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Physicians, researchers, public health practitioners and patients are deluged with unmanageable amounts of information about the best approaches to prevention, treatment and health care



delivery. Over the last 30 years, there has been an exponential rise in the number of published scientific articles across health fields. There have been 131,000 randomized controlled trials (RCTs) completed since 1948,¹ over 2 million articles are published annually in the biomedical literature in over 20,000 journals,² and over 3,330 journals are indexed in MEDLINE.

Systematic Reviews

To address the health information overload, systematic reviews have been developed to synthesize the vast number of studies and data sets culled from those studies. These reviews are useful to health care providers because they link and correlate huge amounts of information in order to identify beneficial or harmful interventions.³ For individuals, systematic reviews can help them to make more informed decisions about their health care. Policymakers can use systematic reviews to formulate practice guidelines, identify appropriate interventions for funding, and promote health care legislation grounded in sound public health science.² Researchers can use the results of systematic reviews to identify opportunities for further study and to insure that they are not inadvertently investigating an intervention which has already been proven effective or ineffective.

Two key terms used to describe the synthesis process have been developed: systematic review and meta-analysis. A systematic review (also known as an overview or research synthesis) is defined as “the application of scientific strategies that limit bias to the systematic assembly, critical appraisal and synthesis of all relevant studies on a specific topic.” A meta-analysis is defined as “a systematic review that employs statistical methods to combine and summarize the results of several studies.”⁴

Key components of a systematic review include:

- a well-formulated question and pre-specified criteria for study inclusion and exclusion,
- a comprehensive and methodical search for studies,
- a critical appraisal of the quality of included studies,
- a synthesis of study findings and, if appropriate, a meta-analysis to determine the effects of the same or similar interventions for the same health care condition.^{1, 5-7}

The Cochrane Collaboration

The Cochrane Collaboration is an international network of researchers, health care providers and individuals whose mission is to prepare, maintain and disseminate systematic, continuously updated reviews of health interventions.⁸⁻¹¹ Named for Professor Archie Cochrane, a British epidemiologist and early advocate of thoughtful, structured research synthesis, the Cochrane Collaboration is working methodically to review *all* controlled trials of health care interventions since the first randomized controlled trial (RCT) was published in 1948. The Collaboration is comprised of 50 collaborative review groups, which are organized around health care topics such as infectious diseases, drugs and alcohol, stroke, schizophrenia, pregnancy, and HIV infection and AIDS. Each of these review groups produces systematic reviews in its respective topic area; however, the interests of these groups often overlap and collaborative efforts between groups are common.

Cochrane HIV/AIDS Group

The Cochrane Review Group on HIV Infection and AIDS (HIV/AIDS Group) began in November 1996 and was officially registered with the Cochrane Collaboration in March 1997. The Group has its editorial base at the University of California, San Francisco. The mission of the Group is to conduct systematic reviews of randomized and other rigorously controlled studies with clinical, serologic, behavioral, economic and other outcomes relating to the prevention and treatment of HIV infection and

Table 1

Examples of Topics under Review within the Cochrane Review Group on HIV Infection and AIDS

Behavioral, Social, and Policy Prevention

- Interventions to modify sexual risk behaviors for preventing HIV infection among various populations
- Interventions for improving condom use in people at risk for sexually transmitted infections, including HIV
- Syringe exchange and pharmacy sales of sterile injection equipment for preventing HIV infection
- Partner notification for preventing sexually transmitted infections, including HIV

Biomedical Prevention

- The effectiveness of condoms in reducing heterosexually transmitted HIV
- Post-exposure prophylaxis to decrease HIV seroconversion
- Population-based interventions for reducing sexually transmitted diseases, including HIV infection
- Vaginal microbicides for preventing sexually transmitted infections, including HIV
- Interventions for preventing perinatal transmission

Therapeutics, Diagnostics and Prognostics

- Hydroxyurea for the treatment of HIV
- Antimicrobials for preventing and treating oropharyngeal infections in persons infected with HIV/AIDS
- Discontinuation of prophylaxis for opportunistic infections with highly active antiretroviral therapy
- The use of antibiotics for prophylaxis of opportunistic infections in HIV infected people in the developing world

Health Services

- Highly active antiretroviral therapy and quality of life
- Interventions to improve adherence to treatments
- Provider training and education for clinicians treating HIV infected individuals
- Symptom self-management

AIDS, as well as to the organization and financing of health care services.

The HIV/AIDS Group has international, multi-disciplinary representation and is an affiliate of the International AIDS Society. In particular, the Group has active members from both developed and developing countries and attempts to address reviews from both perspectives. Additionally, people infected with and affected by HIV are involved throughout the review process.

Review Process

Systematic reviews conducted by the HIV/AIDS Group methodically assess all available evidence about the effects of specific HIV/AIDS interventions. Reviews are designed to support a fully objective analysis and to minimize bias. Tools available to assist reviewers in producing high quality results include:

Review Topic Registration

All reviewers are encouraged to register their review topics with the Cochrane HIV/AIDS Group's editorial team. Once a topic has been registered, a content editor is assigned to offer assistance and advice as needed. Along with the content editor, the editorial team assists reviewers in formulating a focused and well-defined research question with relevant objectives. The

selected research question is then broadcast throughout the Collaboration to seek co-reviewers in other discipline areas such as sexually transmitted diseases, infectious diseases, and drug use.

HIV/AIDS Trial Databases

Once the research question for a systematic review has been determined, reviewers search for appropriate studies to include. The Cochrane HIV/AIDS Group conducts searches of elec-

tronic databases of medical, nursing, psychological and social literature, as well as governmental indices in the US and other countries. Although most studies are identified appropriately in MEDLINE and AIDSLINE, some study designs are not coded correctly¹² and many international journals are not included in either MEDLINE or AIDSLINE. Therefore the HIV/AIDS Group manually searches AIDS specialty journals, whether printed in English or other languages, to identify relevant studies. The Cochrane HIV/AIDS Group also consults with governmental and pharmaceutical organizations to identify on-going, pre-publication, and unpublished studies. All of these identified studies are entered into HIV/AIDS Trial Databases, organized by subject, and made available to reviewers for subsequent reviews.

Software and Methodological Resources

The Cochrane Collaboration has developed review management software (RevMan) with a 300-page electronic handbook to assist reviewers through all stages of review preparation. The software includes templates for tables of included and excluded studies and, when appropriate, uses the tables to create pooled summaries of findings.

Peer Review and Updating

Systematic reviews produced by the HIV/AIDS Group are peer reviewed twice by members of the HIV/AIDS Group and others. Peer reviewers include experts in both content and methodology, health care providers and HIV infected/affected individuals. All Cochrane reviews are updated regularly, as new research results become available.

The Cochrane Library

Cochrane reviews are disseminated through the *Cochrane Library*, an electronic journal which is produced quarterly and distributed on CD-ROM and the Internet to subscribers. Cochrane reviews are indexed in Index Medicus.

Examples of Findings

Currently, there are six completed HIV/AIDS reviews and 18 HIV/AIDS reviews near completion on the *Cochrane Library* as well as 23 HIV/AIDS topic areas in which reviewers are developing a research question. See Table 1 for samples of reviews. Selected findings of completed reviews include:

Adherence

A review of patient support and education for promoting adherence to highly active antiretroviral therapy (HAART) identified only one controlled study. The pharmacist-led intervention significantly improved adherence to HAART but there was less evidence that viral load was subsequently reduced. The review identified the urgent need for controlled trials to determine interventions to improve adherence to HAART and to assess the impact of adherence on viral load.¹³

Perinatal Transmission

Interventions aimed at decreasing the risk of mother-to-child transmission of HIV infection were reviewed. It was found that zidovudine, nevirapine and delivery by elective Caesarean section appear to be very effective in decreasing the risk of mother-to-child transmission of HIV infection. The review also addresses non-medical interventions such as avoidance of breastfeeding and vitamin A supplementation.¹⁴

TB Prevention

A review of studies on the prevention of tuberculosis in HIV-infected persons found that preventive therapy appears to be effective in reducing the incidence of tuberculosis and death from tuberculosis in HIV-infected adults with a positive tuberculin skin test, at least in the short to medium term.¹⁵

Lessons Learned

Since the inception of the Cochrane HIV/AIDS Group, we have found that the following elements are vital in performing high-quality systematic reviews.

Collaboration

Collaboration is essential, both on a discipline and geographic level. For example, three different research projects were simultaneously reviewing interventions to reduce perinatal HIV transmission; through the Cochrane HIV/AIDS Group, reviewers from these projects are collaborating to produce an updated joint review by British, French and African researchers and clinicians.

Comprehensive Literature Search

Reviewers must conduct more than a simple MEDLINE or AIDSLINE search to ensure that all relevant evidence is collected. For example,

in the review of HAART adherence supports,¹⁵ one key study included in the review (and the only rigorously controlled study reviewed) was from a Spanish-language medical journal. The thorough process adopted by the Cochrane Collaboration identified this critical resource and provided for its translation.

Appropriate Methods Used

Reviewers must make *a priori* determinations about methods to be employed in the review to ensure inclusion of only the most well-designed studies and to minimize the possibility of biased results. In many clinical situations, the most well designed studies are RCTs.¹⁶ However, in some topic areas (e.g., reviews of HIV behavioral prevention interventions), RCTs may not be ethical or feasible so other controlled interventions must be considered. And in some instances, such as post-exposure prophylaxis for health care workers, the study that offers the best evidence is an observational, case, control design.

Input of Health Care Providers

Health care providers working in the field of HIV/AIDS prevention and treatment are a vital resource and must be consulted during review development and production. Because the field of knowledge surrounding HIV care and prevention evolves rapidly, the best evidence for treatment decisions may not always be fully defined and published. Practical clinical observations are critical to understanding current “best practice” and experiences. This is especially true in developing countries where antiretroviral therapy and treatment for opportunistic infections are just now becoming available. Based on feedback from clinicians working in southern Africa, for example, the HIV/AIDS Group has sponsored a review of the use of broad-spectrum antibiotics for the prevention of opportunistic infections in HIV-infected individuals in the developing world.

Input of Persons Living with HIV/AIDS

It is similarly essential to seek the input of people infected and affected with HIV infection and AIDS during the review process. For example, community members serving as peer reviewers have requested additional information about adverse events associated with treatments, the costs of interventions, and the impacts of resource limitations. Community members serve a vital role in enhancing the quality and completeness of the reviews.

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Additional Reading

For additional information about systematic reviews and the Cochrane Collaboration:

- Chalmers, AL. *Effectiveness and Efficiency: random reflections on health services*. Royal Society of Medicine Press, London 1999. Mulrow CD, Oxman AD (eds).
- Cochrane Collaboration Handbook [updated September 1997]. In: The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration. Oxford: Update Software 2000, Issue 2.

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Getting Involved

If you are interested in conducting a Cochrane review or would like to convert a published review into Cochrane format, contact the Group coordinator, Gail Kennedy via email: gkennedy@psg.ucsf.edu. For more information about anything in this article, visit the Cochrane HIV/AIDS Web site: <http://hivinsite.uscf.edu/cochrane/>.