders).(36) All focus group participants as well as the individuals who have indicated interest in being informed about the outcomes of this research will be engaged as knowledge user partners to help share the reporting guideline. Additional mechanisms will involve academic media releases (e.g. St. Joseph's Healthcare Hamilton, public health/HIV societies), and web-based social marketing (e.g. Twitter). We will also tailor conference meeting presentations to be educational to inform knowledge-users (e.g. researchers designing HIV drug resistance prevalence studies) about reporting issues and the current gaps at the design stage of HIV drug resistance prevalence studies, and the need for the reporting guideline.

During focus group discussions, we will ask participants about any perceptions of barriers for practice change (e.g. at the level of HIV drug resistance prevalence study design) and uptake of the reporting guideline. We will use this feedback to tailor educational activities (e.g. conference presentations) and dissemination efforts (e.g. preferences for receiving the information) for this audience. For example, to target increased awareness about reporting issues and reporting guideline, we will present findings about the impacts of missing study data, as well as ensure that we target local, national and international conferences for dissemination activities. We will publish manuscripts arising from this work in open-access journals.

Knowledge translation impact and evaluation will be measured at the level of the HIV research community using the following metrics: reach and use indicators (e.g. number of manuscript accesses and citations), collaboration indicators (e.g. endorsement by relevant journals in the field), and practice change indicators (e.g. improvements in reporting over time).(37) For example, indicators of uptake will be measured over time in cross-sectional studies to evaluate changes in reporting practices before and after the publication of the reporting guideline.

Future Directions

The checklist of items and qualitative insights produced by this study will be refined, elaborated, and considered by a writing committee of experts in HIV drug resistance. We will also invite external reviewers from international organisations such as the WHO, The Joint United Nations Programme on HIV/AIDS (UNAIDS), Elizabeth Taylor Foundation and the Centers for Disease Control and Prevention (CDC) to provide feedback on the reporting guidelines.

2.6 Conclusions

We seek to develop both a reporting item checklist for studies of prevalence of HIV drug resistance and a better understanding of what makes a reporting item important to HIV drug resistance prevalence research. The forthcoming reporting item checklist and qualitative insights will directly inform the explanation and elaboration document that will have detailed justifications and rationale for each reporting item in the checklist.

Acknowledgements

The authors have no acknowledgments to provide.

Conflicts of Interest

The authors have none to declare. This research received no specific grant funding from public, commercial, or not-for-profit agencies/sectors.

The next chapter will cover the results of the mixed-methods study, structured for readability as a thesis chapter. The content of this chapter will be later re-structured and revised for publication in a traditional manuscript style as per a target journal's format specifications.

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Chapter 3: Developing a Reporting Item Checklist for Studies on the Prevalence of HIV Drug Resistance

3.1 Background

HIV drug resistance threatens the efficacy of antiretroviral medications (ARVs), many of which risk becoming partly or fully inactive due to resistant strains.(1) In June 2021 the WHO released an update to its HIV drug resistance strategy, highlighting the importance of monitoring and surveillance efforts and in obtaining high quality data on HIV drug resistance prevalence estimates.(2) However, adequate monitoring of HIV drug resistance worldwide is challenged by heterogenous and inadequate data reporting.(3)

Inadequate reporting makes it challenging for readers to assess the reliability and interpretability of research findings.(4-7) Studies that collect information on HIV drug resistance should be reported comprehensively and consistently to allow for the ability to combine studies for better precision. Additionally, such efforts improve interpretability and consideration of the representativeness of the participant sample and techniques used to measure resistance. Our previous work has recommended the need for agreement on a list of key reporting items for studies reporting the prevalence of HIV drug resistance.

In 2010 Moher et al. published guidance for researchers seeking to develop health research reporting guidelines.(4) In accordance with this framework and to initiate the process of developing reporting guidelines for studies of HIV drug resistance prevalence, our prior work evaluated the completeness of reporting of HIV drug resistance prevalence literature, the results of which supported the need for agreement on a list of potential reporting items.(3, 8) We have registered this guideline project on the EQUATOR network as: CEDRIC-HIV (ChEcklist for studies of Drug ResIstanCe in HIV).(9) A progress checklist of CEDRIC-HIV along the steps outlined by Moher et al. is available in Appendix 1. We report this mixed methods study in compliance with the Good Reporting of A Mixed Methods Study (GRAMMS) checklist, available in Appendix 4.(10)

Research objectives

As a part of the CEDRIC-HIV project, this study builds on our previous work that identified the need for reporting guidelines, and seeks to explore the process of identifying potential reporting items and understanding what makes a reporting item important to HIV drug resistance research. The detailed research questions for the thesis work are presented in Chapter 1. Briefly we carried out a mixed methods study including a) quantitative research objective to use survey methodology to identify a list of reporting items considered by participants to be essential for studies on the prevalence of HIV drug resistance, b) focus group methods to identify emergent themes elucidated during discussions over whether reporting items are essential to HIV drug resistance prevalence research, and c) data integration methods to explain the findings of the cross-sectional survey

Research paradigm

We adopted a pragmatist paradigm to inform our research design and approach. We used both deductive and inductive reasoning during focus group discussions to determine the reporting items that would remain in the checklist. Pragmatism is a useful paradigm for mixed-methods research and agreement taking because it allows for the use of "what works" best in data collection and analysis.(11-13) Additionally, the pragmatist paradigm incorporates multiple perspectives, linking both subjective and objective knowledge naturally suited for the integration of the quantitative and qualitative data produced in this study. In the lens of pragmatism we acknowledge that our research occurs within specific sociopolitical and economic contexts.(13) These contexts shape the development of a reporting item checklist that is relevant to authors of HIV drug resistance prevalence research.(12, 14)

Rationale for design

Mixed methods suit research objectives that cannot be met by either qualitative or quantitative methodologies alone, such as the research objectives for this study.(15, 16) Additionally a sequential explanatory mixed methods approach naturally suits the order of steps proposed in Moher's guidance framework, allowing first for the identification of a list of potential reporting items via quantitative methods consecutively followed by group discussion on these items through qualitative methods. Further elaboration on our use of mixed methods can be found in Chapters 1 and 2.

3.2 Methods and Analysis

The methods of this study have been described in detail previously in the protocol chapter (Chapter 2). Briefly, this is a mixed-methods study of authors of HIV drug resistance research.

Research design

We conducted a sequential explanatory mixed methods study among authors of studies of HIV drug resistance prevalence. To complement quantitative data with the qualitative understanding the two phases of this design include: a cross-sectional electronic survey (quantitative phase) followed by focus group discussions (qualitative phase). The research design is informed by grounded theory in its iterative design and system of analysis, where quantitative data analysis informs qualitative data collection to explain why items are important to report in HIV drug resistance prevalence research.

Data integration

Data integration took place in an intermediary stage between the quantitative and qualitative phase where the focus group discussion guide and participants for the focus groups were selected based on the survey results (see Figure 2).

Ethics

This study received ethics approval from the Hamilton Integrated Research Ethics Board (HiREB) project number #11558 on November 11, 2020 and received annual renewal HiREB approval on September 27, 2021.

Sampling

Quantitative phase

Our purposeful convenience sampling frame for the cross-sectional survey included corresponding authors (n=160) from the 650 studies of HIV drug resistance included in our 2020 systematic review of HIV drug resistance prevalence in key global populations.(8) Study invitations were sent to all 160 email addresses. The survey link was also disseminated on social media platforms and among HIV journals with authors who have published research on HIV drug resistance prevalence. Considering a population of 160 and assuming an α level of 0.05 and a 10% margin of error, we arrived at a minimum sample of 61 survey respondents to be representative of the population of HIV drug resistance researchers.(17).

Qualitative phase

In the qualitative phase, we sought a purposeful sample of survey responders from the quantitative phase who indicated in their survey response their willingness to participate in focus group discussions. When selecting participants for these discussions we sought to achieve at least one male and one female participant from as many of the six WHO regions as possible.

Data collection

Quantitative phase

In the quantitative phase, authors of drug resistance prevalence studies were approached to complete a 23-question electronic survey, rating reporting items as ‘essential’, ‘useful but not essential’, or ‘not necessary’. Images of the electronic survey are available in Appendix 2. At the end of each section participants were permitted to suggest any additional items they believed should be considered into an open-text field. To capture participant characteristics basic sociodemographic data of age, sex, country of residence, profession, number of years in primary role was also collected as part of the survey. Participants were also asked whether they were interested in participating in the focus group discussions.

Qualitative phase

In the qualitative phase, selected individuals who participated in the survey and expressed interest in participating in focus group discussions were approached to provide consent prior to the discussions. Focus groups were conducted over Zoom, with both the session audio, video, and chat log being recorded and stored. The facilitator introduced

the session and initiated the discussions based on a focus group guide. During the discussions, participants reviewed the initial draft list of reported items from the quantitative phase and confirmed their choice of whether the items are essential. Participants also reviewed all additionally suggested reporting items brought up in the survey. Focus group discussions lasted about 120 minutes each. Audio files and transcripts were stored in Dropbox, a file hosting service.

Data analysis

Quantitative phase

We conducted a descriptive analysis of quantitative data using R Studio version 4.0.3, summarizing counts (%) for categorical variables, mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous or discrete variables . The coding of the ordinal scale data is as follows: essential (3), useful but not essential (2), and not necessary (1). This ordinal data was used to compute a content validity ratio (CVR) for each reporting item by dividing the number of participants who rated the item as essential by the total number of participants who rated the item. The CVR is a quantitative approach of assessing content validity - assurance that the reporting items measure the content area it is expected to measure.(18) Each CVR was then compared to a table of critical CVR values (CVR_{crit}).(18) Each CVR_{crit} was calculated using the *bitesti* command in STATA and the *critbinom* formula in Excel, producing a CVR_{crit} based on the number of participants who voted on the reporting item. An example calculation is provided in Appendix 5.

Only reporting items with a CVR that exceeds their CVR_{crit} were kept on the draft list of reporting items, however dropped items could be reintroduced if brought up during the focus group discussions.(19) All additionally suggested reporting items from the open-text fields of the survey were summarized and discussed in the qualitative phase, with no criteria for selecting specific items to be presented

Qualitative phase

We conducted a thematic analysis of the qualitative data produced from the focus groups informed by grounded theory. Pre-existing codes or themes were not used to allow for concepts to emerge from the data. The audio-video recordings were transcribed into text transcripts. Open codes were generated by identifying repetitions in the text in Taguette, a free and open-source qualitative data analysis tool.(20, 21) Similar codes were grouped, with themes emerging from these groupings in Taguette. Two coders worked on the data to verify agreement on the generated themes. Disagreement was resolved by discussion. Thematic analyses continued cyclically until no new patterns or themes emerged from the data.

Consensus and agreement

Consensus was achieved statistically in the quantitative phase using item-specific content validity ratios where items with at least 50% of participants rated essential were kept in the initial reporting item checklist. In the qualitative stage, while agreement was not needed on an item to proceed, agreement was inferred when at least one participant verbally spoke on whether a reporting item was essential or not and there were no verbal objections with the statement. Disagreement allowed to further explore the rationale behind reporting and why some people had concerns and why others did not, feeding into the elaboration document. Examples of this discourse is available in the results of the thematic analyses in section 3.3.

Validation checks

In the quantitative phase we estimated a minimum representative sample size and revised and pilot-tested our survey. In the qualitative phase, we used member-checking, audio-video recordings, and duplicate coding to improve the validity of our findings. During the focus group discussions, we minimized facilitator bias by using a discussion guide.

3.3 Results

Quantitative results

Participants

Fifty-one (51) participants responded to the survey for a response rate of 31.8%. The mean age of participants was 48.1 years (SD=10.51) with 17 females (37%), and mean number years of experience in role was 17 (SD = 9.45). At least one participant from each WHO region was represented in the survey, with responses from twenty-four countries. Over a quarter (n=13, 28.3%) of participants were from the African WHO region, with another quarter from the European region (28.3%). Nearly a third of participants were from the Americas region (n=14, 30.4%). The details of socio-demographic characteristics are displayed in Table 3.

Table 3: Socio-demographic characteristics of participants in the quantitative phase of the study (n=51)

Variable	**Statistic**
Age (years): mean (SD)*	48.1 (10.51)
Sex: n (%)[&]	
Male	29 (63.0)
Female	17 (37.0)
WHO Region: n (%)[&]	

African	13 (28.3)
Americas	14 (30.4)
South-East Asian	2 (4.3)
European	13 (28.3)
Eastern Mediterranean	1 (2.2)
Western Pacific	3 (6.5)
Primary role: n (%)*	
Research	16 (35.6)
Academia	10 (22.2)
Clinical	16 (35.6)
Industry	0 (0.0)
Government	3 (6.7)
Years in role: mean (SD) [&]	17 (9.45)

[&]5 missing; *6 missing

The initial reporting item checklist

Of the 23 proposed reporting items, 15 were retained for further evaluation in the focus group discussions based on the CVR (see Table 4, below). 58 additional reporting items were suggested by survey participants and were evaluated in the focus group discussions (see Appendix 6).

Table 4: Initial reporting item checklist, with content validity ratios (CVR) and critical values.

Reporting Item	**N**	**N_e**	**N/2**	**CVR**	**CVR_{crit}**	**Status**
Study-level items						
Setting of study	51	40	25.5	0.569	0.250	Kept
Location of study	51	37	25.5	0.451	0.250	Kept
Study design	51	38	25.5	0.490	0.250	Kept
Sample size justification	51	30	25.5	0.176	0.250	Dropped

Participant items						
Age	50	33	25	0.320	0.253	Kept
Sex	50	33	25	0.320	0.253	Kept
Sexual orientation	50	25	25	0.000	0.253	Dropped
Transmission risk group	50	35	25	0.400	0.253	Kept
Profession	50	14	25	-0.440	0.253	Dropped
Place of residence	50	16	25	-0.360	0.253	Dropped
Ethnicity	50	18	25	-0.280	0.253	Dropped
Level of education	50	09	25	-0.640	0.253	Dropped
Income	50	06	25	-0.760	0.253	Dropped
Exposure to antiretroviral therapy	50	48	25	0.920	0.253	Kept
HIV resistance testing items						
Type of resistance test	50	44	25	0.760	0.253	Kept
Mutation list used	50	46	25	0.840	0.253	Kept
Number of genotypes	50	40	25	0.600	0.253	Kept
Resistance to NNRTI drug class	50	48	25	0.920	0.253	Kept
Resistance to NRTI drug class	50	48	25	0.920	0.253	Kept
Resistance to PI drug class	50	48	25	0.920	0.253	Kept
Resistance to INSTI drug class	50	45	25	0.800	0.253	Kept
Clinical relevance	50	37	25	0.480	0.253	Kept
Other items						
Source of funding	50	21	25	-0.160	0.253	Dropped

N: Number of respondents who rated the reporting item;
N_e: Number of respondents who rated the reporting item as 'essential';
CVR: $[N_e – (N/2)] / (N/2)$

Qualitative results

Participants

Two focus group discussions were conducted including a total of nine participants, with four female participants. The mean age was 55.4 years (SD = 9.13). Six participants had

primary roles in research, 2 participants clinical primary roles, and one participant was from government. The mean years in primary role was 26.6 years (SD = 6.71). Both groups were similar with regards to WHO region, with four of five participants in the first group from the Americas region (USA, Canada) and one from the Eastern Mediterranean region (Tunisia). In the second group three of four participants were from the European region (Italy, Spain, Israel) and one from the Americas (Argentina).

Examples generated from checklist appraisal

During the focus group discussions participants appraised all items including the 58 additionally suggested items for redundancy, clarity, wording in content. The comments from focus groups were fed into the checklist as illustrative examples. Table 5 below highlights the checklist concepts selected in the survey and corresponding examples derived from the focus group discussions:

Table 5: Survey concepts discussed in focus groups along with specific examples

Survey item content	**Examples provided by focus groups**
Study setting	Hospital or community locations, periods of recruitment, data collection, follow-up
Study design	Details on ethics approvals/waivers, consent for use of data beyond study
Participant information	Eligibility criteria, sources and methods of selection of participants, target population, number of individuals at each state of study (recruitment, eligible, included, successfully genotyped), reasons for non-participation, migration status, recent or late-stage infection, viral load at time of specimen collection, CD4 cell count levels,
Laboratory methods	Describe source of samples used (plasma, dried blood spots), methods of viral load testing (assay, limit of detection), method of HIV variant phylogenetic analysis, subtyping tool used (with version), quality assurance methods, definitions of predicted resistance mutations, mutation list used (with version and year), algorithm used to interpret data (with version and year)
Sampling	Sampling strategy, sample size calculations, data source
Main results	Number/proportion with any drug resistance, for each class, and for each drug. Number/proportions with more than one drug resistance mutation, major/clinically relevant versus minor/accessory mutation. Mutation frequency table
Discussion	Generalizability of findings
Additional information	Specify if nucleotide sequence is publicly available upon request, report repository where specimens are stored, DOI, procedures for access, GenBank accession numbers.

The strongest themes that emerged from these discussions were: agreement over reporting item essentiality, concerns over availability and ethics of reporting items, and the importance of setting, context, interpretability, and comparability"..

Agreement over reporting item essentiality

For over 90% of the additionally suggested reporting items participants came to an agreement on whether the item was essential or not. Participants also readily identified several reporting items as non-essential. Participants felt that many study-level reporting items were useful but not essential, and that drug resistance items needed to be revised for clarity before being determined as essential. Between the two groups one group voted that reporting global drug resistance was optional while the other group felt very strongly that it was essential to report.

"Totally agree that there should be information on how that nucleotide sequence was generated"(Group 1; participant 1, male)

"I do agree with this list, I don't usually report any of these" (Group 2; participant 1, female)

Participants also expressed the importance of including various reporting items, such as migration patterns and the impact of clustering. Many reporting items were deemed essential to improve the interpretability and comparability of study findings.

"That is an issue for me, especially here, we do have a lot of immigrants" (Group 2; participant 1, female)

"I think is very important to know the limit of detection, because is very different according to the different methodologies" (Group 2; participant 2, female)

"*This [reporting item] allows you allows you to interpret the study results in the broader context of the population being assessed*" *(Group 1; participant 2, male)*

"If you do report genotyping and you do report a subtype it's critical to say where you took it from" (Group 2; participant 1, female)

Concerns over the availability and ethics of reporting items

Participants in one group voiced concerns on both the feasibility and ethics of asking authors to report certain data, mainly participant-level items like sexual orientation, migration status, ethnicity, place of residence, especially in molecular epidemiology studies that do not typically report this data. Participants also noted that for some items the interpretation is subjective and complicated by the lack of standard definitions for variables e.g., adherence.

"Ethnicity is a vital component, but very difficult to elaborate" (Group 1; participant 3, female)

"We don't have [this data] on genotyping programs" (Group 1; participant 3, female)

"[It is challenging to] measure adherence because it is not standardized and it's not necessarily reliable" (Group 1; participant 2, male)

During the discussion on ethical considerations there was some commentary on the criminalization of HIV in certain settings and the potential to cause undue harm to participants when reporting individual data due to linkages of gene sequences.

"There's a growing concern around the use of molecular epidemiology, particularly in vulnerable populations where certain behaviours are criminalized. We need to keep that in mind and be very cautious when developing this list" (Group 1; participant 2, male)

"Individual genotype reports do not have that [data] and should not have that for ethical reasons" (Group 1; participant 3, female)

"The ethics of all this" (Group 1; participant 3, female)

The importance of setting

Throughout the discussion, participants grounded their opinions in their personal experiences, often assessing the relevance of a reporting item in their own setting and then considering its usefulness globally.

"*Here in [Country] we have information on [whether there is] transmission and resistance in babies" (Group 2; participant 3, male)*

" In [Country] you can have whatever drug that is available really" (Group 2; participant 1, female)

"*It may not be a difficult variable in [City]*" *(Group 1; participant 2, male)*

The importance of interpretability

These considerations transitioned into discussions on whether a reporting item meaningfully contributes towards the interpretability of study results and whether it gives the reader context to the study methodology.

"I think it's important that they report their methods for the interpretation of drug resistance" (Group 1; participant 2, male)

"*You want to know at the time of this study, what was going on or why it was relevant*" *(Group 1; participant 2, male)*

The importance of comparability

Additionally, participants considered whether a reporting item was essential in improving the comparability of HIV drug resistance prevalence data.

"*I think the most important [consideration] is to make the studies comparable*" *(Group 2; participant 3, male)*

"*Without that information, you don't know whether you can generalize beyond the study at all" (Group 1; participant 2, male)*

"You could develop it in North America and that makes sense, but you transfer percentages to countries where percentages aren't used as well and you get incorrect data" (Group 1; participant 2, male)

The importance of context

When determining whether an item was important globally participants emphasized the importance of context- and study-specific guidance to avoid overly generic reporting guidelines. A few participants also voiced their displeasure with both the lack of and current format of reporting for current HIV drug resistance surveillance research, suggesting a need to update some mutation lists.

"In some studies, you would like to report [item] and in others you just don't need it" (Group 2; participant 1, female)

"It depends on the research question or the overall goal of the study" (Group 1; participant 2, male)

"*This makes a lot of sense in low- and middle-income countries, but now with really widespread access to ARV drugs, I'm less sure*" *(Group 1; participant 2, male)*

"It really depends on the country" (Group 2; participant 1, female)

Capturing agreement and disagreement

In two separate focus groups participants evaluated the draft reporting item checklist produced in the quantitative phase and 58 additional suggested items. Participants discussed whether each item should remain on the list and whether any items dropped

from the list should be re-added. From the original items on the survey 'sample size justification' was re-added to the list after being dropped in the quantitative phase. For all other items there was general agreement to include on the reporting item checklist. For the additionally suggested survey items agreement was achieved within each group. Examples of representative agreement are below:

Item: Sampling strategy

- "Yes" *(Group 1; participant 3, female)*
- *"Yes, very important" (Group 1; participant 2, male)*

[several seconds of silence from group]

Item: Date of estimated infection

- *"Perhaps it should be optional or no but not a yes" (Group 2; participant 3, male)*
- "Yes, of course" *(Group 2; participant 1, female)*

[silence from group]

Examples of representative disagreement quotes are below:

Item: Sexual orientation

- *"We don't know sexual orientation. We don't know, ethnicity." (Group 1; participant 3, female)*
- *"I'm basically more inclined to keep sexual orientation and ethnicity in the guideline" (Group 1; participant 4, male)*

Item: Viral load testing methods used

- *"Therefore, it probably should be yes" (Group 1; participant 5, female)*
- *"You can imagine scenarios where it would be important, but I just don't know if that's enough for you to call it out as a yes" (Group 1; participant 1, male)*

3.4 Discussion

Summary of main results

In this paper, we use mixed methods to produce a list of potential reporting items to be considered in reporting guidelines for studies of HIV drug resistance prevalence. Fifty-

eight additional reporting items were suggested by survey participants in the quantitative phase, most of which were deemed essential during focus group discussions. The large number of reporting items generated in the quantitative phase indicate that HIV drug resistance researchers seek much more guidance on what to report in their studies than previously thought, as we initially proposed 23 items. This finding also reflects the diverse needs of reporting guidelines across various types of HIV drug resistance research and country settings (physical locations where research is conducted; e.g. community vs clinical care settings) and contexts (broader complex sociocultural influences). The overwhelming majority of survey participants suggested adding drug-resistance testing items to the checklist. Such items involve details on laboratory methods, data sources, and the year, version and type of mutation list used. Many items further specified the type of HIV drug resistance observed, going beyond overall (global) resistance to the level of drug families and drug classes.

To our knowledge this is the first study to use content validity ratios to quantitatively achieve consensus on a list of reporting items. Content validity ratios are traditionally selected to assess content validity in instrument development research.(22) We found that the use of content validity ratios was a pragmatic and straightforward method to discriminate between essential and non-essential reporting items. Participants also expressed the need to include participant-level reporting items. Many of the added participant-level items centered on the timing of, duration of, or type of exposure to antiretroviral medications, which influence the risk of HIV drug resistance. Between the two study phases there was only one change between the initially suggested survey reporting items in Table 4, implying acceptable consistency. Additionally, there were few discrepancies between focus groups when coming to an agreement on the additionally suggested reporting items. The main barriers to agreement during focus groups were the lack of clarity of the suggested reporting item, as some participants were vague in their suggestions (see Appendix 6) and indecision whether the item should be required for all HIV drug resistance studies or for specific study designs. This is also reflected in one of our focus groups which held considerable discussion on the importance of study- and country-context when constructing the reporting item checklist.

We also explored the perspectives of HIV drug resistance experts on important reporting items for studies of HIV drug resistance prevalence. Overall, participants expressed concern regarding the ethics of requiring reporting of participant personal information for research conducted in settings where HIV is criminalized. Participants also voiced the importance of clarifying whether these reporting guidelines mandate the type of data that must be collected in drug resistance prevalence research, or rather the data to report if already available to the researchers. Such distinction is important given the diverse types of studies in various country settings that produce HIV drug resistance prevalence data and the appreciation that in some circumstances data is available but cannot be reported to protect patient confidentiality.

Importantly, new reporting items also emerged from the focus group discussions around the topic of migration status and clustering of vulnerable populations, reflecting the need for HIV drug resistance prevalence research to stay up-to-date with current global affairs by capturing information on migration patterns and acknowledging that not all populations are homogenous with respect to migration status. Our participants made several comments on the current lack of guidance for reporting HIV drug resistance prevalence data, reaffirming previous recommendations for reporting guidelines and helping specify other areas guidance is needed. These include the 2009 WHO's Surveillance Drug Resistance Mutation list, and WHO definitions for resistance to specific drug classes and the specific drugs included in each class. Overall, support for and willingness to participate in the process to create reporting guidelines for studies of HIV drug resistance is evident among authors of this research. However, participants expressed uncertainty over who the end-users of the reporting guidelines were and whether they were intended for authors of HIV drug resistance research or researchers aiming to synthesize the HIV drug resistance literature.

Strengths and limitations

The strengths of this study include the integration of both quantitative and qualitative methodologies to elicit quantitative consensus and qualitative understanding from researchers on the items that should be reported in studies of HIV drug resistance. Additionally, validation checks were made in both phases of the study to improve data quality. Study limitations include lower than anticipated (~30%) response rates. Additionally, while we had representation from all WHO regions in the survey sample, we would have liked to have had at least one participant from each WHO region participate in the focus group discussions. More comprehensive discussion on the study limitations is provided in Chapter 4.

Implications for future research

As one component of the CEDRIC-HIV project, this paper builds on our previous work that identified the need reporting guidance, exploring the process of identifying reporting items and elucidating what makes a reporting item important to HIV drug resistance research. Our findings should be interpreted as being relevant to authors or users of HIV drug resistance literature in academic, research, clinical, and government settings. We acknowledge that our findings are tied to various socio-economic, cultural and political factors specific to our team in Canada and the participants' own countries of origin.

Future work will revise, and clarify the reporting items identified by this study and how they should be interpreted and adopted. Importantly, there are also several insights from this study that future work to continue the guidelines development process should consider. For example, the elaboration and explanation documents should clearly delineate the types of studies that each reporting item applies to and whether some reporting items are more applicable for certain study designs. For example certain participant items like sexual orientation may be unavailable or unethical to report in

molecular epidemiology studies with HIV drug resistance prevalence data. For reporting items that may result in undue harm for participants in contexts where HIV status, gender identity, or sexual orientation are stigmatized or decriminalized, the guidelines should also touch upon the ethical considerations involved when reporting potentially sensitive data. Further guidance documentation must also detail the procedures if data is unavailable or not reportable and whether authors must explain why the data was not reported. Ultimately, future guidance should thus clearly specify the target users of the reporting guidelines.

3.5 Conclusions

We have developed both a list of potential reporting items for prevalence studies of HIV drug resistance and an understanding of what makes a reporting item important to HIV drug resistance prevalence research. The resultant reporting item checklist and qualitative insights will directly inform the subsequent explanation and elaboration document.

In the next and final chapter, the main take aways of the study are summarized, along with additional discussion on alternative methodologies.

3.6 References

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Chapter 4: Conclusions, Reflection on Methods, and Future Work

4.0 Conclusions

In this mixed methods study, we identified a list of 38 potential reporting items for studies on the prevalence of HIV drug resistance along with qualitative insights on what makes these items important to this research. We also report the emergent themes from the focus group discussions such as concerns over the availability and ethics of reporting certain data, the importance of interpretability, and the need to clarify how the reporting items should be interpreted in both different country and study contexts.

4.1 Insights from the Mixed-methods Methodology

This thesis work highlights how mixed-methods produce insights derived from integrating different methodologies to answer complex research questions. In this sequential explanatory mixed-methods design, the quantitative and qualitative phases were connected (QUAN -> qual) where the focus group participants and discussion guide were informed by the responses to the quantitative survey. The final components of integration will occur in the elaboration documents beyond the scope of this thesis. In this thesis we have presented the quantitative results (reporting item checklist) which informed the qualitative results (themes related to why these items should be reported in studies reporting the prevalence of HIV drug resistance).

4.2 Alternative Methodologies

Content Validity Methods

In Chapter 1 we briefly described the overlap of our methodologies with those observed in content validity studies. The objective of the focus group discussions was to generate discussion among HIV drug resistance researchers on what makes a reporting item important to this research. Alternatively, given that the participants in our study were content experts with research experience or work in the field of HIV drug resistance, we could have designed the qualitative phase as a content review panel instead of a focus group, structured to rigorously appraise the item checklist using qualitative content validity methods. In this approach we would ask the panel to judge whether the reporting items are complete and comprehensive in their definitions of concepts and dimensions.(1) Based on the members' judgement, we would then calculate proportion of agreement for comprehensiveness of each dimension and the checklist overall.(1) These factors in mind, the focus groups were not intended to rigorously appraise the checklist or maximize content validity or transferability, but rather to provide qualitative insights generated from open discussions. As the objectives of this thesis were not to produce a checklist to be directly adopted by end-users, the entire methodology of a content validity study was not appropriate. However, our future elaboration work should consider these content validity methods when developing the full reporting guidelines to increase confidence in their validity and overall adoption.

Delphi Methods

The Delphi method is a structured process of obtaining information from a group of experts through a series of questionnaires, and is often used in health science research to find consensus and formulating guidelines for methodologies issues.(2-4) Delphi techniques have a number of advantageous characteristics including access to a range of experts, good response rates, design simplicity, anonymity and democracy, and cost-effectiveness.(5) In contrast limitations of the technique includes long time-scales as participants are required to respond in a series of rounds that can become long and drawn-out resulting in round-fatigue, loss of motivation, and attrition.(6, 7) Furthermore, researchers may miss valuable information in their Delphi study by focusing on consensus and failing to consider disagreements.(8) For this study, anonymity was not necessary and we focused on the importance of allowing participants to articulate their opinions and disagree with one another during the discussions. Delphi techniques were therefore not suitable to address our research objectives. Had the purpose of this thesis been to directly develop reporting guidelines, the Delphi method would have been a promising approach however this discussion pertains more to the objectives of the CEDRIC-HIV project overall rather than the comparatively more limited scope of this thesis work.(9) Ultimately, survey and focus group methods were the most appropriate to meet the thesis objectives to identify a list of reporting items and an understanding of why these items are important to HIV drug resistance research.

4.3 Limitations

As mentioned in Chapter 1, a strength of mixed methods is the ability to couple the strengths of quantitative and qualitative to compensate for their weaknesses. Some of our remaining concerns are outlined below

We observed a lower than anticipated response rate (~ 30%) to the survey despite multiple reminders. While this proportion is typical for email surveys,(10) the issue of non-response bias remains. Non-response bias refers to the systematic error in estimating a population characteristic based on a sample of survey data due to differences between participants who do and do not respond to the survey.(11) The effects of this bias may be observed in our data in the table of participant characteristics presented in Chapter 3, where only two respondents were from the South-East Asian WHO region, one from the Eastern Mediterranean region, and three from the Western Pacific region. However, our sample included participants from all the WHO regions, both sexes and diverse professions and reflects the amount of HIV drug resistance research coming from these regions based on our sampling frame of 160 emails. Regarding the sampling frame of corresponding authors, we acknowledge that not all authors of HIV drug resistance research were included as the author list derived from the previous systematic review was limited to January 1997 to February 2019. Therefore, potentially eligible authors who published after February 2019 would have not been included in our study. Additionally, it is possible that some of the email addresses retrieved from the articles were no longer active. Another limitation applicable to our qualitative research design is the influence of the group setting, group dynamics, and the group composition on what the participants

say and do not say during the discussions, though these influences may be minimized as the group discussions were held online.(12) Lastly, we observed a small focus group sample of nine participants, limiting the transferability of the focus group insights beyond the focus groups. However the credibility of the qualitative insights remain high as the rationale behind the purposive sampling was to identify information-rich participants who completed the electronic survey to explore our phenomena of interest.(13) Additionally, purposely selecting fewer participants allows for more in-depth information about each person, which often diminishes as the focus group size increases.(14)

4.4 Future Direction

Guideline development is a multi-step process that builds upon prior research in the area. This thesis work continues efforts to develop reporting guidelines for studies on the prevalence of drug resistant HIV. As of June 2022, the subsequent complete reporting item checklist has been written along with the elaboration document. External reviewers have been identified and will be contacted to review the documents for feedback before we seek publication.

4.5 References

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Appendices

Appendix 1: Progress checklist of CEDRIC HIV and the thesis project along the recommended steps for developing a health research reporting guideline a

Item detail	Completion status	Details
Initial steps		
1. Identify the need for a guideline	Completed	Published by Mbuagbaw et al., 2021[b]
1.1 Develop new guidance	Ongoing	
1.2 Extend existing guidance	Not applicable	
1.3 Implement existing guidance	Not applicable	
2. Review the literature	Completed	Published by Macdonald et al., 2020[c]
2.1 Identify previous relevant guidance	Not applicable	
2.2 Seek relevant evidence on the quality of reporting in published research articles	Completed	Published by Mbuagbaw et al., 2021[b]
2.3 Identify key information related to the potential sources of bias in such studies	Completed	Published by Mbuagbaw et al., 2021[b]
3. Obtain funding for the guideline initiative	Not applicable	
Pre-meeting activities		
4. Identify participants	Completed	Conducted as part of this mixed-methods study
5. Conduct a Delphi exercise	Not applicable	
6. Generate a list of items for consideration at the consensus meeting	Completed	Conducted as part of the quantitative phase of the mixed-methods study
7. Prepare for the consensus meeting	Completed	Conducted as part of this mixed-methods study
7.1 Decide size and duration of the face-to-face meeting	Completed	Conducted as part of this mixed-methods study

7.2 Develop meeting logistics	Completed	Conducted as part of this mixed-methods study
7.3 Develop meeting agenda	Completed	Conducted as part of this mixed-methods study
7.3.1 Consider presentations on relevant background topics, including summary of evidence	Completed	Conducted as part of qualitative phase of this mixed-methods study
7.3.2 Plan to share results of Delphi exercise, if done	Not applicable	
7.3.3 Invite session chairs	Not applicable	
7.4 Prepare materials to be sent to participants prior to meeting	Completed	Conducted as part of this mixed-methods study
7.5 Arrange to record the meeting	Completed	Conducted as part of qualitative phase of this mixed-methods study
Consensus meeting		
8. Present and discuss results of pre-meeting activities and relevant evidence	Completed	Conducted as part of qualitative phase of this mixed-methods study
8.1 Discuss the rationale for including items in the checklist	Completed	Conducted as part of qualitative phase of this mixed-methods study
8.2 Discuss the development of a flow diagram	Not applicable	Discussed during focus group discussions - members did not think it was useful
8.3 Discuss strategy for producing documents; identify who will be involved in which activities; discuss authorship	Completed	Conducted as part of qualitative phase of this mixed-methods study
8.4 Discuss knowledge translation strategy	Completed	Conducted as part of qualitative phase of this mixed-methods study and study protocol
Post-meeting activities		
9. Develop the guidance statement	Ongoing	
9.1 Pilot test the checklist	Future work	
10. Develop an explanatory document (E&E)	Ongoing	
11. Develop a publication strategy	Ongoing	

11.1 Consider multiple and simultaneous publications	Ongoing	We have started discussions with journal editors
Post-publication activities		
12. Seek and deal with feedback and criticism	Ongoing	
13. Encourage guideline endorsement	Future work	
14. Support adherence to the guideline	Future work	
15. Evaluate the impact of the reporting guidance	Future work	
16. Develop Web site	Future work	
17. Translate guideline	Future work	
18. Update guideline	Future work	

[a] Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. PLoS Med. 2010;7(2):e1000217.

[b] Mbuagbaw L, Ongolo-Zogo C, Mendoza OC, Zani B, Morfaw F, Nyambi A, et al. Guidelines are needed for studies of pre-treatment HIV drug resistance: a methodological study. BMC Med Res Methodol. 2021;21(1):76.

[c] Macdonald V, Mbuagbaw L, Jordan MR, Mathers B, Jay S, Baggaley R, et al. Prevalence of pretreatment HIV drug resistance in key populations: a systematic review and meta-analysis. J Int AIDS Soc. 2020;23(12):e25656.

Appendix 2: Electronic survey distributed as part of the quantitative phase

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Page 1

Developing guidelines for studies of pre-treatment HIV drug resistance

Thank you for taking part in our study! This survey should take approximately 12 minutes to complete.

Consent

This survey is administered by Dr. Lawrence Mbuagbaw, Department of Health Research Methods, Evidence and Impact, McMaster University. The purpose of the survey is to develop guidelines for studies of HIV drug resistance by achieving consensus on what items should be reported in studies of HIV drug resistance.

This survey should take approximately 12 minutes to complete. People filling out this survey must be authors of studies on HIV drug resistance.

This survey is part of a study that has been reviewed and approved by the Hamilton Integrated Research Ethics Board (HIREB). The HIREB protocol number associated with this survey is [xx]

You are free to complete this survey or not. If you have any concerns or questions about your rights as a participant or about the way the study is being conducted, please contact:

Office of the Chair, Hamilton Integrated Research Ethics Board at 905.521.2100 x 42013

Having read the above, I understand that by clicking the "Yes" button, I agree to take part in this study

◯ Yes
◯ No

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Page 2

About You

What gender do you identify as?

◯ Male
◯ Female
◯ Other

What is your age?

_____

Where is your primary country of residence?

- ◯ Afghanistan
- ◯ Albania
- ◯ Algeria
- ◯ Andorra
- ◯ Angola
- ◯ Antigua & Deps
- ◯ Argentina
- ◯ Armenia
- ◯ Australia
- ◯ Austria
- ◯ Azerbaijan
- ◯ Bahamas
- ◯ Bahrain
- ◯ Bangladesh
- ◯ Barbados
- ◯ Belarus
- ◯ Belgium
- ◯ Belize
- ◯ Benin
- ◯ Bhutan
- ◯ Bolivia
- ◯ Bosnia Herzegovina
- ◯ Botswana
- ◯ Brazil
- ◯ Brunei
- ◯ Bulgaria
- ◯ Burkina
- ◯ Burundi
- ◯ Cambodia
- ◯ Cameroon
- ◯ Canada
- ◯ Cape Verde
- ◯ Central African Rep
- ◯ Chad
- ◯ Chile
- ◯ China
- ◯ Colombia
- ◯ Comoros
- ◯ Congo
- ◯ Congo {Democratic Rep}
- ◯ Costa Rica
- ◯ Croatia
- ◯ Cuba
- ◯ Cyprus
- ◯ Czech Republic
- ◯ Denmark
- ◯ Djibouti
- ◯ Dominica
- ◯ Dominican Republic

- Guinea-Bissau
- Guyana
- Haiti
- Honduras
- Hungary
- Iceland
- India
- Indonesia
- Iran
- Iraq
- Ireland {Republic}
- Israel
- Italy
- Ivory Coast
- Jamaica
- Japan
- Jordan
- Kazakhstan
- Kenya
- Kiribati
- Korea North
- Korea South
- Kosovo
- Kuwait
- Kyrgyzstan
- Laos
- Latvia
- Lebanon

- ◯ Lebanon
- ◯ Lesotho
- ◯ Liberia
- ◯ Libya
- ◯ Liechtenstein
- ◯ Lithuania
- ◯ Luxembourg
- ◯ Macedonia
- ◯ Madagascar
- ◯ Malawi
- ◯ Malaysia
- ◯ Maldives
- ◯ Mali
- ◯ Malta
- ◯ Marshall Islands
- ◯ Mauritania
- ◯ Mauritius
- ◯ Mexico
- ◯ Micronesia
- ◯ Moldova
- ◯ Monaco
- ◯ Mongolia
- ◯ Montenegro
- ◯ Morocco
- ◯ Mozambique
- ◯ {Burma}
- ◯ Namibia
- ◯ Nauru
- ◯ Nepal
- ◯ Netherlands
- ◯ New Zealand
- ◯ Nicaragua
- ◯ Niger
- ◯ Nigeria
- ◯ Norway
- ◯ Oman
- ◯ Pakistan
- ◯ Palau

- ◯ Palau
- ◯ Panama
- ◯ Papua New Guinea
- ◯ Paraguay
- ◯ Peru
- ◯ Philippines
- ◯ Poland

- ◯ Portugal
- ◯ Qatar
- ◯ Romania
- ◯ Russian Federation
- ◯ Rwanda
- ◯ St Kitts & Nevis
- ◯ St Lucia
- ◯ Saint Vincent & the Grenadines
- ◯ Samoa
- ◯ San Marino
- ◯ Sao Tome & Principe
- ◯ Saudi Arabia
- ◯ Senegal
- ◯ Serbia
- ◯ Seychelles
- ◯ Sierra Leone
- ◯ Singapore
- ◯ Slovakia
- ◯ Slovenia
- ◯ Solomon Islands
- ◯ Somalia
- ◯ South Africa
- ◯ South Sudan
- ◯ Spain
- ◯ Sri Lanka
- ◯ Sudan
- ◯ Suriname
- ◯ Swaziland
- ◯ Sweden
- ◯ Switzerland
- ◯ Syria
- ◯ Taiwan
- ◯ Tajikistan
- ◯ Tanzania
- ◯ Thailand
- ◯ Togo
- ◯ Tonga
- ◯ Trinidad & Tobago
- ◯ Tunisia
- ◯ Turkey
- ◯ Turkmenistan
- ◯ Tuvalu
- ◯ Uganda
- ◯ Ukraine
- ◯ United Arab Emirates
- ◯ United Kingdom

- ◯ United Kingdom
- ◯ United States
- ◯ Uruguay
- ◯ Uzbekistan
- ◯ Vanuatu
- ◯ Vatican City
- ◯ Venezuela
- ◯ Vietnam
- ◯ Yemen
- ◯ Zambia
- ◯ Zimbabwe

What is your primary role?

- ◯ Research
- ◯ Academia
- ◯ Clinical
- ◯ Industry
- ◯ Government

How long (in years) have you been in this role?

_____

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Rating Essentiality of Items

The following section will list potential items to be reported in studies of HIV drug resistance prevalence. Please go through each item listed and select a rating of 'essentiality' . Items have been categorized into four categories:

1. Study-level items
2. Participant items
3. HIV resistance testing items
4. Other items

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1. Study-level items

	Not necessary	Useful but not essential	Essential
Setting of study (e.g. hospital, community, prison etc.)	○	○	○
Location of study (e.g. country, city, village)	○	○	○
Study design (e.g. cross - sectional, retrospective etc.)	○	○	○
Sample size justification (i.e. was the sample size justified?)	○	○	○

Are there additional study-level items that should be reported?

○ Yes
○ No

Enter these additional study-level items

_____

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2. Participant items

	Not necessary	Useful but not essential	Essential
Age	○	○	○
Sex/Gender	○	○	○
Sexual orientation	○	○	○
Transmission risk group (e.g. injection drug use)	○	○	○
Profession (e.g. CSW)	○	○	○
Place of residence (e.g. urban, rural)	○	○	○
Ethnicity	○	○	○
Level of education	○	○	○
Income	○	○	○
Exposure to antiretroviral therapy (e.g. treatment-naive)	○	○	○

Are there any additional participant items that should be reported?
○ Yes
○ No

Enter these additional participant-level items

_____

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3. HIV resistance testing items

	Not necessary	Useful but not essential	Essential
Type of resistance test (e.g. Sanger sequencing, next generation sequencing)	○	○	○
Mutation list used (e.g. *WHO SDRM list)	○	○	○
Number of genotypes (as opposed to the number of participants)	○	○	○
Resistance to *NNRTI drug class	○	○	○
Resistance to *NRTI drug class	○	○	○
Resistance to *PI drug class	○	○	○
Resistance to *INSTI drug class	○	○	○
Clinical relevance (e.g. mutations associated with reduced virological response)	○	○	○

*NNRTI: Non-Nucleoside Reverse Transcriptase;
* NRTI: Nucleoside Reverse Transcriptase Inhibitors;
*PI: Protease Inhibitors;
* INSTI: Integrase Strand Transfer Inhibitor;
* World Health Organisation Surveillance Drug Resistance Mutation list;

Are there any additional resistance testing items that should be reported? ○ Yes ○ No

Enter these additional resistance testing items

_____

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4. Other items

	Not necessary	Useful but not essential	Essential
Source of funding	○	○	○

Are there any additional 'other' items that should be reported?
○ Yes
○ No

Enter these additional 'other' items

_____

Thank you for completing our survey. Better guidance on the reporting of drug resistant HIV will help ensure complete and uniform reporting and improve the appropriate interpretation, generalizability and comparability of prevalence estimates.

Appendix 3: Qualitative interview guide used during focus group discussions

Qualitative interview guide

For interviewer:

1. Thank interviewee for participating
2. Introduce yourself
3. Describe the purpose of the interview, benefits and potential harms, permission to record.
4. State the duration of the interview
5. Describe the compensation
6. Determine eligibility
   - Did you take the online survey?
   - Did you express interest in joining the focus group discussion?

If yes to both, proceed to obtain consent and interview.

HIV Expert:

Summary information for focus group:

1. Age
2. Gender
3. Primary role:
   a. Research
   b. Academia
   c. Clinical
   d. Industry
   e. Government
4. WHO region
   a. African Region
   b. Region of the Americas
   c. South-East Asia Region
   d. European Region
   e. Eastern Mediterranean Region
   f. Western Pacific Region

List of potential reporting items and rationale (to be tailored according to quantitative data):

1. Study-level data
   a. Setting of study, e.g. hospital, community, prison etc.
   b. Location of study, e.g. country, city, village
   c. Study design, e.g. cross-sectional, retrospective etc.
   d. Sample size justification, i.e. (was the sample size justified?)
   e. Add any additional items?
   f. Comments on grammar/wording
2. Participant data
   a. Age
   b. Sex/Gender

   a. Sexual orientation
   b. Transmission risk group, e.g. injections drug use
   c. Profession
   d. Place of residence, e.g. urban, rural
   e. Ethnicity
   f. Level of education
   g. Income
   h. Exposure to antiretroviral therapy, e.g. treatment-naïve
   i. Add any additional items?
   j. Comments on grammar/wording

2. Information on resistance testing
   a. Type of resistance test, e.g. Sanger sequencing, next generation sequencing
   b. Mutation list used, e.g. *WHO SDRM list
   c. Number of genotypes (as opposed to the number of participants)
   d. Resistance to NNRTI drug class
   e. Resistance to NRTI drug class
   f. Resistance to PI drug class
   g. Resistance to INSTI drug class
   h. Clinical Relevance, e.g. mutations associated with reduced virological response
   i. Add any additional items?
   j. Comments on grammar/wording

   **NNRTI: Non-Nucleoside Reverse Transcriptase; NRTI: Nucleoside Reverse Transcriptase Inhibitors; PI: Protease Inhibitors, INSTI: Integrase Strand Transfer Inhibitor; World Health Organisation Surveillance Drug Resistance Mutation list; *Surveillance Drug Resistance Mutation*

3. Other information
   a. Source of funding
   b. Add any additional items?
   c. Comments on grammar/wording

Appendix 4: Thesis reporting along the Good Reporting of A Mixed Method Study (GRAMMS) checklist [a]

Guideline	Thesis Chapter: Section(s)
Describe the justification for using a mixed methods approach to the research question	Chapter 2: Methods Chapter 3: Introduction
Describe the design in terms of the purpose, priority and sequence of methods	Chapter 2: Methods Chapter 3: Methods
Describe each method in terms of sampling, data collection and analysis	Chapter 2: Methods Chapter 3: Methods
Describe where integration has occurred, how it has occurred and who has participated in it	Chapter 2: Methods Chapter 3: Methods
Describe any limitation of one method associated with the present of the other method	Chapter 1: Methodology Chapter 3: Discussion Chapter 4: Limitations
Describe any insights gained from mixing or integrating methods	Chapter 4: Insights

[a] O'cathain A, Murphy E, Nicholl J. The quality of mixed methods studies in health services research. Journal of health services research & policy. 2008 Apr;13(2):92-8.

Appendix 5: Content validity ratio (CVR) example calculation for the 'study setting' item

Formula:

$CVR_{item} = \frac{Ne - \frac{N}{2}}{\frac{N}{2}}$

N = is the total number of participants who rated the reporting item

N_e = number of participants who reported that the reporting item was 'essential'

$CVR_{crit(N)}$ = critical CVR value, dependent on value of N.

- $CVR < CVR_{crit}$ = drop item from checklist
- $CVR \geq CVR_{crit}$ = keep item in checklist

Example calculation

$N_{setting} = 51$

$N_{e(setting)} = 40$

$CVR_{setting} = \frac{40 - \frac{51}{2}}{\frac{51}{2}} = \frac{14.5}{25.5} = 0.569$

$\therefore CVR_{crit(51)} = 0.250$

$\therefore 0.569 > 0.250$; keep item in checklist

Appendix 6: Table of additional suggested items from the electronic survey of the quantitative phase (verbatim)

Study-level items	Participant items	Drug resistance items	Other items
1. Sampling year	11. Target population definition	32. Source of sequence data	55. Clinical care v planned prevalence/incidence study
2. Sampling strategy	12. Place of likely HIV acquisition	33. Sequence quality assurance/control methods	56. Ethical items
3. Estimated N of total population	13. Risk factors	34. Laboratory methods used	57. Human resource materials
4. % of total N sampled	14. Care model	35. Viral load testing methods used	58. Reference to previous data in the country/setting under study
5. Total number eligible	15. (Infant population) Maternal breastfeeding	36. Subtyping tool used	
6. Total number screened	16. (Pediatric population) HIV status of mother	37. Subtyping method used	
7. Total number consented	17. Date of HIV diagnosis	38. Predicted resistance classes	
8. ARVs used in study setting	18. Date of estimated infection	39. Type of resistance testing used as standard of care (or comparison)	
9. (For weighted estimates) methods used for weighting	19. Assay used for HIV diagnosis	40. Definitions of ART classes	
10. Locality of principle investigator	20. HIV RNA level (viral load)	41. Definitions of predicted resistance classes	
	21. Assay used for viral load	42. Resistance to more than one class	
	22, Assay limit of detection (LOD)	43. Resistance to individual drugs of each class	
	23. Viral suppression at sampling	44. Resistance to each drug family and global	
	24. CD4 count at sampling	45. Major and minor drug resistance mutation	
	25. Level of adherence	46. HIV variant subtype	
	26. Resistance in participants taking ART	47. HIV variant phylogeny	

	27. Treatment history	48. Transmitted or post-therapy drug resistance	
	28. Antiretroviral regimen	49. Timing of sequence relative to infection	
	29. Time on ART regimen	50. Year of mutation list used	
	30. Type of ART regimen	51. Presence of compensatory mutations	
	31. Use of PreP or PEP	52. Samples collected for resistance analysis	
		53. Justification for sequence collection	
		54. Number of recovered sequences in cohort	