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Research results have expiration dates: ensuring timely systematic reviews

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Abstract

Time and timeliness are key issues in appraising and ensuring the clinical relevance of systematic reviews. Time considerations entering the systematic review process include the history of the clinical problem, disease, or treatment that is the target of the review, and the history of the research conducted to address it. These considerations guide: (i) formulation of the research problems and questions; (ii) setting of parameters for the search and retrieval of studies; (iii) determination of inclusion and exclusion criteria; (iv) appraisal of the clinical relevance of findings; (v) selection of the findings that will be synthesized; and (vi) interpretation of the results of that synthesis.

Keywords

antiretroviral medication adherence; clinical relevance; HIV/AIDS; quantitative research; systematic reviews

Introduction

Systematic reviews are on the crest of a wave of popularity in the health care disciplines as the pressure for evidence-based practice grows more intense. Systematic reviews of research, especially syntheses of research findings, are advanced as a way to make sense of the hundreds of results of the many studies conducted in common domains of research. Researchers and clinicians increasingly rely on systematic reviews to sum up the state of knowledge in a field, obtain answers to research and clinical questions that cannot be answered in individual studies, resolve apparently conflicting results, confirm or provide a basis for altering existing practice, and to direct future research agendas. This growing reliance on systematic reviews is evident, not only in the growing number and variety of published systematic reviews, but also in the burgeoning instructional and advice literature on systematic review, including the regularly updated *Cochrane Handbook for Systematic Reviews* (Higgins and Green 2005), publication of systematic review methods papers, including systematic reviews of systematic reviews (Sander & Kitcher 2006), in virtually all of the major Western medicine, nursing and other health-related journals, and in national funding of studies to develop systematic review methods (Sandelowski *et al*. 2005; Popay 2006).

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One aspect of the systematic review process that has a major impact on the clinical relevance of reviews, but that has yet to be adequately addressed, is the role of time. Reports of systematic reviews typically include the dates of retrieval and publication of the reports selected for review. What is typically not described, however, is what this information might mean for the formulation of the research purpose for a systematic review, the selection of reports for the review, the selection of the findings from those reports to synthesize, the interpretation of review results, or for the overall relevance of the review for current practice. We address these issues in this paper.

Methods

This paper is based on work completed in our ongoing study to develop methods to synthesize qualitative and quantitative research findings in common domains of health-related research. We chose to begin the work of this project with empirical studies of antiretroviral adherence in HIV-positive women of any race, class, or nationality living in the United States. These limitations were set largely to ensure a sample that was methodologically diverse enough to permit, but not so topically or clinically diverse as to preclude, the methodological experimentation at the heart of the project. In addition, we limited retrieval of reports to those published after 1997 in the hopes of capturing studies conducted after highly active antiretroviral therapy (HAART) became widely available. Indeed, it was after this date that researchers became more interested in antiretroviral medication adherence in HIV-positive patients. Especially compelling was the emerging problem of class resistance to protease inhibitors, and the requirement –more urgent for HIV-positive patients than for patients prescribed medications for other conditions – to achieve >95% adherence for full therapeutic effectiveness and to avoid drug resistance (Paterson *et al*. 2000).

Our study thus far includes 42 reports (35 journal articles, six unpublished theses or dissertations and one technical report), retrieved between June 2005 and January 2006. Of these 42 reports, 25 contained data ascertaining the relationship between aspects of the medication regimen (independent variable) and adherence (dependent variable). Yet as we reviewed these studies and began to notice the time-sensitive, or dated, nature of many of the findings concerning medication regimen, we became increasingly concerned that several of the regimen aspects studied (e.g. type and size of pills, number of pills per dose, number of doses per day, diet restrictions surrounding pills) were no longer as relevant today as they once were. For example, it is now commonplace for HIV-positive persons to take two pills once a day (and a one-pill-once-a-day regimen will soon be available). Yet only a few years ago, patients had to use large tool carts on wheels to store all of their medications. Although we had selected 1997 as the beginning publication date for the reports to be included in our study, several of the studies were conducted before the advent of HAART, while others were conducted in the early years of HAART when common reasons for non-adherence included pill burden and meal restrictions. For example, as shown in Column 1 in Table 1, the data for the results featured were collected as far back as 1993 in at least five reports. These concerns led us to focus on time and timeliness as key issues in appraising and ensuring the clinical relevance of systematic reviews.

Results

Time considerations entering the systematic review process include (i) the history of the clinical problem, disease or treatment that is the target of the review, and (ii) the history of the research conducted to address that target.

History of disease and treatment

Foundational to all time considerations is the history of the clinical problem, disease or treatment that is the focus of the systematic review. Understanding the historical context of the target of the review allows reviewers to place study findings into their appropriate interpretive context. A case in point is the field of HIV; few areas of health care have changed as rapidly as the view and treatment of those infected with HIV. In one decade, advances in therapy have transformed HIV/AIDS from a fatal to a chronic disease: from a disease viewed as one that largely gay men died from to a chronic condition anyone could contract and that could not only be lived with, but also lived with well.

Moreover, the treatment guidelines have changed dramatically over the last decade, with drugs and drug regimens promoted and falling out of favour. For example, initially only zidovudine was used to treat HIV infection. Introduced in March 1987, it was administered every 3 hours, around the clock. With the advent of more drugs, the clinical problem became which drugs to select and how to combine the two or more drugs selected for optimal treatment. Guidelines issued in 1990 recommended routine prescription of zidovudine in all cases where the T helper cells destroyed by HIV (CD4) count fell below 500. Revised guidelines indicated that drugs might or might not be prescribed for patients with low CD4 counts but no symptoms (Macilwain 1993). After 1997, guidelines became more precise. Only in 2003 were guidelines fine-tuned to recommend specific drugs and drug combinations.

In addition to rapid changes in the regimens themselves that served as backdrop to studies addressing regimens as independent variables were changes in the philosophy of when to treat HIV infection. The decision of when to treat was initially left largely to the discretion of the clinician. Clinicians were then advised to wait to prescribe medications because so few of them were available and drug resistance was emerging as a serious complication. A brief period existed of ‘hit hard, hit early’ (Ho 1995), in which drugs were prescribed to any seropositive patient who agreed to take the medication, because of the assumption that if the virus was attacked early, it would not establish itself in the patient. Yet medication side-effects and complex dosing requirements made this unworkable for many people. The current era is one of caution, whereby treatment is offered only to patients whose CD4 count is between 200 and 350 and whose viral load is >100 000 (Department of Health and Human Services 2005). Accordingly, changing philosophies about treatment likely explain the ambivalence or lack of knowledge female participants in the reviewed studies often perceived in their providers and the wide differences in the actual regimens studied. The era of treatment uncertainty was likely a contributing factor to these findings in studies of that era aimed at ascertaining the link between medication regimen and adherence.

As shown in Table 1, of the 42 reports of studies reviewed in our project, four indicated that data were collected pre-HAART (1996 or earlier); 27 indicated that data were collected post-HAART (1997–2005); and five indicated that data were collected in the period spanning pre- and post-HAART. (In six reports, the dates of data collection remain unknown as we were unable to obtain this information from primary authors of these reports.) Favouring adherence were regimens featured in the more current studies reviewed, including simpler regimens (Abel & Painter 2003), simpler timing of the medication regimen (Gant & Welch 2004), once- or twice-a-day dosing (Powell-Cope *et al*. 2003), and having fewer pills to take (Stone *et al*. 2001). These factors continue to be relevant as they characterize the most commonly used current regimens to treat anti-retroviral (ARV)-naïve patients. For example, the older protease inhibitor-based preferred regimen involved taking eight pills twice a day with food to reduce gastrointestinal side-effects. In contrast, the newer non-nucleoside reverse transcriptase inhibitors (NNRTI)-based preferred regimen consists of two pills once a day, which should be taken on an empty stomach at bedtime (Department of Health and Human Services 2005).

Although the most prominent side-effects in the NNRTI-based regimen are the neurological effects associated with efavirenz, these effects usually subside after several weeks.

Knowledge of these regimens, and how they have changed dramatically in such a short period of time, served as a backdrop for reviewing the findings; they are listed in Table 1. Of the 42 reports, 17 indicated that medication side-effects were a key factor in non-adherence (Siegel & Gorey 1997;Roberts & Mann 2000;Fourney 1999;Schuman *et al*. 2001;Wilson *et al*. 2001;Erlen *et al*. 2002;Garcia-Teague 2002;Howard *et al*. 2002;Richter *et al*. 2002;Abel & Painter 2003;Douglass *et al*. 2003;Jones *et al*. 2003;Mellins *et al*. 2003;Powell-Cope *et al*. 2003;Gant & Welch 2004;Wood *et al*. 2004;Phillips *et al*. 2005). Also negatively affecting adherence were complexity of drug regimens (Turner *et al*. 2000;Stone *et al*. 2001;Garcia-Teague 2002;Abel & Painter 2003;Gant & Welch 2004) and, specifically, having too many pills to take (Stone *et al*. 2001;Durante *et al*. 2003;Jones *et al*. 2003;Mellins *et al*. 2003;Gant & Welch 2004;Wood *et al*. 2004;Phillips *et al*. 2005), having difficulty fitting the treatment schedule into one's daily schedule (Roberts & Mann 2000;Fourney 1999;Wilson *et al*. 2001;Garcia-Teague 2002;Howard *et al*. 2002;Phillips *et al*. 2005), and dietary requirements or restrictions (Roberts & Mann 2000;Stone *et al*. 2001;Garcia-Teague 2002;Powell-Cope *et al*. 2003;Phillips *et al*. 2005). The characteristics of the pills themselves (e.g. taste, size) were also found to be factors hindering adherence (Roberts & Mann 2000;Garcia-Teague 2002;Powell-Cope *et al*. 2003). Several reports featured fears regarding drug toxicity or lack of efficacy, either for the woman herself (Siegel & Gorey 1997;Fourney 1999;Schuman *et al*. 2001;Siegel *et al*. 2001;Wilson *et al*. 2001;Erlen *et al*. 2002;Richter *et al*. 2002;Durante *et al*. 2003;Roberts & Mann 2003;Phillips *et al*. 2005) or for her unborn child (Siegel *et al*. 2001;Richter *et al*. 2002). Finally, several reports indicated that women did not want others to notice them taking pills, as this would reveal their seropositive status to others (Roberts & Mann 2000;Erlen *et al*. 2002;Garcia-Teague 2002;Sankar *et al*. 2002;Durante *et al*. 2003;Jones *et al*. 2003;Powell-Cope *et al*. 2003;Phillips *et al*. 2005).

Although the negative effects of drug regimens are more prominent in the study results than the positive effects, they are also less relevant to current practice. For example, the problem of medication side-effects has been greatly reduced by the newer regimens. Moreover, better understanding of the side-effects of these newer regimens has led to improved supportive or pharmacologic assistance to offset them. Because more drug options exist, clinicians can avoid drugs that tend to cause severe side-effects. Contemporary regimens are much simpler, typically involve a smaller pill burden (i.e. number, size and taste), once- to twice-a-day dosing, and often have no dietary requirements or restrictions, thereby making them easier to adhere to as prescribed. They also make it easier to maintain privacy.

One way of dealing with these rapid changes in treatment regimens is to use time as a variable to be studied. The history of treatment was actually the independent variable in Schrimshaw *et al*.'s (2005) study, one of the 42 studies we reviewed. Indeed, this study serves as a model for using history as one way to group studies in systematic reviews for analysis and interpretation. Explicitly addressing antiretrovi-ral adherence in women in the pre-HAART and HAART eras, they found that in comparison with women in the HAART era, women in the pre-HAART era were more likely to report that they were not currently taking any antiretroviral medication; were more likely to be on single drug monotherapies, as opposed to dual therapies; held more negative views of toxicity of therapy as a whole; were more likely to base their views on others' experiences; were less likely to report benefits of therapy; were more likely to hold strongly negative attitudes about the side-effects of therapy; and were more likely to discontinue therapy as a way to manage side-effects. In comparison with women in the pre-HAART era, women in the HAART era were more likely to be on triple drug combination therapy, as opposed to dual drug therapy; held more balanced views of costs and benefits of therapy; were less generally negative about therapy as a whole; held more negative

views of specific drugs as opposed to all drugs; were less likely to be concerned about the safety of medications; were more likely to be concerned about the daily hassles of taking the medications; were more likely to see and report benefits of therapy; were more likely to be optimistic about therapy; and were more likely to tolerate or try to manage side-effects (as opposed to discontinuing therapy), or expect to be switched to another drug.

Following this model, the studies we reviewed can be grouped for analysis encompassing pre-HAART (<1996), complex HAART (1996–2005) and simpler HAART (>2005) regimens. This would permit analysis of how and what studies in each group contributed to the findings.

History of research on target disease or treatment

In addition to changes that must be accounted for in systematic reviews in the evolution of a target disease and its treatment are changes in the research addressing them. Thorne *et al*. (2002) emphasized the importance of assessing larger trends and patterns in the way clinical problems are studied, including such key factors as changes in theoretical frameworks and methodological fashions and fads. In the case of the antiretroviral adherence reports in our study, key considerations included mapping the different ways that adherence and non-adherence were conceptually and operationally defined and measured, and then linked to drug regimens. We discerned from this work that at least 30 different definitions of adherence were used. Over the years, antiretroviral adherance studies have shown varying alleglances to self-report, pill counts, MEMS caps, direct observation and review of pharmaceutical records as ways to capture adherance practices. In the studies we reviewed, adherance was measured using standardized tools in 14 of the reports, author-developed questionnaires in 9 of the reports, pill counts in four reports, pharmacy records in three reports, and MEMS (Medication Event Monitoring System) caps, in two reports (some reports used multiple measures). Especially relevant to time is that embedded in these definitions and measures are temporal definitions of adherence. For example, adherence was variously operationalized as having taken drugs as prescribed over the last day, 2 days, 3 days, 4 days, 6 days (out of a week), 1 week, 2 weeks, 1 month, 3 months, 6 months, or all the time; some of the studies did not specify what time period they were measuring.

Yet another time-related trend is that virtually all of the studies we reviewed were cross-sectional, as opposed to longitudinal, in design, thereby perpetuating the view of adherence as a yes/no, static outcome, as opposed to a dynamic process that changes over time. Of the 42 reports, only four offered results at two or more time points. In addition, the reports of studies are characterized by a lack of information on treatment experience (i.e. whether participants were treatment-naïve or treatment-experienced) and on where in the disease and treatment life cycle participants were at the time of data collection. Of the 42 reports, only five offered information on treatment experience, which would be critical to frame the participants' encounters with antiretroviral medications, especially now that treatment changes are generally made with resistance testing after the first failed regimen. Twenty-eight studies offered information on participants' HIV disease severity, but offered no other information to link disease severity and treatment experience.

Already well documented in the systematic review literature is the role methodological differences play in multiplying the heterogeneity of studies in common domains of research (Glasziou & Sanders 2002; Deeks *et al*. 2005). In the adherence studies we reviewed, the temporal dimensions embedded in the very design of studies and in the conceptualization and operationalization of the key dependent variable constitute a source of heterogeneity that have to be accounted for in determining what findings are comparable enough to be combined.

Discussion

Time is a key element that must be managed throughout the trajectory of the systematic review process to ensure clinically relevant research syntheses. Time considerations enter into the: (i) formulation of research problem and question; (ii) setting of parameters for search and retrieval of studies; (iii) determination of inclusion and exclusion criteria; (iv) appraisal of the clinical relevance of findings; (v) selection of the findings that will be synthesized; and (vi) interpretation of the results of that synthesis.

In addition to documenting the temporal boundaries for inclusion and when reports were retrieved, reviewers should draw from their knowledge of the diagnosis or treatment under review to interpret the significance of these temporal parameters. Reviewers must address how they will treat reports where the dates of data collection are unavailable. They must also differentiate between reports that are temporally irrelevant and therefore are candidates for exclusion, and reports in which only certain findings are temporally irrelevant but others remain relevant and therefore remain candidates for inclusion. We are in the process of answering these questions as we begin selecting results for synthesis.

Authors of primary reports should always include the period of data collection and the timing of data collection vis-à-vis the target events featured in the study (e.g. interviews were conducted within 2 months of diagnosis). And publishers of systematic reviews should attempt to reduce the time between submission of a completed review and its publication to preserve its timeliness. With rapid advances in health care and proliferation of studies in which these advances play a central role, systematic reviews become out-of-date virtually as soon as they are completed.

In conclusion, time is a key factor in the systematic review process, an important covariate in assessing the heterogeneity of studies, and a major determinant of the clinical relevance of systematic reviews. Indeed, the viability of systematic reviews as a foundation for evidence-based practice rests on adequate considerations of time.

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Table 1

Temporal profile of reports (n = 42)

Year(s) data collected	References	Department of Health and Human Services Guidelines
Do not know	Misener & Sowell 1998	
Do not know	Fourney 1999	
Do not know	Richter *et al*. 2002	
Do not know	Douglass *et al*. 2003	
Do not know	Feigel 2003	
Do not know	Phillips *et al*. 2005	
1993–1995	Mostashari *et al*. 1998	No guidelines in place
1993–1996	Laine *et al*. 2000	No guidelines in place
1993–1996	Patania 2003	No guidelines in place
1993–1997	Turner *et al*. 2000	1993–1996: No guidelines 1997: Dual NRTI backbone + 1 PI
1993–2000	Stone *et al*. 2001	1993–1996: No guidelines 1997: Dual NRTI backbone + 1 PI 1998: Dual NRTI backbone + 1 or 2 PIs (EFZ added in Dec. 1998) 1999: Dual NRTI backbone (6 combos) + 1 or 2 PIs, or EFZ 2000: Dual NRTI backbone (4 combos) + 1 or 2 PIs, or EFZ
1994–1995	Siegel & Gorey 1997	No guidelines in place
1994–1996; 2000–2003	Schrimshaw *et al*. 2005	1994–1996: No guidelines in place 2000: Dual NRTI backbone (4 combos) + 1 or 2 PIs, or EFZ 2001–2002: EFZ, PI, or boosted PI + dual NRTI backbone 2003: EFZ + 3TC + (AZT or TDF or d4T) OR LPV/r + 3TC + (AZT or d4T)
1996–1997	Schuman *et al*. 2001	1996: No guidelines 1997: Dual NRTI backbone + 1 PI
1996–1997	Siegel *et al*. 2001	1996: No guidelines 1997: Dual NRTI backbone + 1 PI
1997	Mann 2001	Dual NRTI backbone + 1 PI
1997	Roberts & Mann 2000	Dual NRTI backbone + 1 PI
1997	Roberts & Mann 2003	Dual NRTI backbone + 1 PI
1997–1998	Ickovics *et al*. 2002	1997: Dual NRTI backbone + 1 PI 1998: Dual NRTI backbone + 1 or 2 PIs (EFZ added in Dec. 1998)
1997–1999	Jones *et al*. 2003	1997: Dual NRTI backbone + 1 PI 1998: Dual NRTI backbone + 1 or 2 PIs (EFZ added in Dec. 1998) 1999: Dual NRTI backbone + 1 or 2 PIs, or EFZ
1997–2000	Sharpe *et al*. 2004	1997: Dual NRTI backbone + 1 PI 1998: Dual NRTI backbone + 1 or 2 PIs (EFZ added in Dec. 1998) 1999: Dual NRTI backbone (6 combos) + 1 or 2 PIs, or EFZ 2000: Dual NRTI backbone (4 combos) + 1 or 2 PIs, or EFZ
1998	Durante *et al*. 2003	Dual NRTI backbone + 1 or 2 PIs (EFZ added in Dec. 1998)
1998	Erlen *et al*. 2002	Dual NRTI backbone + 1 or 2 PIs (EFZ added in Dec. 1998)
1998–1999	Mellins *et al*. 2002	1998: Dual NRTI backbone + 1 or 2 PIs (EFZ added in Dec. 1998) 1999: Dual NRTI backbone + 1 or 2 PIs, or EFZ
1998–1999	Mellins *et al*. 2003	1998: Dual NRTI backbone + 1 or 2 PIs (EFZ added in Dec. 1998) 1999: Dual NRTI backbone + 1 or 2 PIs, or EFZ
1998–1999	Sowell *et al*. 2001a	1998: Dual NRTI backbone + 1 or 2 PIs (EFZ added in Dec. 1998) 1999: Dual NRTI backbone + 1 or 2 PIs, or EFZ
1998–1999	Sowell *et al*. 1999	1998: Dual NRTI backbone + 1 or 2 PIs (EFZ added in Dec. 1998) 1999: Dual NRTI backbone + 1 or 2 PIs, or EFZ
1998–1999	Sowell *et al*. 2001b	1998: Dual NRTI backbone + 1 or 2 PIs (EFZ added in Dec. 1998) 1999: Dual NRTI backbone + 1 or 2 PIs, or EFZ
1998–1999	Wilson *et al*. 2002	1998: Dual NRTI backbone + 1 or 2 PIs (EFZ added in Dec. 1998) 1999: Dual NRTI backbone + 1 or 2 PIs, or EFZ
1998–1999	Wilson *et al*. 2001	1998: Dual NRTI backbone + 1 or 2 PIs (EFZ added in Dec. 1998) 1999: Dual NRTI backbone + 1 or 2 PIs, or EFZ
1999	Howard *et al*. 2002	Dual NRTI backbone + 1 or 2 PIs, or EFZ
1999	Nguyen 2000	Dual NRTI backbone + 1 or 2 PIs, or EFZ
1999–2000	Kalichman *et al*. 2001	1999: Dual NRTI backbone (6 combos) + 1 or 2 PIs, or EFZ 2000: Dual NRTI backbone (4 combos) + 1 or 2 PIs, or EFZ
1999–2000	Murphy *et al*. 2002	1999: Dual NRTI backbone (6 combos) + 1 or 2 PIs, or EFZ 2000: Dual NRTI backbone (4 combos) + 1 or 2 PIs, or EFZ
1999–2000	Sankar *et al*. 2002	1999: Dual NRTI backbone (6 combos) + 1 or 2 PIs, or EFZ 2000: Dual NRTI backbone (4 combos) + 1 or 2 PIs, or EFZ
1999–2002	Hirokawa 2003	1999: Dual NRTI backbone (6 combos) + 1 or 2 PIs, or EFZ 2000: Dual NRTI backbone (4 combos) + 1 or 2 PIs, or EFZ 2001–2002: EFZ, PI, or boosted PI + dual NRTI backbone
2000	Powell-Cope *et al*. 2003	Dual NRTI backbone + 1 or 2 PIs, or EFZ
2000–2001	Abel & Painter 2003	2000: Dual NRTI backbone + 1 or 2 PIs, or EFZ 2001: EFZ, PI, or boosted PI + 2 NRTIs
2000–2001	Garcia-Teague 2002	2000: Dual NRTI backbone + 1 or 2 PIs, or EFZ 2001: EFZ, PI, or boosted PI + 2 NRTIs
2001	Gant & Welch 2004	EFZ, PI, or boosted PI + 2 NRTIs
2001	Wood *et al*. 2004	EFZ, PI, or boosted PI + dual NRTI backbone
2001–2003	Wyatt *et al*. 2004	2001–2002: EFZ, PI, or boosted PI + dual NRTI backbone

Year(s) data collected	References	Department of Health and Human Services Guidelines
		2003: EFZ + 3TC + (AZT or TDF or d4T) OR LPV/r + 3TC + (AZT or d4T)

AZT, zidovudine; d4T, stavudine; EFZ, efavirz; LPV, lopinavir; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; r, ritonavir; 3TC, lamivudine; TDF, tenofovir.