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# Critical EPICOT items were absent in Cochrane human immunodeficiency virus systematic reviews: a bibliometric analysis

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## Abstract

**Objectives:** To summarize the current gaps in human immunodeficiency virus (HIV) research evidence, describe the adequacy of reporting ''implications for research,'' and map the number of studies that inform reviews with the prevalence of HIV for each country.

**Study Design and Setting:** A bibliometric analyses of HIV reviews in the Cochrane Database of Systematic Reviews with content analysis of the ''implications for research'' section.

**Results:** We analyzed 103 high-quality reviews published as of March 2014. They included a median of five studies (min 0 and max 44). Almost all the reviews recommended more trials (89.3%). Limitations in trial design, duration, setting, sample size, and choice of participants were also noted. Reporting of EPICOT+ items was as follows: evidence (35.9%), population (57.3%), intervention (71.8%), comparison (20.4%), outcomes (57.3%), time stamp (34.0%), and disease burden (13.6%). The primary studies were conducted in 67 countries. Six of the top 10 countries in which primary studies were conducted had a high HIV prevalence.

**Conclusion:** Knowledge gaps were identified for research in younger participants, over longer periods, using more pragmatic interventions, conducted in resource-limited settings and incorporating economic evaluations. Implications for research are not always reported according to the EPICOT+ format. Not all countries with a high prevalence of HIV are contributing sufficiently to HIV research. 

*Keywords:* HIV research; Implications for research; Knowledge gaps; EPICOT+; Cochrane

## 1. Introduction

The Cochrane Collaboration is a world leader in the production and dissemination of high-quality systematic reviews [1]. Apart from the robust and standardized methodologies that characterize Cochrane reviews, they go a step further to describe the implications for practice, policy, and research [2]. The implications for research section generally describes qualitative and quantitative gaps in the synthesized evidence and is intended to identify research questions that have not been addressed [2]. These ''research gaps'' may relate to the quality of the research (risk of bias), the quantity of evidence (number of studies or total number of participants included in each of these studies), or the applicability of the evidence (geographic or clinical settings in which the studies were conducted). Currently, the way implications for research are reported is not uniform across Cochrane reviews. Efforts have been made to provide guidance on how research recommendations should be formulated, such that it is clear how the research agenda can be moved forward [3,4]. Clearly formulated research recommendations include information about the state of current evidence; the population studied; the interventions, comparisons, and outcomes of interest; and the date of the recommendations [3].

Conflict of interest: B.Z. has worked for the Cochrane HIV Group as assistant trial search coordinator at the South African Cochrane Center. T.K. is the Center Manager of the South African Cochrane Center. V.W., L.M., S.M., B.Z., T.K., and N.V.M. are authors of Cochrane reviews.

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**What is new?**

**Key findings**

- More HIV research is required: in younger participants, over longer periods, using more pragmatic interventions, conducted in resource-limited settings and incorporating economic evaluations.

**What this adds to what was known?**

- It is unclear what knowledge gaps exist in HIV research and how investigators should design studies to respond to implementation needs.

**What is the implication and what should change now?**

- Investigators and funders should design HIV research to address these knowledge gaps. Publishers should enforce better reporting standards.

Over the past 2 decades, enormous advances in human immunodeficiency virus (HIV) care have reduced morbidity and mortality [5]. These advancements include improvements in therapy (i.e., antiretroviral treatment) and preventive measures (i.e., behavior change, barrier methods, prophylactic therapy). Although the number of new infections is on the decline, close to 35 million people are living with HIV worldwide [5]. This implies that the currently applied interventions are already demonstrating positive effects as mortality due to HIV is reducing. However, there are still many new infections leading to a large number of people living with HIV as a chronic disease [5]. Thus, innovative strategies are required to prevent new infections and to ensure that people living with HIV have healthy and productive lives.

HIV is not a homogenous condition. It involves people with different social, economic, and geographic, cultural, and medical backgrounds. Management may differ for each of these groups, and their needs should be addressed in research endeavors. For example, research should explore the needs of high-risk social groups, such as men who have sex with men, commercial sex workers, health workers, and injection drug users; it should be relevant for individual economic or collective economic situations (personal income, availability of health insurance); it must consider geographic and cultural factors that affect behavior and care seeking behaviors and consider the most common comorbidities affecting people living with HIV (tuberculosis, cardiovascular disease, hepatitis B, hepatitis C). Many people living with HIV belong to one or more of these groups and it is unclear how much of the research evidence responds to their needs. Extrapolating research findings from one population to another may not always be appropriate [6], and limitations in applicability should be adequately reported [7], as they may inform future research endeavors.

Analyzing the content of the ''implications for research'' section can provide useful information and opportunities for clinical research. The purpose of our research is to inform researchers, funders, government, and academic bodies on potentially important foci for HIV research. It will also serve to discourage research endeavors in domains where strong evidence already exists and to avoid duplication of efforts. This piece of work will strengthen the argument for transparently describing the applicability of research findings for end users of the evidence.

## 2. Objectives

Our objectives were to describe the adequacy of reporting implications for research, to map the number of studies that inform Cochrane reviews with the prevalence of HIV for each geographic region, and to summarize the current gaps in HIV research evidence from Cochrane reviews published with the HIV/AIDS review group (https://hiv.cochrane.org/).

## 3. Methods

### 3.1. Design

A bibliometric analysis of HIV reviews in the Cochrane Library with content analysis of the ''implications for research'' section.

### 3.2. Data sources

We extracted data from all the reviews ($n = 103$) of the Cochrane HIV/AIDS group (http://hiv.cochrane.org/our-reviews) in the Cochrane Library, published as full reviews.

These reviews were grouped into four main categories:

1. Reviews of behavioral, social, or policy interventions for HIV prevention ($n = 16$).
2. Reviews of biomedical prevention ($n = 16$).
3. Reviews of health services and care ($n = 9$).
4. Reviews of therapeutics, prognostics, and diagnostics ($n = 62$).

Full-text manuscripts for all published reviews as of the March 13, 2014, were retrieved. The most recent and updated citations were used.

### 3.3. Data extraction and management

Data extraction was conducted in pairs by any of seven reviewers (L.M., T.K., V.W., S.M., S.R., B.Z., and N.V.M.) using a standardized and piloted data extraction form. Disagreements were resolved by discussion and consensus. We

extracted basic bibliometric data, category of review, number and location of included studies in the reviews, and the implications for research. The locations of the included studies were extracted from the "Table of included studies." The implications for research data were categorized as follows: no more trials required, more trials required overall, more trials required with better quality, more trials required in different settings, more trials in different population, more trials with different intervention, more trials with different outcomes, more trials with longer follow-up, further evidence unlikely to come from trials, and process information required. We also evaluated the completeness of these implications for research using the EPICOT+ framework (evidence, participants, interventions, comparison, outcomes, and time frame) [3]. In this framework, for research recommendations to be most useful, they should provide an overview of the evidence; describe the participants in whom further research is required; evaluate the interventions, comparisons, outcomes, and time frame of the research; and relate all this to the disease burden.

### 3.4. Assessment of methodological quality of included reviews

The methodological quality of each included review was independently assessed by any pair of seven reviewers (L.M., T.K., V.W., S.M., S.R., B.Z., and N.V.M.) using AMSTAR: A MeaSurement Tool to Assess Reviews instrument [8]. AMSTAR assesses the degree to which review methods avoided bias by evaluating the methods reported against 11 distinct criteria. Each item on AMSTAR is rated as yes (clearly done), no (clearly not done), cannot answer, or not applicable. The tool has been shown to have good face and content validity for measuring the methodological quality of systematic reviews. For all items, except item 4, a rating of "yes" is considered adequate. For item 4, a rating of "no" (i.e., the review did not exclude unpublished or gray literature) is considered adequate. A review that adequately meets all the 11 criteria is considered to be a review of the highest quality.

### 3.5. Data synthesis

We described the characteristics of included reviews and their categories; if implications for research were reported, their recommendations and how these recommendations were reported. Data are presented as counts and percentages. We planned to report our results in light of the quality assessment of the reviews using AMSTAR [2], but all the included studies were of high quality. We also evaluated and displayed the ecologic relationship between disease prevalence and number of trials. HIV prevalence data were obtained from the UNAIDS data tool (AIDSinfo; http://www.unaids.org/en/dataanalysis/datatools/aidsinfo/). This relationship is displayed as a graph.

## 4. Results

### 4.1. Included reviews

On March 13, 2014, there were 103 reviews published by the Cochrane Review Group on HIV/AIDS. The reviews were of high quality, with a mean AMSTAR rating of 9.43 (standard deviation = 1.5). They included a median of five primary studies (first quartile = 2; third quartile = 11). The studies were conducted in 67 countries.

### 4.2. Adequacy of reporting as per EPICOT+

The most adequately reported item was the intervention (71.8%). Only 13.6% related their implications for research to the disease burden. The population was reported in 57.3%, the comparison in 20.4%, the outcome in 57.3%, and a summary of the evidence leading to these conclusions in 35.9% of the reviews. Thirty-four percent of the reviews included a time stamp (Fig. 1). Only four studies reported all EPICOT items (3.8%). No studies reported all EPICOT items and disease burden (EPICOT+).

### 4.3. Implications for research

All the reviews had an "implications for research" section that covered recommendations regarding future directions for research (Fig. 2). Almost all the reviews recommended more trials (89.3%), with 51.5% recommending changes to the outcomes, 47.6% recommending changes to the interventions, and 33.0% recommending higher quality studies. Two reviews did not find any eligible trials. Up to 26.2% recommended data from nonrandomized studies, and 1.9% recommended qualitative studies.

### 4.4. Research gaps in HIV

We have summarized the key findings from these reviews in Table 1. We highlight the participants, interventions, comparisons, outcomes, time frame, and settings for which further research would be informative.

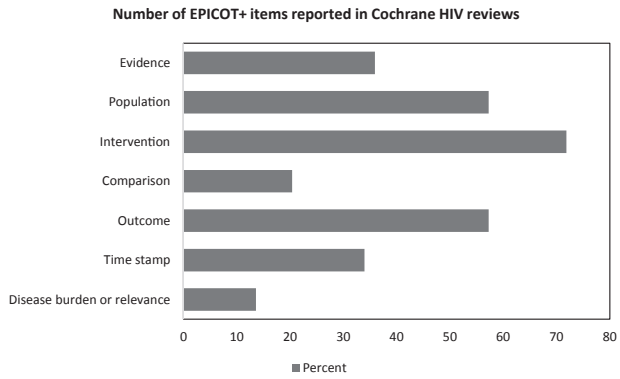


**Fig. 1.** Percentage of Cochrane HIV reviews reporting EPICOT+ items. HIV, human immunodeficiency virus.

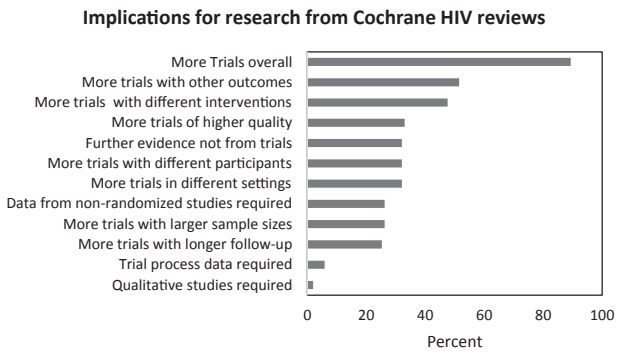


**Fig. 2.** Implications for research reported in Cochrane HIV reviews. HIV, human immunodeficiency virus.

### 4.5. Geographic coverage

Among the 103 reviews, we looked at the countries in which the primary studies were conducted. Studies were conducted in 67 countries. In seven reviews, we were unable to determine some of the countries in which the primary studies were conducted. The United States (52), South Africa (30), Uganda (19), Kenya and Thailand (16 each), France (15), the United Kingdom (14), Zimbabwe (13), Canada, Tanzania, and Zambia (12 each), Australia (11), and Italy (10) occupied the top 10 positions for contributing evidence in HIV Cochrane reviews. Of these countries, South Africa, Kenya, Uganda, Tanzania, Zimbabwe, and Zambia are among the top 10 countries with the highest numbers of people living with HIV (UNAIDS, 2015). Fig. 3 is an illustration of HIV prevalence compared with country contributions to HIV research in the Cochrane library. Country contributions refer to the number of times a study from a given country appeared in a Cochrane review.

## 5. Discussion

The findings from many systematic reviews often go unused simply because patients, clinicians, and care givers cannot apply their findings in everyday practice. This is often because ''research-important'' outcomes are not always ''patient-important'' outcomes [1]. As researchers strive to look into patient relevant issues with regards to the effects of interventions, we must also endeavor to provide stakeholder-relevant recommendations for further research. We summarized the current gaps in HIV research evidence from Cochrane HIV reviews, described the adequacy of reporting implications for research, and mapped the number of studies that inform reviews with the prevalence of HIV for each geographic region. This content analysis of HIV reviews in the Cochrane library brings us one step closer to developing a useful resource for research planning with actionable guidance in HIV research.

### 5.1. EPICOT+

Although reporting implications for research according to EPICOT+ is not a requirement of Cochrane reviews, many authors addressed these items, though none address all of them. Arguably, some of these items may not necessarily be reported as stand-alone items. For example, the state of the evidence is already summarized in the results section, and therefore, some authors may not find it useful to repeat this information. In addition, each Cochrane review clearly states the date of the search in the Section 3, thereby inherently including a time stamp. However, implications for research will clearly be incomplete and for the most part uninformative if the participants, interventions, comparisons, and outcomes that are to be the subject of further research are not highlighted. These are the key items that authors are invited to report as per the Cochrane Handbook (handbook.cochrane.org). However, these reporting standards do not seem to be enforced by editorial boards. More efforts should therefore be expended on providing more detail on these research gaps.

### 5.2. Implications for research

Our findings suggest that there is a need for more HIV trials. It is essential that future trials incorporate strategies to reduce the risk of bias and target population subsets for whom such research is relevant. In many instances, other nonrandomized studies, qualitative studies, and economic analyses are required to inform decision makers. For trials to be most useful, they should report on important outcomes and incorporate longer follow-up times. For studies to be relevant and not amount to a waste in resources and participants time, investigators should ensure that the information generated from their trials can be used to inform practice, policy, and research. They should also be adaptable to the target population.

### 5.3. Research gaps in HIV

The research gaps we retrieved from these reviews reflect applicability issues with clinical trials that have been raised in other articles [7]. For example, the stringent inclusion criteria often leave out participants for whom information is required. They also point to lapses in reporting interventions in sufficient detail to permit replication (in primary studies) and consolidate our findings on the geographic misdistribution of HIV research. One may view these research gaps as limitations in the accessibility of research information—for readers, in which case adherence to optimal reporting standards is key or simply as design and methodological flaws that limit the usability of findings [15,16]. Either way, resources are expended and evidence needs are not met in full.

**Table 1.** Summary of research gaps from HIV reviews published in the Cochrane library

| Domain | Recommendations | Examples |
|---|---|---|
| Participants | • Infants<br>• Children<br>• Adolescents<br>• Carers of people or children with HIV<br>• Different severities of disease and comorbidities<br>• Diversity in use of antiretroviral therapy (ART)<br>• Disaggregation of data by age<br>• Ethnicity<br>• Access to health insurance<br>• Pregnant women<br>• Commercial sex workers<br>• Truck drivers<br>• MSM<br>• Transgender<br>• Participants who do not use health facilities<br>• Traditional healers | In the review on interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children, limited data were found on children and adolescents [9]. |
| Interventions | • Insufficient description of interventions<br>• Different modalities of administration<br>• Interventions to promote VCT and reduce stigma<br>• Provider-level interventions<br>• System-level interventions<br>• Combined interventions<br>• Preventive interventions<br>• Educational interventions | In the review on progressive resistive exercise interventions for adults living with HIV/AIDS, the authors suggested combining progressive resistance exercise with other interventions like testosterone or whey protein [10]. |
| Comparisons | • Dosing schedules<br>• Timing of switching | In the review on antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals, the authors recommended comparing different dosing schedules [11]. |
| Outcomes | • Cost effectiveness<br>• Quality of life<br>• Adverse events<br>• Using standardized measures<br>• Acceptability of interventions<br>• Culture specificity<br>• Lipid profiles<br>• Retention in care<br>• Survival<br>• HIV incidence<br>• Stigma<br>• Female empowerment<br>• Development of drug resistance<br>• Cognitive performance<br>• Disease progression<br>• Behavioral outcomes<br>• Satisfaction with care<br>• Provider satisfaction<br>• Metabolic changes | In the review on motivational interviewing for improving outcomes in youth living with HIV, the authors found no evidence for outcomes such as adherence to medication, quality of life, and mortality [12]. |
| Time frame | • Longer term | In the review on antiretroviral PrEP for preventing HIV in high-risk individuals, the authors recommended more research on long-term efficacy [11]. |
| Setting | • Developing countries<br>• Select research setting as per disease burden<br>• Resource poor settings<br>• Community settings | In the review on antiretroviral regimens for patients with HIV who fail first-line antiretroviral therapy, the authors suggested further trials in low- and middle-income countries [13]. |
| Other issues | • Fit of intervention with current practice<br>• Strategies to enhance access<br>• Combinations of the above | In the review on ART for treating HIV infection in ART-eligible pregnant women, the authors recommended further research on strategies to improve access to medication [14]. |

*Abbreviations*: HIV, human immunodeficiency virus; MSM, men who have sex with men; VCT, voluntary counseling and testing.

### 5.4. Geographic coverage

The geographic coverage of studies included in Cochrane HIV reviews in part reflects disease prevalence, as countries such as South Africa, Kenya, Uganda, Tanzania, Zimbabwe, and Zambia with the highest number of people living with HIV also contributed highly to Cochrane HIV reviews. Understandably, many factors other than disease burden affect research output, such as funding and research capacity, both of which are often

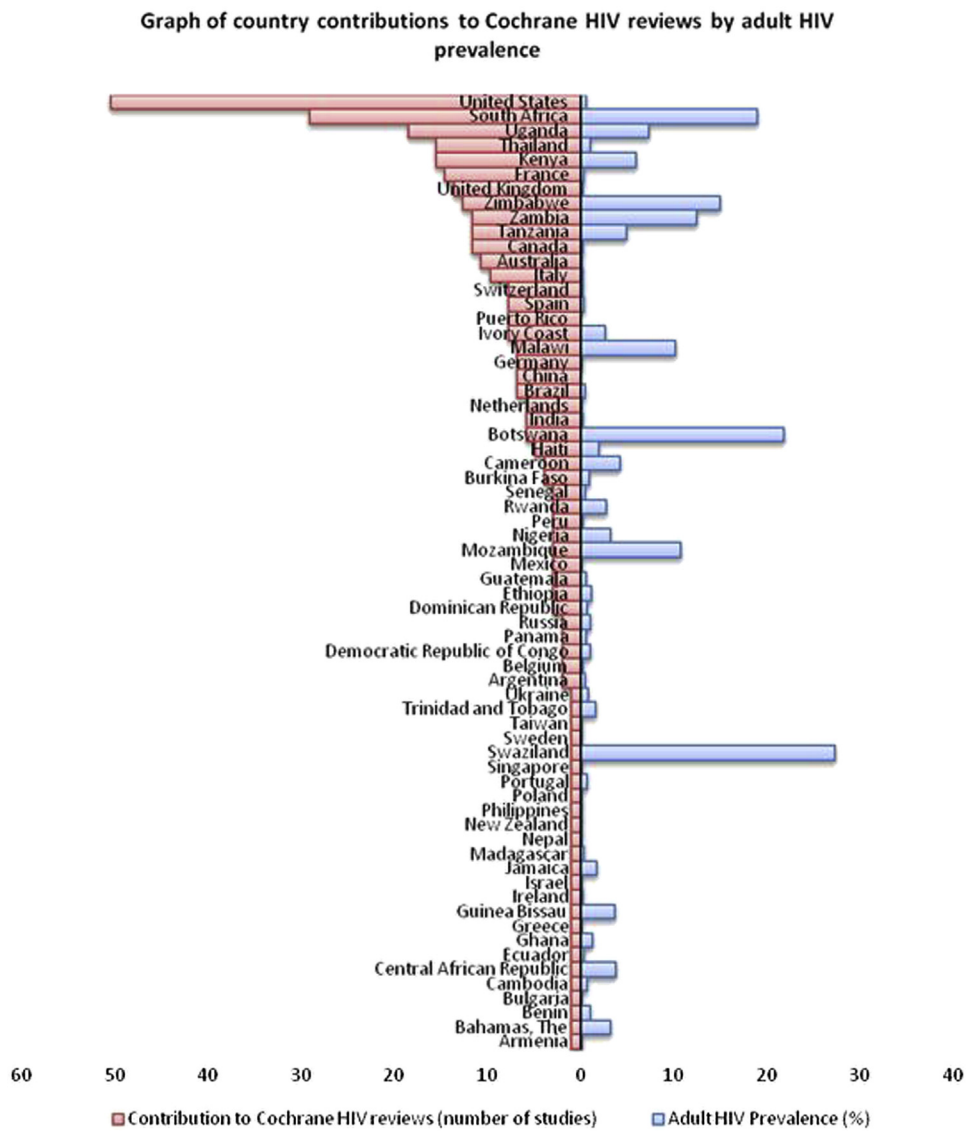


**Fig. 3.** Country contributions to Cochrane HIV reviews by adult HIV prevalence. HIV, human immunodeficiency virus.

scarce in the parts of the world that a mostly affected by HIV. This point is illustrated by the number of US-based studies contributing to Cochrane HIV reviews which corresponds to the significant investments in HIV research [17]. Indeed, this directly weakens the applicability of HIV research because the studies are conducted in settings other than those in which it is most needed or going to be applied [7]. However, it would appear the situation is improving because African countries are balancing research output with disease burden as compared with 10 years ago [18].

### 5.5. Limitations

Despite rigorous duplicate data extraction, our findings should be interpreted with caution as they reflect only a portion of HIV research conducted in the world and as with all bibliometric analyses are limited by the contents of the database studied. We recognize that a number of important studies may not have made it into Cochrane reviews simply because they did not meet the eligibility criteria defined by the authors or no Cochrane reviews have been developed which would have included these studies. In addition, seven reviews included data from multicountry studies which could not be allocated to any single country. As such, we may be underestimating contributions from certain countries. Another possible limitation is that we are evaluating a section of the review based on our opinion of best practice. At the moment, this is not part of the author guidance on writing these sections and we anticipated finding gaps in reporting. However, we feel this is an important approach for demonstrating gaps and creating a case for improvements in systematic review reporting.

## 6. Conclusion

We have developed a list of research gaps that researchers, funders, and decision makers should consider when conducting or funding HIV research. We have also identified gaps in how authors of systematic reviews report their implications for research, primarily in the areas relating implications for research to the burden of disease, time frame of the study, and relevant comparator. These results are being provided to the Cochrane Infectious Disease Group to inform their editorial policies.

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