Adherence to HAART: A Systematic Review of Developed and Developing Nation Patient-Reported Barriers and Facilitators

Edward J. Mills[1*], Jean B. Nachega[1,2], David R. Bangsberg[3], Sonal Singh[1,2], Beth Rachlis[4], Ping Wu[5], Kumanan Wilson[1,6], Iain Buchan[7], Christopher J. Gill[8], Curtis Cooper[1,9]

1 Centre for International Health and Human Rights Studies, Toronto, Ontario, Canada, **2** Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America, **3** San Francisco General Hospital, AIDS Division, University of California San Francisco, San Francisco, California, United States of America, **4** BC Centre for Excellence in HIV/AIDS, University of British Columbia, Vancouver, British Columbia, Canada, **5** Canadian College of Naturopathic Medicine, North York, Ontario, Canada, **6** Department of Medicine, University of Toronto, Toronto, Ontario, Canada, **7** Evidence for Population Health Unit, University of Manchester, Manchester, United Kingdom, **8** Center for International Health and Development, Boston University School of Public Health, Boston, Massachusetts, United States of America, **9** Division of Infectious Diseases, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada

Funding: This work was supported by the Ontario HIV Treatment Network (OHTN). EJM is supported by the Canadian Institutes for Health Research. JBN is supported by grants AI005535901 and K23A106858201 from the US National Institutes of Health. BR is supported by the British Columbia Michael Smith Foundation. KW is supported by Canadian Institutes for Health Research. DRB is supported by the NIH (AA015287, MH54907, AI27763), and The Doris Duke Charitable Foundation. CC is supported by the Ontario HIV Treatment Network.

Competing Interests: The authors have declared that no competing interests exist.

Academic Editor: Amir Attaran, University of Ottawa, Ottawa, Ontario, Canada

Citation: Mills EJ, Nachega JB, Bangsberg DR, Singh S, Rachlis B, et al. (2006) Adherence to HAART: A systematic review of developed and developing nation patient-reported barriers and facilitators. PLoS Med 3(11): e438. doi:10.1371/journal.pmed.0030438

Received: December 8, 2005
Accepted: September 4, 2006
Published: November 21, 2006

Copyright: © 2006 Mills et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abbreviations: HAART, highly active antiretroviral therapy

* To whom correspondence should be addressed. E-mail: millsej@univmail.cis.mcmaster.ca

ABSTRACT

Background

Adherence to highly active antiretroviral therapy (HAART) medication is the greatest patient-enabled predictor of treatment success and mortality for those who have access to drugs. We systematically reviewed the literature to determine patient-reported barriers and facilitators to adhering to antiretroviral therapy.

Methods and Findings

We examined both developed and developing nations. We searched the following databases: AMED (inception to June 2005), Campbell Collaboration (inception to June 2005), CinAhl (inception to June 2005), Cochrane Library (inception to June 2005), Embase (inception to June 2005), ERIC (inception to June 2005), MedLine (inception to June 2005), and NHS EED (inception to June 2005). We retrieved studies conducted in both developed and developing nation settings that examined barriers and facilitators addressing adherence. Both qualitative and quantitative studies were included. We independently, in duplicate, extracted data reported in qualitative studies addressing adherence. We then examined all quantitative studies addressing barriers and facilitators noted from the qualitative studies. In order to place the findings of the qualitative studies in a generalizable context, we meta-analyzed the surveys to determine a best estimate of the overall prevalence of issues. We included 37 qualitative studies and 47 studies using a quantitative methodology (surveys). Seventy-two studies (35 qualitative) were conducted in developed nations, while the remaining 12 (two qualitative) were conducted in developing nations. Important barriers reported in both economic settings included fear of disclosure, concomitant substance abuse, forgetfulness, suspicions of treatment, regimens that are too complicated, number of pills required, decreased quality of life, work and family responsibilities, falling asleep, and access to medication. Important facilitators reported by patients in developed nation settings included having a sense of self-worth, seeing positive effects of antiretrovirals, accepting their seropositivity, understanding the need for strict adherence, making use of reminder tools, and having a simple regimen. Among 37 separate meta-analyses examining the generalizability of these findings, we found large heterogeneity.

Conclusions

We found that important barriers to adherence are consistent across multiple settings and countries. Research is urgently needed to determine patient-important factors for adherence in developing world settings. Clinicians should use this information to engage in open discussion with patients to promote adherence and identify barriers and facilitators within their own populations.

The Editors' Summary of this article follows the references.

Introduction

The introduction of antiretrovirals has been credited with extending the life span of people living with HIV/AIDS [1]. However, treatment efficacy relies on access to treatment and excellent adherence, which has proven to be a serious challenge to those receiving highly active antiretroviral therapy (HAART) [2,3]. The regimens are often complicated, can require dietary restrictions, and may lead to adverse effects [4]. Non-adherence to antiretroviral therapy in adult populations has been shown to range from 33%–88%, depending on how adherence is defined and evaluated [5]. Research indicates that consistently high levels of adherence are necessary for reliable viral suppression [6,7] and prevention of resistance [8], disease progression [9], and death [10]. As successful HIV treatment requires exceptional adherence to antiretroviral therapy, interventions to improve and maintain adherence are needed.

Several studies have been conducted that examine factors affecting adherence to HAART. We used a novel methodology to synthesize the information from these studies by performing a systematic review on all the literature available in this field using content analysis, particularly focusing on the currently existing qualitative studies and examining their generalizability through quantitative data. We examined both developed and developing nation patient populations [11].

Methods

Search Strategy

We performed a systematic, all-language literature search for all qualitative studies and quantitative surveys that addressed barriers and motivators influencing adherence to antiretroviral regimens in HIV-positive individuals.

We (EJM and BR) searched the following databases: AMED (inception to June 2005), Campbell Collaboration (inception to June 2005), CinAhl (inception to June 2005), Cochrane Library (inception to June 2005), Embase (inception to June 2005), ERIC (inception to June 2005), MedLine (inception to June 2005), and NHS EED (inception to June 2005). Unpublished studies were also sought using the search terms "adherence" and "HIV" on Clinicaltrials.gov, the UK National Research Register, and conference abstracts from international conference Web sites: International AIDS Society conferences (inception to 2005) and Conferences on Retroviruses and Opportunitistic Infections (inception to 2005). Our search strategy combined terms that represented attitudes, barriers, and anxieties. Our search vocabulary included "HIV" or "AIDS", "compliance OR adherence", "factors OR determinant* OR barriers", "motivate* OR facilit*", and "HAART OR antiretroviral*". The detailed search strategy is available from the corresponding author upon request. We supplemented this search by reviewing the bibliographies of key papers.

Study Selection

Two members of the study team (BR and PW) independently reviewed the abstracts. Eligible studies met the following criteria: (1) reported an original research study, (2) contained content addressing barriers or facilitators to antiretroviral adherence, and (3) were either a qualitative study or quantitative survey. The studies were divided to represent developed or developing nations, as according to the United Nations Human Development Index (HDI) [12]. The HDI is a composite index that measures a country's average achievements in three basic aspects of human development: longevity, knowledge, and a decent standard of living.

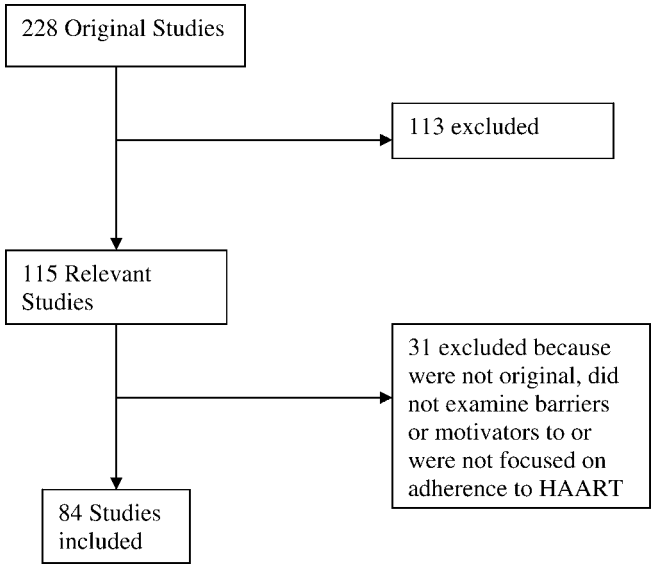

Figure 1. Flow Chart of Studies Included in Review
doi: 10.1371/journal.pmed.0030438.g001

Data Extraction

Two reviewers (BR and PW) independently extracted data and appraised both quality and content. From an initial review of qualitative studies by BR and PW, a coding template was iteratively developed to categorize key barriers to adherence to HAART. The reviewers then conducted a second review of the papers and identified whether they contained the barriers present in the complete template. At each stage of the data abstraction, the reviewers discussed the studies to determine consensus regarding the identification and coding of themes. We analyzed the themes presented in the qualitative studies. After the initial viewing of the selected articles, these themes were grouped into categories. Barriers/facilitators fell under the following subheadings: (1) patient-related, (2) beliefs about medication, (3) daily schedules, and (4) interpersonal factors/relationships. To determine the extent to which these themes exist in the wider communities of developed and developing nations, the reviewers then abstracted data from the survey studies to determine if the issues addressed in the qualitative studies had been asked about in the surveys. We abstracted data on the prevalence of the issues as reported in the surveys.

We extracted data on the quality of both qualitative and quantitative studies using pre-determined criteria for quality. We previously reported our rationale for assessing the quality of qualitative studies and in this study have extended our quality assessment to examine quantitative surveys [13]. Although no formal criteria exist for appraising the quality of surveys, we a priori determined that the following criteria are important across surveys: 1) the survey included members of the target community in the preparation of the survey tool, 2) the survey instrument was assessed for face validity, 3) the

Table 1. Study Characteristics

Reference	Country	Population	Focus of Study	Setting	Notes
Abel, 2003 [18]	US	$n = 6$; 100% women; (2 African-American, 1 Hispanic, 3 white)	Factors that influence adherence to ART were explored from perspective of women	Clinic	
Adamian, 2004 [30]	US	$n = 20$; 14 men/6 women (18 African-American, 1 white, 1 multiracial)	Pilot study to assess patients' perceptions of and attitudes toward the motivational interviewing session	Clinic	Study also tested and assessed motivational interviewing model
Adam, 2003 [45]	Canada	$n = 35$; 31 men/ 4 women (no ethnicity info given)	Paper examines difficulties with ART adherence particularly related to dosing schedules and food prohibitions with the structure of everyday lives	Clinic	
Aversa, 1996 [46]	US	$n = 99$; 74 men/24 women (71% white: 25% African-American: 4% Hispanic)	Study examines variables related to alteration of ART regimens, independent of medical advice	Via telephone	
Barton Laws, 2000 [31]	US	$n = 25$ (sub-sample from group of 61); 17 men/8 women (9 Euro-American, 3 African-American, 12 Latino/Latina, 1 Portuguese)	Describe patients' medication-taking behaviour and factors related to non-adherence.	Homes, hospitals, residential substance abuse treatment programs, and/or offices	
Brigido, 2001 [47]	Brazil	$n = 182$; 126 men/56 women	To assess if adherence to antiretroviral medication would correlate to clinical and laboratory outcomes	Clinic	
Golin, 2002 [19]	US	$n = 24$; 16 men/8 women (12 African-American: 12 white)	To understand barriers to ART adherence faced by patients living with HIV in the southeastern US	Clinic	
Goode, 2003 [48]	Australia	$n = 18$ (11 boys/7 girls) (no ethnicity info given)	To examine beliefs about pediatric HAART from the caregivers' perspective in addition to examining these beliefs in relation to the day-to-day lives of children and their families	Telephone interview	Ten families were urban, and eight were rural; rural families had more difficulty integrating morning dose; in addition, there was a lower level of support compared with urban families
Graney, 2003 [32]	US	$n = 67$; 44 men/13 women (82% African-American)	Study seeks to document relationships between HIV/AIDS medication regimen adherence and characteristics of the regimen itself, social factors, psychological factors, and health-care practitioner factors	Inner-city clinic	
Hammami, 2004 [44]	Belgium	$n = 11$; caregivers; 8 mother; 1 adoptive parent; 2 self-care; age 0.25–18.75 y	To understand adherence behaviour in a pediatric population, as reported by caregivers	Medical center	
Hills, 2003 [33]	US	$n = 78$ (no demographic/ethnicity given specific to study; only general clinic population)	Explore patterns and explanations of adherence to antiretroviral therapies from the patients' perspective	Clinic	
Johnston-Roberts, 2003 [108]	US	$n = 20$; 100% women (50% Hispanic, 35% African-American, 15% white)	Explore, using HIV-positive women's own recollections collected in diary format, how and why women intentionally fail to adhere to ART	Journal entry	Followed one entry (a 42–y-old Hispanic woman)
Johnston-Roberts, 2002 [34]	US	$n = 28$; 15 men/13 women (46% white, 36% African-American, 14% Hispanic, 4% other)	Explore the connections between HIV-positive patients' adherence to antiretroviral medication regimens and their beliefs about and satisfaction with their primary care physicians	Clinic	
Johnston-Roberts, 2000 [54]	US	$n = 38$; 100% women (50% Hispanic, 35% African-American, 15% white)	Explore, from HIV-positive women's own perspectives, the barriers they faced in adhering to combination antiretroviral therapies	Journal entries	

Table 1. Continued.

Reference	Country	Population	Focus of Study	Setting	Notes
Ka'opua, 2004 [53]	US	$n = 80$; 57 men/23 women (40 Native Hawaiian, 40 white)	To understand HAART adherence among Native Hawaiians, a group with historic difficulty in using Western health-care services because of cultural conflict	AIDS center	Native Hawaiians significantly more likely than white participants to view family support as a critical strategy for adherence
Kemppainen, 2004 [49]	US	$n = 46$; 38 men/8 women (12 African-American, 24 white, 5 Hispanic, and 5 mixed)	To identify factors and circumstances that influence the ability of persons with HIV/AIDS and severe mental illness to comply with ART regimens	Day care program to treat HIV and severe mental illness	Non-white persons and those living alone were more likely to rely on the use of reminders and cues
Klitzman, 2004 [35]	US	$n = 152$; 96 men/56 women (47 white, 40 Latino/Latina, 60 African-American, 5 other)	To understand whether and how HAART affects views and patterns of disclosure and how disclosure interacts with treatment decisions	Clinic	
Malcolm, 2003 [36]	US	$n = 44$; 28 men/16 women (17 "people of color"/ 27 white)	Examine the health-related attitudes and beliefs of HIV/AIDS patients with excellent adherence to HAART and how they differ from those of patients with suboptimal adherence	Clinic	
Meystre-Agustoni, 2000 [37]	Switzerland	$n = 37$; 25 men/12 women (no ethnicity information given)	Explore patients' perceptions of HAART	Clinic	
Miller, 2002 [20]	US	$n = 30$; 23 men/7 women (21 Latino, 7 African-American, 2 white)	Assessed barriers to adherence to antiretroviral regimens by conducting focus groups and asking patients about their preferences for different aspects of antiretroviral regimens	Clinic	
Misener, 1998 [21]	US	$n = 22$; 100% women (18 African-American, 4 white)	To describe the influences affecting decisions made by women in the southern US to accept and adhere to antiretroviral therapy	Social service agency	
Murphy, 2003 [23]	US	$n = 81$; 45 men/36 women (22% Central American, 61% Mexican, 6% Mexican-American or Chicano, 1% South American, 4% mixed, and 5% other)	Three aims: (1) to determine what barriers impede adherence, (2) what strategies facilitate adherence, and (3) investigate the health-care provider–patient relationship and how it may affect adherence	Clinic	Language barriers reported; use of translators not always seen as a sufficient remedy
Murphy, 2000 [22]	US	$n = 39$; 27 men/12 women (3% Asian/Pacific Islander, 44% African-American, 6% Latino, 3% Native American, 39% white, 6% other or mixed)	Determine what strategies facilitate adherence, determine what barriers prevent adherence, and investigate the health-care provider–patient relationship and how it may affect adherence	Clinic	
Oggins, 2003 [38]	US	$n = 62$; 40 men/22 women (21 African-American, 7 Asian, 2 Haitian, 12 Latino/Latina, 9 European American, 11 Native American)	To explore the reasons for low adherence to HIV-medication regimens among ethnic minority groups	Private homes, health agencies, or via telephone	Study indicates that non-adherence may be associated with important misconceptions about HIV, confusion about relationship between HIV and AIDS etc.
Powell-Cope, 2003 [24]	US	$n = 24$; 100% women (22 African-American, 2 white)	To obtain complementary data on the complex set of beliefs, attitudes, and behaviours that are related to adherence in indigent, substance-abusing women.	Clinic	Apart from qualitative focus groups, quantitative surveys were also used
Proctor, 1999 [25]	US	$n = 39$; 27 men/12 women (19 white, 16 African-American, 4 Hispanic)	To understand the barriers to adherence to HAART faced by people living with HIV/AIDS	University medical centers and clinics	Secondary objective of study was to develop a survey questionnaire based on data collected

Table 1. Continued.

Reference	Country	Population	Focus of Study	Setting	Notes
Reback, 2003 [39]	US	$n = 23$; 100% men (87% white, 19% Latino, 4% Native American)	To understand the meaning of reported HIV medication adherence among gay and bisexual men who are dependent on or abuse methamphetamine	Treatment center	
Remien, 2003 [50]	US	$n = 110$; 70 men/40 women (33% white, 31% Hispanic, 43% African-American, 2% other)	To present qualitative data relating to adherence to antiretroviral therapy for HIV disease from a diverse sample in four US cities	Clinics and community-based service organizations	
Richter, 2002 [26]	US	$n = 33$; 100% women, 100% African-American	To examine attitudes and beliefs of African-American women of child-bearing age living with HIV, about pregnancy and antiretroviral therapy	Community-based organizations	
Ryan, 2003 [40]	US	$n = 27$; 21 men/6 women (64% African-American)	Exploratory study examines the contextual factors that lead to episodic non-adherence to HAART	Not specified	Population consisted of past and current drug users
Sankar, 2002 [51]	US	$n = 15$; 100% women (100% African-American)	To identify sources of authority that either promote or discourage adherence; also, to explore how women resolve conflicts between conflicting sources of influence	Clinic	
Schilder, 2001 [27]	Canada	$n = 47$; 27 gay men, 10 bisexual men, 10 transgendered men (16 First Nations, 31 white, 1 Asian, 1 Latino, 1 French Canadian, 1 Jewish)	To characterize the relationship between identity and health-care experiences (including ART utilization) among HIV-positive sexual minority males	Community agencies and hospitals	
Stone, 1998 [28]	US	$n = 56$; 28 men/28 women (16 African-American, 12 Latino/Latina, 28 white)	To gather qualitative data regarding HIV/AIDS patients' perspectives about HIV-1 protease inhibitors and about their experiences taking and adhering to regimens containing PIs	Health centers and hospital clinics	
Weiser, 2003 [52]	Botswana	$n = 109$; 54 men/55 women (no ethnicity information given)	To improve antiretroviral therapy treatment delivery, social, cultural, and structural determinants of treatment adherence were studied	Clinics	
Westerfelt, 2004 [29]	US	$n = 21$; 100% men, 100% white	To explore adherence issues among HIV-positive individuals to provide information to design interventions to help individuals achieve higher rates of adherence to ART	Immunology center	Population reflects state epidemic
Wilson, 2002 [41]	US	$n = 66$; 90% men/10% women (50% white, 27.3% African-American, 10.6% Hispanic, 4.5% Native American, 1.5% Filipino, 4.5% other)	To explain how ethnically diverse men and women infected with HIV manage their interacting symptom clusters and medication side effects as well as their treatment adherence choices	Clinic	
Witteveen, 2002 [42]	The Netherlands	$n = 27$; 16 men/11 women (ethnicity not given)	To provide better insights to the extent of adherence to HAART in "hard drug" users	Clinic	
Wood, 2004 [43]	US	$n = 36$; 100% women (19 Latina, 10 Euro-American, 5 African-American, 2 Cape Verdean)	The study seeks to better understand the patterns, barriers, and facilitators to medication adherence in women caring for children	Health agency	

doi:10.1371/journal.pmed.0030438.t001

Table 2. Reporting Criteria of Qualitative Studies

Reference	Were Data Described Verbatim?	If Interview Was Conducted, Were the Questions Pre-Defined?	If Focus Group Used, Was the Facilitator Trained?	Was Saturation Mentioned?	Was There a Description of How Themes Were Identified?	Were Participants' Answers Reviewed for Clarification?	Were Sequences from the Original Data Presented?	Were the Findings Analyzed by More than One Assessor?
Abel, 2003 [18]	✓			✓	✓	✓	✓	✓
Adamian, 2004 [30]	✓	✓			✓		✓	
Adam, 2003 [45]	✓	✓		✓	✓	✓	✓	
Aversa, 1996 [46]	✓	✓			✓		✓	✓
Barton Laws, 2000 [31]	✓	✓			✓		✓	✓
Brigido, 2001 [47]		✓						✓
Golin, 2002 [19]	✓		✓	✓	✓		✓	✓
Goode, 2003 [48]	✓	✓			✓		✓	
Graney, 2003 [32]		✓			✓			
Hammami, 2004 [44]		✓		✓	✓		✓	✓
Hill, 2003 [33]		✓		✓	✓		✓	✓
Johnston-Roberts, 2003 [108]					✓		✓	✓
Johnston-Roberts, 2002 [34]	✓	✓			✓		✓	✓
Johnston-Roberts, 2000 [54]			✓	✓	✓		✓	
Ka'opua, 2004 [53]	✓				✓		✓	✓
Kemppainen, 2004 [49]	✓				✓		✓	✓
Klitzman, 2004 [35]	✓	✓		✓	✓		✓	✓
Malcolm, 2003 [36]	✓	✓		✓	✓		✓	✓
Meystre-Agustoni, 2000[[37				✓	✓		✓	
Miller, 2002 [20]	✓		✓		✓			
Misener, 1998 [21]	✓		✓	✓	✓		✓	✓
Murphy, 2003 [23]	✓	✓	✓		✓		✓	
Murphy, 2000 [22]	✓	✓	✓		✓		✓	
Oggins, 2003 [38]	✓	✓				✓	✓	✓
Powell-Cope, 2003 [24]		✓	✓		✓			✓
Proctor, 1999 [25]	✓	✓	✓	✓	✓		✓	✓
Reback, 2003 [39]	✓	✓			✓		✓	
Remien, 2003 [50]	✓	✓		✓	✓		✓	✓
Richter, 2002 [26]	✓	✓	✓	✓	✓		✓	✓
Ryan, 2003 [40]	✓	✓		✓	✓		✓	✓
Sankar, 2002 [51]	✓	✓		✓	✓		✓	✓
Schilder, 2001 [27]	✓	✓			✓		✓	✓
Stone, 1998 [28]	✓		✓	✓	✓		✓	✓
Weiser, 2003 [52]		✓						✓
Westerfelt, 2004 [29]			✓		✓		✓	✓
Wilson, 2002 [41]	✓	✓			✓		✓	
Witteveen, 2002 [42]	✓	✓						✓
Wood, 2004 [43]	✓	✓		✓			✓	

✓ indicates that the methodological item was reported in the original text.

doi:10.1371/journal.pmed.0030438.t002

Table 3. Quality Criteria for Survey Studies

Countries	Reference	Population Involvement in Survey Development	Face Validity	Random Sampling	Response Rate Calculations	Attempt to Contact Non-Responders
Developed countries	Ammassari, 2001[[56]		✓			
	Brook, 2001[[55]			✓		
	Catz, 2000 [58]	✓				
	Chesney, 2000 [59]	✓	✓			
	Eldred, 1998[[61]	✓	✓		✓	
	Erlen, 2002 [62]					
	Ferguson, 2002 [4]		✓			
	Gibb, 2003 [65]				✓	
	Giacomet, 2003 [64]					
	Harzke, 2004 [66]		✓			
	Heckman, 2004 [67]		✓		✓	
	Horne, 2004 [69]		✓		✓	
	Johnson, 2003 [70]		✓		✓	
	Kalichman, 1999 [71]		✓			
	Kerr, 1999 [72]	✓	✓			
	Kleeberger, 2001 [73]	✓	✓			
	Marhefka, 2004 [74]		✓		✓	
	Moatti, 2000 [75]				✓	
	Mohammed, 2004 [76]		✓		✓	
	Mostashari, 1998 [79]				✓	
	Muma, 1995[80]		✓		✓	
	Murphy, 2003[81]		✓		✓	
	Nieuwkerk, 2001[83]				✓	
	Palmer, 2003 [84]		✓		✓	
	Reddington, 2000 [86]				✓	
	Reynolds, 2004 [87]		✓		✓	
	Savini, 2003 [88]		✓			
	Schneider, 2004[89]		✓		✓	
	Siegel, 2000[90]		✓			
	Simoni, 2002[91]		✓	✓		
	Spire, 2002[92]		✓		✓	
	Stein, 2000[93]				✓	
	Tucker, 2004[95]		✓	✓		
	Wagner, 2004[97]		✓		✓	
	Walsh, 2001[98]		✓		✓	
	Weidle, 1999[99]				✓	
	Wilson, 2001[100]	✓	✓		✓	
Developing countries	Byakika-Tusiime J, 2005[57]		✓		✓	
	Cupsa, 2000[60]				✓	
	Fassinou, 2004[63]				✓	
	Hofer, 2004[68]				✓	
	Molassiotis, 2002[77]		✓		✓	
	Monreal, 2002[78]				✓	
	Nachega, 2004[82]		✓	✓	✓	
	Pinheiro, 2002[85]		✓		✓	
	Stout, 2004[94]					✓
	van Oosterhout, 2005[96]				✓	

✓ indicates that the methodological item was reported in the original text.

doi:10.1371/journal.pmed.0030438.t003

survey population was randomly selected, 4) a rationale for determining the response rate was provided, and 4) the investigators attempted to contact non-responders. We did not propose a cut-off score for higher-quality surveys versus lower-quality surveys.

Statistical Analysis

We measured chance-adjusted inter-rater agreement for eligibility using the κ statistic. EM and PW conducted all statistical analyses. When information on proportions was available in the quantitative studies, we first stabilized the variances of the raw proportions (r/n) using a Freeman-Tukey-type arcsine square-root transformation [14], and then conducted weighted analysis of studies using methods described by Fleiss [15]. The pooled proportion is calculated as the back-transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed-effects model and DerSimonian-Laird weights for the random-effects model. The random-effects model recognizes that the studies are a sample of all potential studies and incorporates an additional between-study component to the estimate of variability [16]. Thus, larger studies with smaller variances have relatively more impact on the final estimate. We present the weighted mean with 95% confidence intervals, with lower confidence intervals truncated at zero. The I^2 statistic was calculated as a measure of

Table 4. Barriers to Adherence Identified in Qualitative Studies (Developed Countries)

Qualitative Studies	Patient Variables												
	Fear of Disclosure	Feeling Low/ Depressed/ Hopeless/ Angry/ Stressed	Concurrent Substance Abuse	Simply Forgot	Suspicions of Medicine/ Medical Establishment	Want to Be Free of Meds/ Feel Normal/ Holistic Approach	Want to Maintain Control	Treatment is Reminder of HIV Status	Don't Understand Treatment/ Misinformed	Doubt HIV Status/ Haven't Accepted It	Financial Constraints	No Self Worth/ Doubt Ability to Adhere	Homeless/ Other Concurrent Illness
Abel, 2003[18]								✓		✓			
Adamian, 2004[30]		✓											
Adam, 2003[45]	✓	✓											
Aversa, 1996[46]		✓									✓		
Barton Laws, 2000[31]	✓	✓	✓	✓		✓	✓		✓		✓		
Golin, 2002[19]	✓	✓											
Goode, 2003[48]													
Graney, 2003[32]	✓			✓		✓		✓					
Hammami, 2004[44]	✓			✓		✓				✓		✓	
Hill, 2003[33]	✓	✓	✓	✓			✓	✓	✓	✓			
Johnston Roberts, 2003[108]	✓	✓				✓	✓						
Johnston Roberts, 2002[34]													
Johnston Roberts, 200054]						✓	✓	✓					
Ka'opua, 2004[53]													
Kemppainen, 2004[49]	✓	✓	✓					✓					
Klitzman, 2004[35]	✓				✓							✓	
Malcolm, 2003[36]	✓	✓	✓		✓				✓				
Meystre-Agustoni, 2000[37]	✓			✓		✓	✓						
Miller, 2002[20]	✓												
Misener, 1998[21]					✓	✓							
Murphy, 2003[23]	✓	✓	✓										
Murphy, 2000[22]	✓												
Oggins, 2003[38]			✓		✓		✓	✓	✓				
Powell-Cope, 2003[24]	✓	✓	✓	✓									
Proctor, 1999[25]	✓	✓		✓									
Reback, 2003[39]			✓					✓					
Remien, 2003[50]	✓	✓	✓	✓	✓	✓							
Richter, 2002[26]		✓			✓								
Ryan, 2003[40]	✓	✓	✓	✓									✓
Sankar, 2002[51]	✓		✓		✓					✓		✓	
Schilder, 2001[27]	✓		✓										
Stone, 1998[28]	✓			✓			✓						
Westerfelt, 2004[29]	✓	✓				✓							
Wilson, 2002[41]		✓	✓		✓		✓	✓					
Witteven, 2002[42]	✓	✓	✓		✓				✓	✓	✓		✓
Wood, 2004[43]		✓						✓				✓	

doi:10.1371/journal.pmed.0030438.t004

Table 4. Extended

Qualitative Studies	Beliefs about Medication								
	Side Effects (Real or Anticipated)	Regimens Complicated/ Confusing	Taste/Size/ Number/ Frequency of Dosing	Not Convinced of Efficacy	Feel Fine/ Healthy	Uncertainty of Long-Term Effects	Decreased Quality of Life/ Feel Worse	Unwanted Changes in Body Image	Too Toxic/ Harmful
Abel, 2003[18]	✓	✓	✓			✓		✓	
Adamian, 2004[30]	✓					✓			
Adam, 2003[45]	✓		✓	✓				✓	
Aversa, 1996[46]	✓			✓		✓	✓		✓
Barton Laws, 2000[31]	✓								
Golin, 2002[19]									
Goode, 2003[48]	✓	✓	✓			✓			
Graney, 2003[32]	✓	✓			✓	✓			
Hammami, 2004[44]	✓				✓				
Hill, 2003[33]					✓				
Johnston Roberts, 2003[108]	✓								
Johnston Roberts, 2002[34]									
Johnston Roberts, 200054]	✓	✓	✓					✓	
Ka'opua, 2004[53]									
Kemppainen, 2004[49]	✓	✓	✓			✓			
Klitzman, 2004[35]	✓								
Malcolm, 2003[36]									
Meystre-Agustoni, 2000[37]	✓							✓	
Miller, 2002[20]	✓		✓				✓		
Misener, 1998[21]	✓			✓					
Murphy, 2003[23]	✓	✓	✓	✓					
Murphy, 2000[22]	✓	✓			✓				
Oggins, 2003[38]	✓				✓		✓		✓
Powell-Cope, 2003[24]	✓	✓	✓		✓		✓		
Proctor, 1999[25]	✓	✓	✓	✓	✓		✓		
Reback, 2003[39]									
Remien, 2003[50]	✓	✓	✓						
Richter, 2002[26]	✓	✓		✓					✓
Ryan, 2003[40]									
Sankar, 2002[51]									✓
Schilder, 2001[27]	✓	✓							
Stone, 1998[28]	✓	✓						✓	
Westerfelt, 2004[29]	✓		✓		✓				
Wilson, 2002[41]	✓								
Witteven, 2002[42]	✓	✓	✓	✓			✓		
Wood, 2004[43]	✓				✓				

Table 4. Extended.

Qualitative Studies	Daily Schedules									
	Disruptions in Daily Routine/ Chaotic Life	Inconvenient/ Difficult to Incorporate	Work/Family/ Caregiving Responsibilities	Dietary Requirements Difficult to Balance	Fell Asleep	Being Away from Home/ Not Carrying Meds/ Storage Concerns	Too Busy/ Distracted	No Time to Refill/ Pharmacy Problems	Middle of the Day/ Early Morning Dose	Difficult to Travel to Appointments
Abel, 2003[18]			✓	✓						
Adamian, 2004[30]	✓			✓						
Adam, 2003[45]	✓		✓	✓						
Aversa, 1996[46]		✓								
Barton Laws, 2000[31]		✓	✓		✓	✓		✓		
Golin, 2002[19]	✓	✓		✓	✓				✓	
Goode, 2003[48]		✓							✓	
Graney, 2003[32]		✓	✓							
Hammami, 2004[44]	✓	✓								
Hill, 2003[33]						✓	✓			
Johnston Roberts, 2003[108]	✓	✓								
Johnston Roberts, 2002[34]										
Johnston Roberts, 200054]	✓	✓	✓							
Ka'opua, 2004[53]										
Kemppainen, 2004[49]	✓				✓					
Klitzman, 2004[35]			✓							
Malcolm, 2003[36]										
Meystre-Agustoni, 2000[37]	✓	✓	✓							
Miller, 2002[20]		✓	✓							
Misener, 1998[21]										
Murphy, 2003[23]	✓									
Murphy, 2000[22]	✓			✓				✓		
Oggins, 2003[38]		✓								
Powell-Cope, 2003[24]			✓		✓	✓	✓	✓		
Proctor, 1999[25]	✓			✓				✓		
Reback, 2003[39]	✓			✓	✓	✓				
Remien, 2003[50]										
Richter, 2002[26]										
Ryan, 2003[40]	✓				✓	✓	✓			
Sankar, 2002[51]							✓			
Schilder, 2001[27]	✓	✓	✓							
Stone, 1998[28]		✓	✓							
Westerfelt, 2004[29]		✓			✓		✓		✓	
Wilson, 2002[41]	✓	✓								
Witteven, 2002[42]	✓					✓			✓	
Wood, 2004[43]	✓									

doi:10.1371/journal.pmed.0030438.t004

Table 4. Extended

Qualitative Studies	Interpersonal Relationships			
	Negative View/Lack of Trust in Provider	Social Isolation	Negative Social Support	Negative Publicity/ Historical Knowledge
Abel, 2003[18]				
Adamian, 2004[30]				
Adam, 2003[45]			✓	✓
Aversa, 1996[46]				✓
Barton Laws, 2000[31]	✓			
Golin, 2002[19]				
Goode, 2003[48]		✓		
Graney, 2003[32]				
Hammami, 2004[44]		✓	✓	
Hill, 2003[33]		✓		
Johnston Roberts, 2003[108]				✓
Johnston Roberts, 2002[34]	✓			
Johnston Roberts, 200054]				
Ka'opua, 2004[53]				
Kemppainen, 2004[49]	✓	✓		
Klitzman, 2004[35]			✓	✓
Malcolm, 2003[36]	✓	✓		✓
Meystre-Agustoni, 2000[37]				
Miller, 2002[20]				
Misener, 1998[21]	✓		✓	✓
Murphy, 2003[23]	✓	✓	✓	
Murphy, 2000[22]	✓			
Oggins, 2003[38]	✓			✓
Powell-Cope, 2003[24]	✓			
Proctor, 1999[25]		✓		
Reback, 2003[39]				
Remien, 2003[50]	✓	✓		
Richter, 2002[26]				
Ryan, 2003[40]				
Sankar, 2002[51]		✓		✓
Schilder, 2001[27]	✓			
Stone, 1998[28]			✓	✓
Westerfelt, 2004[29]				
Wilson, 2002[41]				
Witteven, 2002[42]	✓	✓		
Wood, 2004[43]				

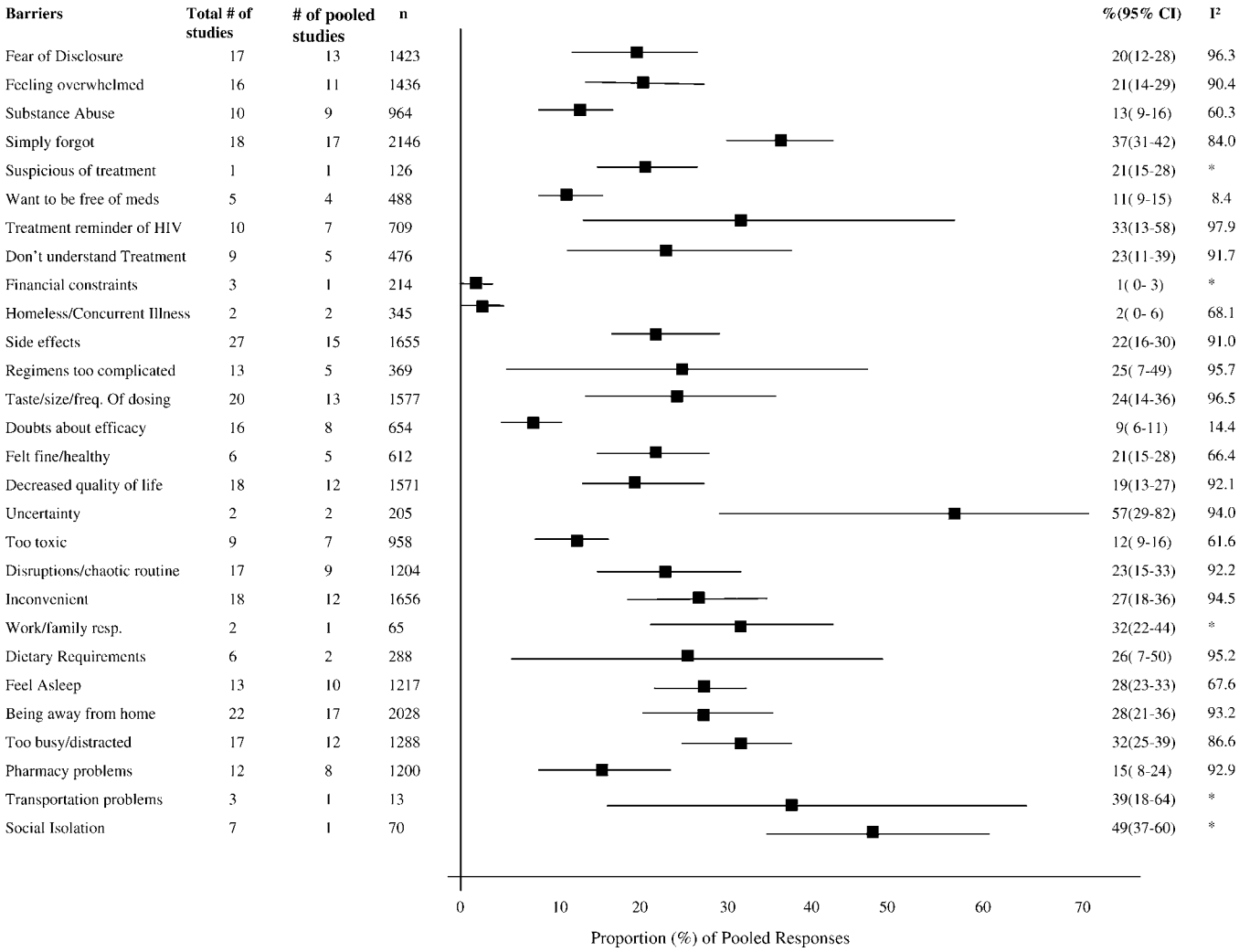

Figure 2. Barriers Reported in Developed Countries
doi:10.1371/journal.pmed.0030438.g002

the proportion of the overall variation in the meta-analyses that was attributable to between-study heterogeneity [17].

Results

Study Selection and Characteristics

The primary literature search produced 228 studies. There was near-perfect agreement between EJM and BR on choosing the 115 applicable studies from the reviewed abstracts ($K \geq 0.8$). Of these, 31 were excluded as they were either not original studies or did not examine factors that influence adherence to antiretroviral therapy. The remaining 84 studies were included in our analysis (see Figure 1). There was perfect agreement on the final studies selected between BR and PW. All studies were published in English.

Thirty-seven of the studies were qualitative (see Tables 1 and 2). Twelve used focus groups (total number of patients, $n = 415$) [18–29], 15 used semi-structured interviews ($n = 729$) [30–44], and nine used open-ended questioning ($n = 694$) [45–53] to explore barriers and facilitators to adherence. One study employed a writing intervention to solicit barriers and motivators to adherence [54]. The 47 remaining studies employed a quantitative methodology (surveys) and used structured questionnaires or structured interviews (total $n = 12,902$ [55]) [4,56–100] to determine potential factors. Table 3 displays the quality criteria results for the quantitative studies. No studies reported following up with non-responders to the surveys. Of the total sample of eligible studies, 72 were conducted in developed countries [4,18–25,30–39,44–46,48–50,53–56,58,59,61,62,64–67,69–76,79–81,83,84,86,87,108], and 12 in developing nations [47,52,57,60,63,68,77,78,82,85,94,96]. Fifty-six were from the United States [4,18–26,28,30–36,38–40,46,49–51,53,54,58,59,61,62,66,67,70,71,73,74,76,79–81,84,86,88–91,93,95,108], three from Canada [27,45,72], three from the United Kingdom [55,69,98], two from Italy [56,64], two from France [75,92], two from The Netherlands [42,83], and one each from Australia [48], Switerland [37], and Belgium [44]. Two studies were multinational [65,87]. The studies conducted in developing countries included four from Brazil [47,68,78,85], and one each from Uganda [57], Cote d'Ivoire [63], South Africa [82], Malawi [96], Botswana [52], Costa Rica

Table 5. Facilitators Reported in Qualitative Studies

Qualitative Studies	Patient Variables				Beliefs about Medication		
	Self Efficacy/ Self Meaning	Medication Takes Priority over Substance Abuse	Accepted HIV Status/ Learned to Manage	Seeing Positive Results	Understand Need for Compliance	Belief in Efficacy of Drugs/ Faith in Treatment	Simple Regimen
Abel, 2003[18]			✓		✓	✓	✓
Adamian, 2004[30]					✓		
Adam, 2003[45]	✓			✓		✓	
Aversa, 1996[46]							
Barton Laws, 2000[31]							
Golin, 2002[19]	✓					✓	
Goode, 2003[48]							
Graney, 2003[32]	✓		✓	✓	✓		
Hammami, 2004[44]	✓		✓		✓	✓	
Hill, 2003[33]							
Johnston Roberts, 2003[108]							
Johnston Roberts, 2002[34]							
Johnston Roberts, 2000[54]							
Ka'opua, 2004[53]	✓					✓	
Kemppainen, 2004[49]	✓		✓			✓	✓
Klitzman, 2004[35]							
Malcolm, 2003[36]	✓	✓			✓		
Meystre-Agustoni, 2000[37]							
Miller, 2002[20]							
Misener, 1998[21]						✓	
Murphy, 2003[23]	✓	✓				✓	✓
Murphy, 2000[22]						✓	
Oggins, 2003[38]							
Powell-Cope, 2003[24]				✓	✓	✓	
Proctor, 1999[25]							
Reback, 2003[39]							
Remien, 2003[50]	✓			✓		✓	
Richter, 2002[26]	✓			✓	✓		
Ryan, 2003[40]		✓					
Sankar, 2002[51]	✓		✓				
Schilder, 2001[27]							
Stone, 1998[28]	✓		✓	✓	✓		
Westerfelt, 2004[29]	✓		✓				
Wilson, 2002[41]	✓		✓				
Wittevee, 2002[42]	✓	✓			✓	✓	
Wood, 2004[43]							

doi:10.1371/journal.pmed.0030438.t005

[94], Romania [60], and China [77]. Tables 4 and 5 outline the factors affecting HAART adherence reported by HIV-positive individuals from developed and developing countries as determined by the qualitative studies.

Barriers and Facilitators Listed by Patients in Developed Countries: Themes from Qualitative Studies

Barriers. Thirty-three individual themes of barriers were recorded in 34 qualitative studies (see Table 4).

Patient-related: Thirteen barriers were patient-related and included: a fear of disclosure and wanting to avoid taking medications in public places (23/34) [18–20,22–25,27–29,31–33,35–37,40,42,44,45,49–51,108]; feeling depressed, hopeless, or overwhelmed (18/34) [19,23–26,29,31,33,36,40,41,43,45,46,49,50]; having a concurrent addiction (14/34) [23,24,27,31,33,36,39–42,49–51,81]; and forgetting to take medication at the specified time (11/34) [20,24,25,28,31–33,37,40,44,50]. Other barriers include: being suspicious of treatment/medical establishment (9/34) [21,26,35,36,38,41,42,50,51]; wanting to be free of medications or preferring a natural approach (10/34) [20,21,29,31,32,37,44,50,54,108]; feeling that treatment is a reminder of HIV status (8/34) [18,32,38,39,41,43,49,54]; wanting to be in control (7/34) [28,31,37,38,41,54,108]; not understanding treatment instructions (5/34) [31,33,36,38,42]; still having doubt or not being able to accept HIV status (5/34) [18,33,42,44,51]; and a lack of self-worth (4/34) [35,43,44,51]. Financial constraints [31,42,46], being homeless [40,42], and having other concurrent illnesses affecting adherence were also cited.

Beliefs about medication: There were eight reported barriers pertaining to beliefs/perceptions about medications. Some common barriers in this category included: side effects (either real or anticipated) (27/34) [18,20,21,23–32,35,37,38,41–46,48–50,54,108]; complicated regimens (12/34) [18,22,23,26–28,32,42,48–50,54]; and the taste, size, dosing frequency, and/or pill count (12/34) [18,20,23–25,29,45,48–50,54]. In nine studies, when individuals prescribed HAART felt healthy, adherence was often negatively affected [22,24,25,29,32,33,38,43,44]. Other barriers included: doubting the efficacy of HAART (7/34) [21,23,25,26,42,45,46]; having a decreased quality of life (6/

Table 5. Extended.

Qualitative Studies	Daily Schedules		Interpersonal Relationships				
	Having a Fixed Routine	Use of Reminder Tools	Having Social Support/ Open Disclosure	Good Relationship with Provider	Living for Someone	Part of Decision Making	Family/ Friends Help Remind
Abel, 2003[18]		✓	✓	✓		✓	✓
Adamian, 2004[30]	✓		✓	✓			
Adam, 2003[45]	✓		✓		✓		
Aversa, 1996[46]							
Barton Laws, 2000[31]							
Golin, 2002[19]			✓	✓	✓		✓
Goode, 2003[48]							
Graney, 2003[32]	✓		✓	✓			
Hammami, 2004[44]	✓	✓	✓	✓			
Hill, 2003[33]							
Johnston Roberts, 2003[108]				✓			
Johnston Roberts, 2002[34]				✓		✓	
Johnston Roberts, 2000[54]							
Ka'opua, 2004[53]			✓	✓			✓
Kemppainen, 2004[49]	✓	✓	✓	✓			
Klitzman, 2004[35]			✓				✓
Malcolm, 2003[36]	✓		✓	✓		✓	
Meystre-Agustoni, 2000[37]							
Miller, 2002[20]							
Misener, 1998[21]				✓	✓		
Murphy, 2003[23]	✓	✓	✓	✓	✓		✓
Murphy, 2000[22]	✓	✓	✓	✓		✓	
Oggins, 2003[38]							
Powell-Cope, 2003[24]				✓			
Proctor, 1999[25]							
Reback, 2003[39]							
Remien, 2003[50]			✓	✓	✓		
Richter, 2002[26]	✓		✓		✓		
Ryan, 2003[40]	✓	✓	✓				✓
Sankar, 2002[51]			✓	✓	✓		
Schilder, 2001[27]							
Stone, 1998[28]				✓	✓		
Westerfelt, 2004[29]				✓			
Wilson, 2002[41]							
Wittevee, 2002[42]	✓	✓	✓	✓			
Wood, 2004[43]							

34) [20,24,25,38,42,46]; uncertainty of long-term effects (6/34) [30,32,45,46,48,49]; and unwanted changes in body image (5/34) [18,28,37,45,54].

Daily schedules: Nine common barriers were related to daily schedules and included: disruptions in routine or having a chaotic schedule (16/34) [19,22,23,25,27,30,37,39–45,54,108]; finding HAART too inconvenient or difficult to incorporate (14/34) [19,20,27–29,31,32,37,38,41,44,46,48,54,108]; and difficulties coordinating adherence with work, family, or caregiving responsibilities (11/34) [18,20,24,27,28,31,32,37,45,54]. Individuals in seven studies found it difficult to balance the numerous strict dietary requirements associated with HAART [18,19,22,25,30,39,45]. Six studies cited sleeping through a dose [19,29,31,39,40,49]. Other barriers included: being away from home and not bringing medication (6/34) [24,31,33,39,40,42]; being too distracted or busy (5/34) [24,29,33,40,51]; and having no time to refill prescriptions, or other pharmacy-related problems (4/34) [22,24,25,31]. Finally, four studies described difficulties with a particular dose, particularly the middle-of-day or early-morning dose [19,29,42,48].

Interpersonal relationships: Interpersonal relationships can affect adherence behaviors. Twelve studies noted a lack of trust or a dislike of a patient's health-care provider as an impediment to adherence [21–24,27,31,34,36,38,42,49,50]. Ten studies noted social isolation [23,25,33,36,42,44,48–51]. Nine studies noted negative publicity regarding HAART or the medical establishment [21,28,35,36,38,44–46,51]. Finally, five studies noted that having a discouraging social network often deterred patients from successful adherence (5/34) [21,23,28,35,45].

Facilitators. Patient-related: Fourteen factors facilitating successful adherence to HAART were abstracted. Patient-related facilitators included having self-worth (15/23) [19,23,26,28,29,32,36,41,42,44,45,49–51,53], medication taking priority over substance use (4/23) [23,36,40,42] and seeing positive results when adhering to HAART (6/23) [24,26,28,32,45,50]. Also, those patients who had accepted their HIV-seropositivity reported improved adherence (8/23) [18,28,29,32,41,44,49,51].

Beliefs about medication: The most common motivator (12/23) to adherence is a belief in the efficacy of HAART and

Table 6. Barriers Reported in Quantitative Studies (Surveys)

Countries	Reference	Patient Variables						
		Fear of Disclosure	Feeling Over-whelmed	Concurrent Substance Abuse	Simply Forgot	Suspicions of Treatment	Want to be Free of Meds/ Feel Normal/ Holistic Approach	Want to Maintain Control
Developed countries	Ammassari, 2001[56]	✓						
	Brook, 2001[55]	✓						
	Catz, 2000[58]	✓	✓					
	Chesney, 20[59]	✓	✓		✓			
	Eldred, 1998[61]		✓	✓	✓			
	Erlen, 2002[62]	✓		✓	✓			
	Ferguson, 2002[4]	✓			✓			
	Gibb, 2003[65]	✓						
	Giacomet, 2003[64]							
	Harzke, 2004[66]		✓		✓			
	Heckman, 2004[67]		✓		✓			
	Horne, 2004[69]	✓	✓			✓		
	Johnson, 2003[70]						✓	
	Kalichman, 1999[71]		✓	✓	✓		✓	
	Kerr, 1999[72]		✓	✓	✓			
	Kleeberger, 2001[73]	✓	✓		✓			
	Marhefka, 2004[74]	✓			✓			
	Moatti, 2000[75]				✓			
	Mohammed, 2004[76]	✓	✓	✓	✓		✓	
	Mostashari, 1998[79]							
	Muma, 1995[80]		✓		✓			
	Murphy, 2003[81]	✓	✓		✓			
	Nieuwkerk, 2001[83]				✓			
	Palmer, 2003[84]	✓		✓	✓			
	Reddington, 2000[86]	✓			✓			
	Reynolds,2004[87]	✓	✓		✓			
	Savini, 2003[88]							
	Schneider, 2004[89]							
	Siegel, 2000[90]							
	Simoni, 2002[91]			✓	✓		✓	
	Spire, 2002[92]		✓	✓	✓			
	Stein, 2000[93]	✓	✓	✓	✓			
	Tucker, 2004[95]			✓				
	Wagner, 2004[97]							
	Walsh, 2001[98]	✓	✓	✓	✓		✓	
	Weidle, 1999[99]				✓			
	Wilson, 2001[100]	✓						
Developing countries	Byakika-Tusiime, 2005[57]				✓			
	Cupsa, 2000[60]					✓		
	Fassinou, 2004[63]							
	Hofer, 2004[68]							
	Molassiotis, 2002[77]	✓	✓		✓			
	Monreal, 2002[78]				✓			
	Nachega, 2004[82]	✓						
	Pinheiro, 2002[85]	✓	✓					
	Stout, 2004[94]				✓			
	van Oosterhout, 2005[96]				✓			

doi:10.1371/journal.pmed.0030438.t006

"having faith" in the treatment [18,19,21–24,42,44,45,49,50,53]. Other motivators included understanding the need for strict compliance (9/23) [18,24,26,28,30,32,36,42,44], and having a simple regimen (3/23)[18,21,49].

Daily schedules: Twelve studies reported learning to balance HAART with daily schedules as a facilitator of adherence. Having a routine in which taking antiretrovirals could be easily incorporated (11/23) [22,23,26,30,32,36,40,42,44,45,49], and making use of reminder tools (7/23) [18,22,23,40,42,44,49] are both reported to be effective tools for optimizing adherence.

Interpersonal relationships: Positive interpersonal relationships were reported as necessary for successful adherence. Having a trusting relationship with a health-care provider was reported as a facilitator of adherence in 17 studies [18,19,21–24,28,29,32,34,36,42,44,45,49–51,53,108]. In addition, openly disclosing HIV status to family and friends and having a strong support network was reported as influential to adherence (18/23) [18,19,22,23,26,30,32,35,36,40,42–45,49–51,53]. Other motivators included: living for someone, especially, children (9/23) [19,21,23,26,28,43,45,50,51]; being actively involved in treatment decision making (4/23) [18,22,34,36]; and using friends and family as reminders (6/23) [18,19,23,35,40,53].

Table 6. Extended.

Countries	Reference	Patient Variables						
		Treatment Reminder of HIV Status	Don't Understand Treatment/ Misinformed	Doubt HIV Status/ Haven't Accepted It	Financial Constraints	No Self Worth/ Doubt Ability to Adhere	Homeless/ Other Concurrent Illness	Prefer Holistic/ Natural Approach
Developed countries	Ammassari, 2001[56]							
	Brook, 2001[55]					✓		
	Catz, 2000[58]	✓	✓					
	Chesney, 20[59]							
	Eldred, 1998[61]				✓		✓	
	Erlen, 2002[62]							
	Ferguson, 2002[4]	✓	✓		✓			
	Gibb, 2003[65]							
	Giacomet, 2003[64]							
	Harzke, 2004[66]							
	Heckman, 2004[67]							
	Horne, 2004[69]		✓					
	Johnson, 2003[70]	✓						
	Kalichman, 1999[71]		✓					
	Kerr, 1999[72]							
	Kleeberger, 2001[73]							
	Marhefka, 2004[74]							
	Moatti, 2000[75]							
	Mohammed, 2004[76]	✓						
	Mostashari, 1998[79]	✓						
	Muma, 1995[80]	✓	✓		✓			
	Murphy, 2003[81]	✓	✓					
	Nieuwkerk, 2001[83]							
	Palmer, 2003[84]							
	Reddington, 2000[86]		✓			✓		
	Reynolds,2004[87]							
	Savini, 2003[88]					✓		
	Schneider, 2004[89]							
	Siegel, 2000[90]		✓			✓		
	Simoni, 2002[91]	✓						
	Spire, 2002[92]							
	Stein, 2000[93]							
	Tucker, 2004[95]							
	Wagner, 2004[97]							
	Walsh, 2001[98]	✓	✓					
	Weidle, 1999[99]						✓	
	Wilson, 2001[100]	✓						
Developing countries	Byakika-Tusiime, 2005[57]		✓		✓		✓	
	Cupsa, 2000[60]		✓					✓
	Fassinou, 2004[63]		✓					
	Hofer, 2004[68]		✓					
	Molassiotis, 2002[77]							
	Monreal, 2002[78]							✓
	Nachega, 2004[82]							
	Pinheiro, 2002[85]							
	Stout, 2004[94]							
	van Oosterhout, 2005[96]				✓			

Common themes from surveys and quantitative studies. Figure 2 displays the pooled results of studies assessing barriers and reporting proportions of responders. Table 6 displays the surveys that did inquire of the issues addressed in the qualitative studies. There were three barriers described in qualitative reports but not in the quantitative studies. These were: having suspicions regarding HAART, wanting to be in control, and doubting or having difficulty accepting one's HIV status.

Eight quantitative studies reported facilitators to adherence (see Table 7). Four themes for facilitation of adherence were mentioned in the qualitative studies that were not discussed in the relevant quantitative studies (i.e., having medication take priority over substance abuse, having a simple regimen, using reminder tools, and living for someone).

Barriers Listed by Patients in Developing Countries: Themes from Qualitative Studies

As there were only two studies identified, we describe the findings here. Eighteen specific barriers are cited in two studies [47,52].

Patient-related: The most common patient-related barriers were: having a co-existing substance addiction, simply forgetting, and financial constraints [47,52]. Other barriers affecting adherence incorporated: a fear of disclosure [52];

Table 6. Extended.

Countries	Reference	Beliefs about Medication								
		Side Effects (Real or Anticipated)	Regimens Compli-cated/ Confusion	Taste/Size/ Number/ Frequency of Dosing	Not Convinced of Efficacy	Feel Fine/ Healthy	Uncertainty of Long-Term Effects	Decreased Quality of Life/Feel Worse	Unwanted Changes in Body Image	Too Toxic/ Harmful
Developed countries	Ammassari, 2001[56]	✓		✓			✓			
	Brook, 2001[55]	✓		✓						
	Catz, 2000[58]	✓	✓		✓			✓	✓	
	Chesney, 20[59]	✓		✓				✓		✓
	Eldred, 1998[61]	✓		✓	✓			✓		✓
	Erlen, 2002[62]	✓								
	Ferguson, 2002[4]	✓	✓	✓	✓	✓		✓		
	Gibb, 2003[65]			✓						
	Giacomet, 2003[64]			✓	✓					
	Harzke, 2004[66]	✓		✓	✓					
	Heckman, 2004[67]	✓						✓		
	Horne, 2004[69]	✓		✓			✓			
	Johnson, 2003[70]	✓		✓				✓		
	Kalichman, 1999[71]	✓	✓	✓	✓					
	Kerr, 1999[72]	✓						✓		
	Kleeberger, 2001[73]	✓	✓	✓				✓		✓
	Marhefka, 2004[74]	✓	✓	✓				✓		
	Moatti, 2000[75]	✓								
	Mohammed, 2004[76]	✓		✓						✓
	Mostashari, 1998[79]									
	Muma, 1995[80]	✓	✓		✓			✓		
	Murphy, 2003[81]		✓	✓	✓	✓		✓		✓
	Nieuwkerk, 2001[83]							✓		
	Palmer, 2003[84]	✓		✓	✓	✓		✓		✓
	Reddington, 2000[86]	✓	✓	✓						
	Reynolds,2004[87]	✓		✓		✓		✓		✓
	Savini, 2003[88]	✓	✓	✓						
	Schneider, 2004[89]									
	Siegel, 2000[90]	✓	✓		✓			✓		
	Simoni, 2002[91]		✓	✓	✓	✓		✓		
	Spire, 2002[92]	✓			✓					
	Stein, 2000[93]	✓	✓	✓						
	Tucker, 2004[95]		✓		✓					
	Wagner, 2004[97]	✓								
	Walsh, 2001[98]	✓		✓	✓			✓		
	Weidle, 1999[99]		✓		✓					✓
	Wilson, 2001[100]	✓			✓	✓		✓		✓
Developing countries	Byakika-Tusiime, 2005[57]	✓	✓							
	Cupsa, 2000[60]	✓			✓					
	Fassinou, 2004[63]		✓				✓			
	Hofer, 2004[68]				✓			✓		
	Molassiotis, 2002[77]	✓		✓		✓		✓		✓
	Monreal, 2002[78]	✓	✓							
	Nachega, 2004[82]		✓	✓						
	Pinheiro, 2002[85]	✓		✓	✓	✓		✓		
	Stout, 2004[94]									
	van Oosterhout, 2005[96]	✓								

difficulty understanding both treatment instructions; the need for compliance [47]; and the presence of concurrent diseases or illnesses, including malnutrition [52].

Beliefs about medication: Barriers reflective of patient beliefs regarding antiretrovirals included: side effects (either real or anticipated) [52]; complicated regimens [52]; the taste, size, and frequency of dosing [52]; having doubts about HAART efficacy [47]; feeling fine or healthy [52]; a decreased quality of life while taking medications, or feeling too sick [52]; and being uncertain about potential long-term effects of HIV treatment [47].

Daily schedules: Trouble incorporating work and family responsibilities with HAART was seen as a barrier to adherence in both studies. Traveling long distances to receive treatment was common, and not surprisingly, transportation difficulties were often reported to be a major hindrance to adherence (2/2). Other barriers included running out of medications or having an irregular supply [52]; being away from home [52]; and being too busy or distracted to properly comply [52].

No studies mentioned interpersonal relationships as a barrier to adherence in this population.

No facilitators to adherence were discussed in any study in a developing nation setting.

Table 6. Extended.

Countries	Reference	Daily Schedules				
		Disruptions in Daily Routine/ Chaotic Life	Inconvenient/ Difficult to Incorporate	Work/Family/ Caregiving Responsibilities	Dietary Requirements Difficult to Balance	Fell Asleep
Developed countries	Ammassari, 2001[56]		✓			✓
	Brook, 2001[55]	✓				✓
	Catz, 2000[58]	✓	✓			
	Chesney, 20[59]	✓	✓			✓
	Eldred, 1998[61]		✓		✓	
	Erlen, 2002[62]					✓
	Ferguson, 2002[4]		✓			✓
	Gibb, 2003[65]	✓	✓	✓		
	Giacomet, 2003[64]				✓	
	Harzke, 2004[66]					
	Heckman, 2004[67]		✓		✓	
	Horne, 2004[69]		✓			
	Johnson, 2003[70]		✓			
	Kalichman, 1999[71]	✓				✓
	Kerr, 1999[72]	✓	✓			✓
	Kleeberger, 2001[73]	✓				✓
	Marhefka, 2004[74]	✓	✓	✓	✓	
	Moatti, 2000[75]	✓				
	Mohammed, 2004[76]	✓	✓			✓
	Mostashari, 1998[79]					
	Muma, 1995[80]		✓			
	Murphy, 2003[81]	✓				
	Nieuwkerk, 2001[83]	✓	✓			
	Palmer, 2003[84]		✓			✓
	Reddington, 2000[86]	✓				
	Reynolds,2004[87]	✓	✓			✓
	Savini, 2003[88]				✓	
	Schneider, 2004[89]					
	Siegel, 2000[90]					
	Simoni, 2002[91]					
	Spire, 2002[92]					✓
	Stein, 2000[93]	✓				✓
	Tucker, 2004[95]	✓				
	Wagner, 2004[97]		✓			
	Walsh, 2001[98]	✓			✓	✓
	Weidle, 1999[99]					
	Wilson, 2001[100]	✓	✓			
Developing countries	Byakika-Tusiime, 2005[57]					
	Cupsa, 2000[60]					
	Fassinou, 2004[63]					
	Hofer, 2004[68]					
	Molassiotis, 2002[77]	✓				✓
	Monreal, 2002[78]					✓
	Nachega, 2004[82]				✓	
	Pinheiro, 2002[85]	✓				
	Stout, 2004[94]	✓				✓
	van Oosterhout, 2005[96]					

Themes from surveys and quantitative studies. Ten surveys were found in developing settings (see Figure 3). No quantitative study enquired of difficulties with morning or afternoon doses, work and family responsibilities, or listed inconvenience as a barrier.

Discussion

To our knowledge, this is the first systematic review to examine the concerns of HIV patients to maintaining adherence. We found that fear of disclosure, forgetfulness, a lack of understanding of treatment benefits, complicated regimens, and being away from their medications were consistent barriers to adherence across developed and developing nations. More common to developing settings were issues of access, including financial constraints and a disruption in access to medications. While there is a tremendous paucity of qualitative research in developing settings, our findings indicate that many barriers to adherence can be addressed with patients through discussion and education regarding treatment benefits to health. In developing settings, access to medications is the greatest concern. Indeed, discussion in both economic settings may alleviate patients' suspicions regarding treatment and address prac-

Table 6. Extended.

Countries	Reference	Daily Schedules				
		Being Away from Home/ Not Carrying Meds/ Storage Concerns	Too Busy/ Distracted	No Time to Refill/ Pharmacy Problems	Middle of the Day/ Early Morning Dose	Difficult to Travel to Appointments
Developing countries	Ammassari, 2001[56]	✓				
	Brook, 2001[55]	✓				
	Catz, 2000[58]	✓	✓			✓
	Chesney, 20[59]	✓				
	Eldred, 1998[61]	✓		✓		
	Erlen, 2002[62]	✓		✓		
	Ferguson, 2002[4]	✓	✓	✓	✓	
	Gibb, 2003[65]	✓	✓			
	Giacomet, 2003[64]					
	Harzke, 2004[66]					
	Heckman, 2004[67]					
	Horne, 2004[69]					
	Johnson, 2003[70]					
	Kalichman, 1999[71]	✓	✓			
	Kerr, 1999[72]	✓	✓			
	Kleeberger, 2001[73]	✓	✓	✓		
	Marhefka, 2004[74]	✓	✓	✓	✓	✓
	Moatti, 2000[75]	✓	✓			
	Mohammed, 2004[76]	✓	✓	✓		
	Mostashari, 1998[79]					
	Muma, 1995[80]					
	Murphy, 2003[81]	✓	✓			
	Nieuwkerk, 2001[83]	✓				
	Palmer, 2003[84]	✓	✓			
	Reddington, 2000[86]	✓	✓			
	Reynolds,2004[87]	✓	✓	✓		
	Savini, 2003[88]					
	Schneider, 2004[89]					
	Siegel, 2000[90]					
	Simoni, 2002[91]	✓	✓	✓		
	Spire, 2002[92]	✓	✓			
	Stein, 2000[93]	✓	✓			
	Tucker, 2004[95]			✓		✓
	Wagner, 2004[97]					
	Walsh, 2001[98]	✓	✓	✓		
	Weidle, 1999[99]			✓		
	Wilson, 2001[100]			✓		
Developed countries	Byakika-Tusiime, 2005[57]	✓	✓	✓		
	Cupsa, 2000[60]			✓		
	Fassinou, 2004[63]	✓		✓		
	Hofer, 2004[68]					
	Molassiotis, 2002[77]	✓	✓	✓		
	Monreal, 2002[78]			✓		
	Nachega, 2004[82]	✓		✓		
	Pinheiro, 2002[85]	✓				
	Stout, 2004[94]	✓	✓			✓
	van Oosterhout, 2005[96]			✓		

tical barriers to improve adherence. This study should also be used to guide the development of interventions aiming to improve adherence in any setting.

This study has several important strengths. The methods we employed to tabulate these findings come from a multi-step process. We first systematically identified qualitative and quantitative studies examining the questions. We then extracted the themes from the qualitative studies and determined which of them were sampled in the quantitative studies. Finally, we synthesized the available quantitative data. By systematically determining the existence and prevalence of barriers in multiple qualitative and quantitative studies, we believe that stronger inferences can be made into patient-related adherence obstacles and facilitators. We have previously demonstrated that surveys benefit from systematically examining qualitative studies, as this improves content validity [13,101]. To this end, our review of qualitative studies identified several key themes addressing barriers to adherence that were not examined in larger quantitative studies. The presence of barriers in more than one qualitative study, consisting of populations of patients representing different patient populations, supports the conclusion that these barriers are somewhat applicable. Our meta-analysis of survey data is a relatively new process that we have previously

Table 6. Extended.

Countries	Reference	Interpersonal Factors			
		Negative View/ Lack of Trust in Provider	Social Isolation	Negative Social Support	Negative Publicity/ Historical Knowledge
Developed countries	Ammassari, 2001[56]				
	Brook, 2001[55]				
	Catz, 2000[58]		✓		
	Chesney, 20[59]				
	Eldred, 1998[61]				
	Erlen, 2002[62]		✓		
	Ferguson, 2002[4]		✓	✓	
	Gibb, 2003[65]				
	Giacomet, 2003[64]				
	Harzke, 2004[66]		✓		✓
	Heckman, 2004[67]				
	Horne, 2004[69]				
	Johnson, 2003[70]				
	Kalichman, 1999[71]				
	Kerr, 1999[72]				
	Kleeberger, 2001[73]		✓		
	Marhefka, 2004[74]				
	Moatti, 2000[75]				
	Mohammed, 2004[76]				
	Mostashari, 1998[79]				
	Muma, 1995[80]				✓
	Murphy, 2003[81]				
	Nieuwkerk, 2001[83]				
	Palmer, 2003[84]				
	Reddington, 2000[86]		✓		
	Reynolds,2004[87]				
	Savini, 2003[88]				
	Schneider, 2004[89]				
	Siegel, 2000[90]	✓			✓
	Simoni, 2002[91]				
	Spire, 2002[92]	✓			
	Stein, 2000[93]				
	Tucker, 2004[95]	✓	✓	✓	
	Wagner, 2004[97]				
	Walsh, 2001[98]				✓
	Weidle, 1999[99]				
	Wilson, 2001[100]				
Developing countries	Byakika-Tusiime, 2005[57]				
	Cupsa, 2000[60]				
	Fassinou, 2004[63]				
	Hofer, 2004[68]	✓			
	Molassiotis, 2002[77]				
	Monreal, 2002[78]				
	Nachega, 2004[82]				
	Pinheiro, 2002[85]				
	Stout, 2004[94]				
	van Oosterhout, 2005[96]				

demonstrated [102,103], and can permit stronger inferences into the generalizability of our findings. Finally, our criteria to assess the quality of both qualitative studies and surveys are a new contribution to the methodological literature. Recognizing that the absence of reporting particular methodological criteria may not reflect what was actually conducted during a study [104], we invite discussion regarding the relative usefulness and applicability of these criteria.

This work has several limitations. We aimed to reduce reviewer bias by conducting abstraction independently, in duplicate. We cannot, however, know to what extent we may miss themes or to what extent reporting bias of the original report may have contributed. We emphasize that our methodology is specific but not sensitive for identifying themes. Reporting bias in the included manuscripts may have limited our ability to identify all barriers and facilitators to adherence. A broad range of economic and social conditions fall under the Human Development Index. It would wrong to assume that all individuals living in a HDI-categorized "developed" nation are in a better economic situation than all individuals living in a "developing" nation. Detailed information pertaining to this was rarely available in the original reports included in this review. It is possible that

Table 7. Facilitators Reported in Quantitative Studies (Surveys)

Countries	Reference	Patient Related				Medication/Regimen Beliefs		
		Self-Meaning/ Self-Efficacy	Medication Takes Priority over Substance Use	Accepted HIV Status/ Learned to Manage	Seeing Positive Results	Understand Need for Compliance	Belief in Efficacy of Drugs/ Faith in Treatment	Simple Regimen
Developed countries	Ammassari 2001[56]							
	Brook, 2001[55]							
	Catz, 2000[58]							
	Chesney, 2000[59]							
	Erlen, 2002[62]							
	Eldred, 2002[61]							
	Ferguson, 2002[4]							
	Gibb, 2003[65]							
	Giacomet, 2003[64]							
	Harzke, 2004[66]						✓	
	Heckman, 2004[67]							
	Horne, 2004[69]							
	Johnson, 2003[70]	✓		✓		✓	✓	
	Kalichman, 1999[71]							
	Kerr, 1999[72]							
	Kleeberger, 2001[73]							
	Marhefka, 2004[74]							
	Moatti, 2000[75]							
	Mohammed, 2004[76]							
	Mostashari, 1998[79]				✓		✓	
	Muma, 1995[80]						✓	
	Murphy, 2003[81]							
	Nieuwkerk, 2001[83]							
	Palmer, 2003[84]							
	Reddington, 2000[86]							
	Reynolds, 2004[87]	✓			✓			
	Savini, 2003[88]							
	Schneider, 2004[89]			✓		✓	✓	
	Siegel, 2000[90]	✓					✓	
	Simoni, 2002[91]							
	Spire, 2002[92]							
	Stein, 2000[93]							
	Tucker, 2004[95]							
	Wagner, 2004[97]	✓		✓	✓	✓		
	Walsh, 2001[98]							
	Weidle, 1999[99]							
	Wilson, 2001[100]							
Developing countries	Byakika-Tusiime, 2005[57]							
	Cupsa, 2000[60]							
	Fassinou, 2004[63]							
	Hofer, 2004[68]						✓	
	Molassiotis, 2002[77]							
	Montreal, 2002[78]							
	Nachega, 2004[82]							
	Pinheiro, 2002[85]	✓					✓	
	Stout, 20004[94]							
	Van Oosterhout, 2005[96]							

doi:10.1371/journal.pmed.0030438.t007

surveys used in developing nations were similar to surveys used in developed nations. However, the validity of these surveys in developing settings may not be appropriate, and we press for further qualitative research on this topic. Detailed population descriptions (e.g., education level) and the regional conditions from which this study is produced (e.g., gross national product) would benefit interpretation of future studies in this field. There are several interpretations of appropriate adherence and execution of drug regimens. We did not evaluate patients' perceptions of what "adherence" mean to them, whether it meant acceptance, execution, or persistence of drug therapy [105]. In our meta-analyses of pooled survey data, we found large heterogeneity (as displayed by the I^2 values in Figures 2 and 3), indicating large variation between the surveys. Very little methodological literature deals with pooling proportions, and our findings call for further exploration to determine the importance of this heterogeneity. Finally, there were few studies in developing countries that studied early adopters to antiretroviral therapy. These individuals may not be representative of the larger epidemic and may not have experienced longer-term side effects of therapy.

Table 7. Extended.

Countries	Reference	Daily Schedules		Interpersonal Relationships				
		Have Fixed Routine	Use Reminder Tools	Having Social Support/ Open with Friends and Family	Good Relationship with Provider	Living for Someone	Part of Decision Making with Provider	Family/ Friends Help Remind
Developed countries	Ammassari 2001[56]							
	Brook, 2001[55]							
	Catz, 2000[58]							
	Chesney, 2000[59]							
	Erlen, 2002[62]							
	Eldred, 2002[61]							
	Ferguson, 2002[4]							
	Gibb, 2003[65]							
	Giacomet, 2003[64]							
	Harzke, 2004[66]			✓	✓			
	Heckman, 2004[67]							
	Horne, 2004[69]							
	Johnson, 2003[70]			✓				✓
	Kalichman, 1999[71]							
	Kerr, 1999[72]							
	Kleeberger, 2001[73]							
	Marhefka, 2004[74]							
	Moatti, 2000[75]							
	Mohammed, 2004[76]							
	Mostashari, 1998[79]			✓	✓			✓
	Muma, 1995[80]							
	Murphy, 2003[81]							
	Nieuwkerk, 2001[83]							
	Palmer, 2003[84]							
	Reddington, 2000[86]							
	Reynolds, 2004[87]			✓				
	Savini, 2003[88]							
	Schneider, 2004[89]				✓		✓	
	Siegel, 2000[90]							
	Simoni, 2002[91]							
	Spire, 2002[92]							
	Stein, 2000[93]							
	Tucker, 2004[95]							
	Wagner, 2004[97]	✓			✓			
	Walsh, 2001[98]							
	Weidle, 1999[99]							
	Wilson, 2001[100]							
Developing countries	Byakika-Tusiime, 2005[57]							
	Cupsa, 2000[60]							
	Fassinou, 2004[63]							
	Hofer, 2004[68]							
	Molassiotis, 2002[77]							
	Montreal, 2002[78]							
	Nachega, 2004[82]							
	Pinheiro, 2002[85]							
	Stout, 20004[94]							
	Van Oosterhout, 2005[96]							

It is important to note that the qualitative studies generated a richer spectrum of barriers and facilitators than did the quantitative studies. Qualitative studies are superior at identifying patient-important barriers and facilitators. We would submit that the ideal study of adherence would be one that occurs across several phases and incorporates both qualitative and quantitative elements. For example, to avoid biasing one's investigation with a priori assumptions about what may be important factors relating to adherence in a given population, it is logical to commence a study with qualitative research, thereby allowing the local population to tell the researchers what they believe to be important barriers, rather than the reverse. By using questionnaires developed in settings that are economically or culturally foreseeably different, the surveys force respondents to answer potentially irrelevant questions.

Clearly, the evidence base for barriers and facilitators of adherence is far richer from developed countries than from developing countries. In our analysis we found only two qualitative studies published from developing nation settings. This is sadly paradoxical, given that the vast majority of HIV/AIDS patients live in the developing world, and over the coming decades will constitute a growing proportion, and probably the majority, of the world's HAART recipients.

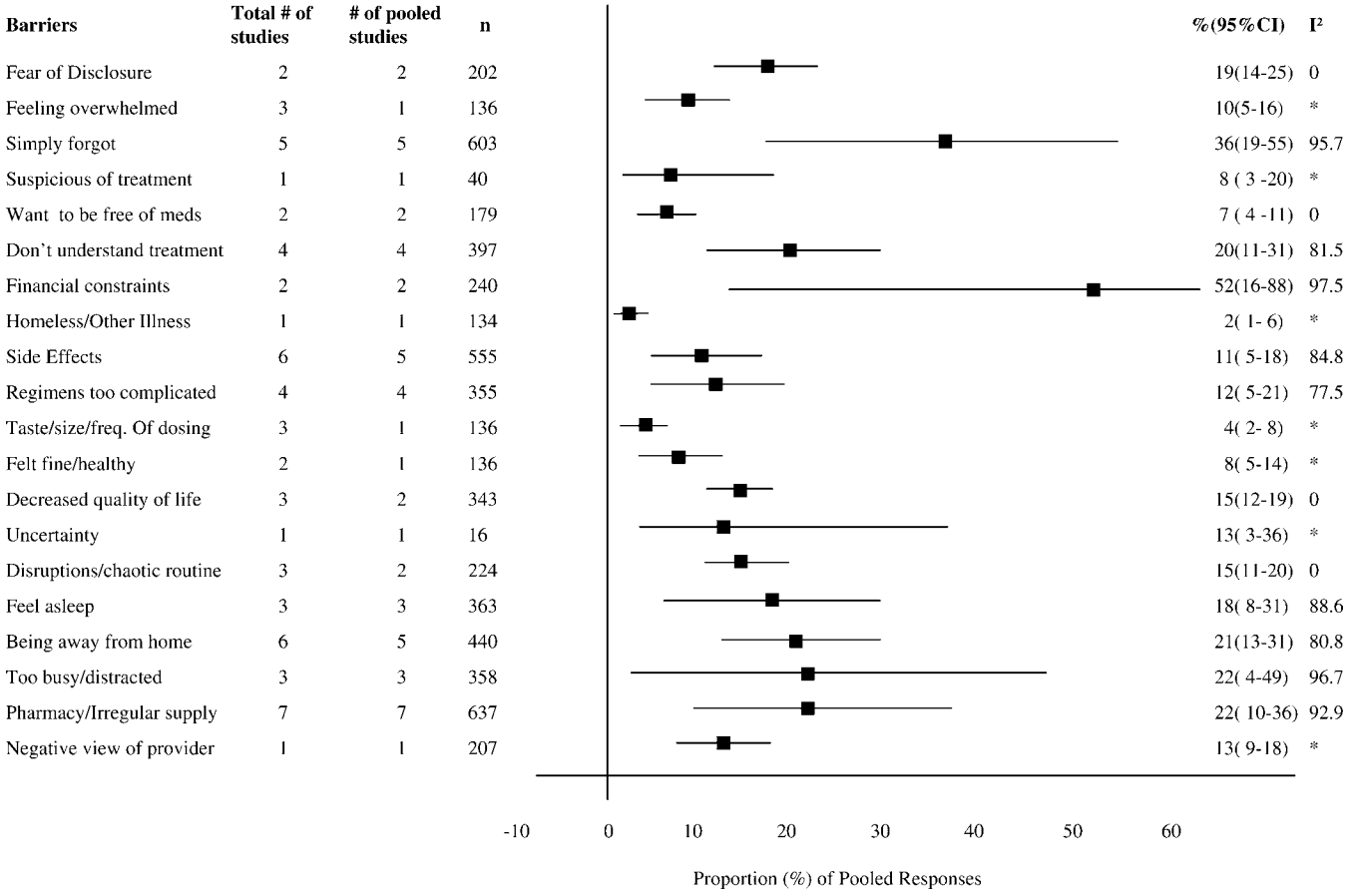

Figure 3. Barriers Reported in Developing Countries
doi:10.1371/journal.pmed.0030438.g003

Consequently, we see further research on HAART adherence in developing countries that incorporates both qualitative and quantitative elements as a priority.

Our findings should influence adherence program delivery systems in developing settings. We found that issues such as fear of disclosure, suspicions about treatment, forgetfulness, and irregular supply were important barriers identified by large proportions of the populations studied. It seems appropriate that before mandating any adherence program, such as disclosure or accompagnateurs, opportunities should be provided for individuals who require opting out [106,107]. Further, in developing settings, the reliability of medication access is an important adherence barrier that individuals have little opportunity to facilitate. Patient-level adherence can be determined only when a steady supply of medication exists.

We identified a broad range of barriers and facilitators to adherence. These barriers should be inferred as guides for interventional research to improve adherence rates. Given the many factors tabulated in this review, clinicians should use this information to engage in open discussion with patients to promote adherence and identify barriers and facilitators within their own populations. The methodology we used to pool the quantitative data is novel and may prove a useful methodological tool for generalizing patient-important issues.

Acknowledgments

Author contributions. EJM, JN, SS, BR, PW, KW, and CC designed the study. EJM, JN, DRB, SS, BR, PW, and CC analyzed the data. EJM, JN, DRB, SS, BR, PW, KW, IB, CJG, and CC contributed to writing the paper. DRB contributed to the editing of the manuscript and interpretation of data in context of international adherence literature. BR was involved in article selection. PW was involved in paper searching (from abstract to full text), paper review, data extraction and analysis.

References

1. Hogg RS, O'Shaughnessy MV, Gataric N, Yip B, Craib K, et al. (1997) Decline in deaths from AIDS due to new antiretrovirals. Lancet 349: 1294.
2. Mannheimer SB, Matts J, Telzak E, Chesney M, Child C, et al. (2005) Quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence. AIDS Care 1: 10–22.
3. Altice FL, Mostashari F, Friedland GH (2001) Trust and the acceptance of and adherence to antiretroviral therapy. J Acquir Immune Defic Syndr 1: 47–58.
4. Ferguson T, Stewart KE, Funkhouser E, Tolson J, Westfall AO, et al. (2002) Patient-percieved barriers to antiretroviral adherence: associations with race. AIDS Care 5: 607–617.
5. Friedland G, Williams A (1999) Attaining higher goals in HIV treatment: The central importance of adherence. AIDS (Suppl 1): S61–S72.
6. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, et al. (2000) Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 1: 21–30.
7. Bangsberg DR, Hecht FM, Charlebois ED, Zolopa AR, Holodniy M, et al. (2000) Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. AIDS 4: 357–366.
8. Bangsberg DR, Charlebois ED, Grant RM, Holodniy M, Deeks SG, et al. (2003) High levels of adherence do not prevent accumulation of HIV drug resistance mutations. AIDS 13: 1925–1932.

9. Bangsberg DR, Perry S, Charlebois ED, Clark RA, Roberston M, et al. (2001) Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS 9: 1181–1183.
10. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, et al. (2003) Is there a baseline CD4 cell count that precludes a survival response to modern antiretroviral therapy? AIDS 5: 711–720.
11. Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, et al. (2006) Adherence to antiretroviral therapy in sub-Saharan Africa and North America: A meta-analysis. JAMA 6: 679–690.
12. United Nations Development Programme (2004) Human Development Reports. Available: http://hdr.undp.org. Accessed 4 October 2006.
13. Mills E, Jadad AR, Ross C, Wilson K (2005) Systematic review of qualitative studies exploring parental beliefs and attitudes toward childhood vaccination identifies common barriers to vaccination. J Clin Epidemiol 11: 1081–1088.
14. Freeman MF, Tukey JW (1950) Transformations related to the angular and the square root. Ann Math Stat: 607–611.
15. Fleiss JL (1993) The statistical basis of meta-analysis. Stat Methods Med Res 2: 121–145.
16. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 3: 177–188.
17. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 11: 1539–1558.
18. Abel E, Painter L (2003) Factors that influence adherence to HIV medications: Perceptions of women and health care providers. J Assoc Nurses AIDS Care 4: 61–69.
19. Golin C, Isasi F, Bontempi JB, Eng E (2002) Secret pills: HIV-positive patients' experiences taking antiretroviral therapy in North Carolina. AIDS Educ Prev 4: 318–329.
20. Miller L, Huffman HB, Weidmer BA, Hays RD (2002) Patient preferences regarding antiretroviral therapy. Int J STD AIDS 13: 593–601.
21. Misener T, Sowell RL (1998) HIV-infected women's decisions to take antiretrovirals. West J Nurs Res 4: 431–447.
22. Murphy D, Johnston Roberts K, Martin DJ, et al. (2000) Barriers to antiretroviral adherence among HIV-infected adults. AIDS Patient Care STDS 1: 47–58.
23. Murphy D, Johnston Roberts K, Hoffman D, et al. (2003) Barriers and successful strategies to antiretroviral adherence among HIV-infected monolingual Spanish-speaking patients. AIDS Care 2: 217–230.
24. Powell-Cope G, White J, Henkelman EJ, Turner BJ (2003) Qualitative and quantitative assessments of HAART adherence of substance abusing women. AIDS Care 2: 239–249.
25. Proctor V, Tesfa A, Tompkins DC (1999) Barriers to adherence to highly active antiretroviral therapy as expressed by people living with HIV/AIDS. AIDS Patient Care STDS 9: 535–544.
26. Richter D, Sowell RL, Pluto DM (2002) Attitudes toward antiretroviral therapy among African American women. Am J Health Behav 1: 25–33.
27. Schilder A, Kennedy C, Goldstone IL, Ogden RD, Hogg RS, et al. (2001) "Being dealt with as a whole person." Care seeking and adherence: The benefits of culturally competent care. Soc Sci Med 52: 1643–1659.
28. Stone V, Clarke J, Lovell J, Steger KA, Hirschhorn LR, et al. (1998) HIV/AIDS patients' perspectives on adhering to regimens containing protease inhibitors. J Gen Intern Med 13: 586–593.
29. Westerfelt A (2004) A qualitative investigation of adherence issues for men who are HIV positive. Social Work 2: 231–240.
30. Adamian M, Golin CE, Shain LS, DeVellis B (2004) Brief motivational interviewing to improve adherence to antiretroviral therapy: Development and qualitative plot assessment of an intervention. AIDS Patient Care STDS 4: 229–238.
31. Barton Laws M, Wilson IB, Bowser DM, Kerr SE (2000) Taking antiretroviral therapy for HIV infection: Learning from patients' stories. J Gen Intern Med: 848–858.
32. Graney M, Bunting SM, Russell CK (2003) HIV/AIDS medication adherence factors: Inner-city clinic patients' self-reports. Tenn Med 2: 73–78.
33. Hill Z, Kendall C, Fernandez M (2003) Patterns of adherence to antiretrovirals: Why adherence has no simple measure. AIDS Patient Care STDS 10: 519–525.
34. Johnston Roberts K (2002) Physician-patient relationships, patient satisfaction and antiretroviral medication adherence among HIV-infected adults attending a public health clinic. AIDS Patient Care STDS 1: 43–50.
35. Klitzman R, Kirshenbaum SB, Dodge B, Remien RH, Ehrhardt AA, et al. (2004) Intricacies and inter-relationships between HIV disclosure and HAART: A qualitative study. AIDS Care 5: 628–640.
36. Malcolm S, Ng JJ, Rosen RK, Stone VE (2003) An examination of HIV/AIDS patients who have excellent adherence to HAART. AIDS Care 2: 251–261.
37. Meystre-Agustoni G, Dubois-Arber F, Cochand P, Telenti A (2000) Antiretroviral therapies from the patient's perspective. AIDS Care 6: 717–721.
38. Oggins J (2003) Notions of HIV and medication among multiethnic people living with HIV. Health Social Work 1: 53–63.
39. Reback C, Larkins S, Shoptaw S (2003) Methamphetamine abuse as a barrier to HIV medication adherence among gay and bisexual men. AIDS Care 6: 775–785.
40. Ryan G, Wagner GJ (2003) Pill taking 'routinization': A critical factor to understanding episodic medication adherence. AIDS Care 6: 795–806.
41. Wilson H, Hutchinson SA, Holzemer WL (2002) Reconciling incompatibilities: A grounded theory of HIV medication adherence and symptom management. Qual Health Res 10: 1309–1322.
42. Witteveen E, van Ameijden EJC (2002) Drug users and HIV-combination therapy (HAART): Factors with impede or facilitate adherence. Subst Use Misuse 14: 1905–1925.
43. Wood S, Tobias C, McCree J (2004) Medication adherence for HIV positive women caring for children: In their own words. AIDS Care 7: 909–913.
44. Hammami N, Nostlinger C, Hoeree T, Lefevre P, Jonckheer T, et al. (2004) Integrating adherence to highly active antiretroviral therapy into children's daily lives: A qualitative study. Pediatrics 5: e591–e597.
45. Adam B, Maticka-Tyndale E, Cohen JJ (2003) Adherence practices among people living with HIV. AIDS Care 2: 263–274.
46. Aversa S, Kimberlin C (1996) Psychosocial aspects of antiretroviral medication use among HIV patients. Patient Educ Couns 29: 207–219.
47. Brigido L, Rodrigues R, Casseb J, Oliveira D, Rossetti M, et al. (2001) Impact of adherence to antiretroviral therapy in HIV-1-infected patients at a university public service in Brazil. AIDS Patient Care STDS 11: 587–593.
48. Goode M, McMaugh A, Crisp J, Wales S (2003) Adherence issues in children and adolescents receiving highly active antiretroviral therapy. AIDS Care 3: 403–408.
49. Kemppainen J, Levine R, Buffum M, Holzemer W, Finley P, et al. (2004) Antiretroviral adherence in persons with HIV/AIDS and severe mental illness. J Nerv Ment Dis 192: 395–404.
50. Remien R, Hirky AE, Johnson MO, Weinhardt LS, Whittier D, et al. (2003) Adherence to medication treatment: A qualitative study of facilitators and barriers among a diverse sample of HIV+ men and women in four US cities. AIDS Behavior 1: 61–72.
51. Sankar A, Luborsky M, Schuman P, Roberts G (2002) Adherence discourse among African-American women taking HAART. AIDS Care 2: 203–218.
52. Weiser S, Wolfe W, Bangsberg D, Thior I, Gilbert P, et al. (2003) Barriers to antiretroviral adherence for patients living with HIV infection and AIDS in Botswana. J Acquir Immune Defic Syndr 3: 281–288.
53. Ka'opua L, Mueller CW (2004) Treatment adherence among Native Hawaiians living with HIV. *Social Work* 1: 55–62.
54. Johnston Roberts K, Mann T (2000) Barriers to antiretroviral medication adherence in HIV-infected women. AIDS Care 4: 377–386.
55. Brook M, Dale A, Tomlinson D, Waterworth C, Daniels D, et al. (2001) Adherence to highly active antiretroviral therapy in the real world: Experience of twelve English HIV units. AIDS Patient Care STDS 9: 491–494.
56. Ammassari A, Murri R, Pezzotti P, Trotta MP, Ravasio L, et al. (2001) Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. J Acquir Immune Defic Syndr 5: 445–449.
57. Byakika-Tusiime J, Oyugi JH, Tumwikirize WA, Katabira ET, Mugyenyi PN, et al. (2005) Adherence to HIV antiretroviral therapy in HIV+ Ugandan patients purchasing therapy. Int J STD AIDS 16: 38–41.
58. Catz S, Kelly JA, Bogart LM, Benotsch EG, McAuliffe TL (2000) Patterns, correlates and barriers to medication adherence among persons prescribed new treatments for HIV disease. Health Psychol 2: 124–133.
59. Chesney M, Ickovics JR, Chambers DB, Gifford AL, Neidig J, et al. (2000) Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: The AACTG adherence instruments. AIDS Care 3: 255–266.
60. Cupsa A, Ghenonea C, Bulucea D, Dinescu S (2000) Factors with a negative influence on compliance to antiretroviral therapies. Ann N Y Acad Sci 918: 351–354.
61. Eldred L, Wu AW, Chaisson RE, Moore RD (1998) Adherence to antiretroviral and pneumocystis prophylaxis in HIV disease. J Acquir Immune Defic Syndr Hum Retrovirol 2: 117–125.
62. Erlen J, Sereika SM, Cook RL, Hunt SC (2002) Adherence to antiretroviral therapy among women with HIV infection. J Obstet Gynecol Neonatal Nurs 31: 470–477.
63. Fassinou P, Elenga N, Rouet F, Laguide R, Kouakoussui KA, et al. (2004) Highly active antiretroviral therapies among HIV-1 infected children in Abidjan, Cote d'Ivoire. AIDS 18: 1905–1913.
64. Giacomet V, Albano F, Starace F, de Franciscis A, Giaquinto C, et al. (2003) Adherence to antiretroviral therapy and its determinants in children with human immunodeficiency virus infection: A multicenter, national study. Acta Paediatr 92: 1398–1402.
65. Gibb D, Goodall RL, Giacomet V, McGee L, Compagnucci A, et al. (2003) Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. Pediatr Infect Dis J 22: 56–62.
66. Harzke A, Williams ML, Nilsson-Schonnesson L, Ross MW, Timpson S, et al. (2004) Psychosocial factors associated with adherence to antiretroviral medications in a sample of HIV-positive African American drug users. AIDS Care 4: 458–470.
67. Heckman B, Catz SL, Heckman TG, Miller JG, Kalichman SC (2004) Adherence to antiretroviral therapy in rural persons living with HIV disease in the United States. AIDS Care 2: 219–230.

68. Hofer C, Schechter M, Harrison LH (2004) Effectiveness of antiretroviral therapy among patients who attend public HIV clinics in Rio de Janeiro, Brazil. J Acquir Immune Defic Syndr 4: 967–971.
69. Horne R, Buick D, Fisher M, Leake H, Cooper V, et al. (2004) Doubts about necessity and concerns about adverse effects: Identifying the types of beliefs that are associated with non-adherence to HAART. Int J STD AIDS 15: 38–44.
70. Johnson M, Catz SL, Remien RH, Rotheram-Borus MJ, Morin SF, et al. (2003) Theory-guided, empirically supported avenues for intervention on HIV medication nonadherence: Findings from the healthy living project. AIDS Patient Care STDS 12: 645–656.
71. Kalichman S, Catz S, Ramachandran B (1999) Barriers to HIV/AIDS treatment and treatment adherence among African-American adults with disadvantaged education. J Natl Med Assoc 91: 439–446.
72. Kerr T, Palepu A, Barnes G, Walsh J, Hogg R, et al. (1999) Psychosocial determinants of adherence to highly active antiretroviral therapy among injection drug users in Vancouver. Antiviral Ther 9: 407–414.
73. Kleeberger C, Phair JP, Strathdee SA, Detels R, Kingsley L, et al. (2001) Determinants of heterogenous adherence to HIV-antiretroviral therapies in the multicenter AIDS Cohort Study. J Acquir Immune Defic Syndr 26: 82–92.
74. Marhefka S, Farley JJ, Rodrigue JR, Sandrik LL, Sleasman JW, et al. (2004) Clinical assessment of medication adherence among HIV-infected children: Examination of the Treatment Interview Protocol (TIP). AIDS Care 3: 323–337.
75. Moatti J, Carrieri MP, Spire B, Gastaut JA, Cassuto JP, et al. (2000) Adherence to HAART in French HIV-infected injecting drug users: The contribution of buprenorphine drug maintenance treatment. AIDS 14: 151–155.
76. Mohammed H, Kieltyka L, Richardson-Alston G, Magnus M, Fawal H, et al. (2004) Adherence to HAART among HIV-infected persons in rural Louisiana. AIDS Patient Care STDS 5: 289–296.
77. Molassiotis A, Nahas-Lopez V, Chung WY, Lam SW, Li CK, et al. (2002) Factors associated with adherence to antiretroviral medication in HIV-infected patients. Int J STD AIDS 13: 301–310.
78. Monreal M, da Cunha RV, Trinca LA (2002) Compliance to antiretroviral medication as reported by AIDS patients assisted at the University Hospital of the Federal University of Mato Grosso do Sul. Braz J Infect Dis 1: 8–14.
79. Mostashari F, Riley E, Selwyn PA, Altice FL (1998) Acceptance and adherence with antiretroviral therapy among HIV-infected women in a correctional facility. J Acquir Immune Defic Syndr Hum Retrovirol 4: 341–348.
80. Muma R, Ross MW, Parcel GS, Pollard RB (1995) Zidovudine adherence among individuals with HIV infection. AIDS Care 4: 439–447.
81. Murphy D, Sarr M, Durako SJ, Moscicki AB, Wilson CM, et al. (2003) Barriers to HAART adherence among human immunodeficiency virus-infected adults. Arch Pediatr Adolesc Med 157: 249–255.
82. Nachega J, Stein DM, Lehman DA, Hlatshwayo D, Mothopeng R, et al. (2004) Adherence to antiretroviral therapy in HIV-infected adults in Soweto, South Africa. AIDS Res Hum Retroviruses 10: 1053–1056.
83. Nieuwkerk P, Sprangers MA, Burger DM, Hoetelmans RM, Hugen PW, et al. (2001) Limited patient adherence to highly active antiretroviral therapy for HIV-1 infection in an observational cohort study. Arch Intern Med 161: 1962–1968.
84. Palmer N, Salcedo J, Miller AL, Winiarski M, Arno P (2003) Psychiatric and social barriers to HIV medication adherence in a triply diagnosed methadone population. AIDS Patient Care STDS 12: 635–644.
85. Pinheiro C, de-Carvalho-Leite JC, Drachler ML, Silveira VL (2002) Factors associated with adherence to antiretroviral therapy in HIV/AIDS patients: A cross-sectional study in Southern Brazil. Braz J Med Biol Res 35: 1173–1181.
86. Reddington C, Cohen J, Baldillo A, Toye M, Smith D, et al. (2000) Adherence to medication regimens among children with human immunodeficiency virus infection. Pediatr Infect Dis J 19: 1148–1153.
87. Reynolds N, Testa MA, Marc LG, Chesney MA, Neidig JL, et al. (2004) Factors influencing medication adherence beliefs and self-efficacy in persons naive to antiretroviral therapy: A multicenter, cross-sectional study. AIDS Behavior 2: 141–150.
88. Savini C, James CW, DiGuglielmo DJ (2003) Survey of patient and clinician attitudes on adherence in a rural HIV clinic. J Assoc Nurses AIDS Care 3: 72–75.
89. Schneider J, Kaplan SH, Greenfield S, Li W, Wilson IB (2004) Better physician-patient relationships are associated with higher reported adherence to antiretroviral therapy in patients with HIV infection. J Gen Intern Med 19: 1096–1103.
90. Siegel K, Karus D, Schrimshaw EW (2000) Racial differences in attitude toward protease inhibitors among older HIV-infected men. AIDS Care 4: 423–434.
91. Simoni J, Frick PA, Lockhart D, Liebovitz D (2002) Mediators of social support and antiretroviral adherence among an indigent population in New York City. AIDS Patient Care STDS 9: 431–439.
92. Spire B, Duran S, Souville M, Leport C, Raffi F, et al. (2002) Adherence to highly active antiretroviral therapies (HAART) in HIV-infected patients: From a predictive to a dynamic approach. Soc Sci Med 54: 1481–1496.
93. Stein M, Rich JD, Maksad J, Chen MH, Hu P, et al. (2000) Adherence to antiretroviral therapy among HIV-infected methadone patients: Effect of ongoing illicit drug use. Am J Drug Alcohol Abuse 2: 195–205.
94. Stout B, Leon MP, Niccolai LM (2004) Nonadherence to antiretroviral therapy in HIV-positive patients in Costa Rica. AIDS Patient Care STDS 5: 297–304.
95. Tucker JS, Orlando M, Burnam MA, Sherbourne CD, Kung FY, et al. (2004) Psychosocial mediators of antiretroviral nonadherence in HIV-positive adults with substance use and mental health problems. Health Psychol 4: 363–370.
96. van Oosterhout JJ, Bodasing N, Kumwenda JJ, Nyirenda C, Mallewa J, et al. (2005) Evalution of antiretroviral therapy results in a resource-poor setting in Blantyre, Malawi. Trop Med Int Health 5: 464–470.
97. Wagner G, Kanouse DE, Koegel P, Sullivan G (2004) Correlates of HIV antiretroviral adherence in persons with serious mental illness. AIDS Care 4: 501–506.
98. Walsh J, Horne R, Dalton M, Burgess AP, Gazzard BG (2001) Reasons for non-adherence to antiretroviral therapy: Patients' perspectives provide evidence of multiple causes. AIDS Care 6: 709–720.
99. Weidle PJ, Ganera CE, Irwin KL, McGowan JP, Ernst JA, et al. (1999) Adherence to antiretroviral medications in an inner city population. J Acquir Immune Defic Syndr 5: 498–502.
100. Wilson TE, Ickovics JR, Fernandez MI, Koenig LJ, Walter E, et al. (2001) Self-reported zidovudine adherence among pregnant women with human immunodeficiency virus infection in four US states. Am J Obstet Gynecol 184: 1235–1240.
101. Mills EJ, Montori VM, Ross CP, Shea B, Wilson K, et al. (2005) Systematically reviewing qualitative studies complements survey design: An exploratory study of barriers to paediatric immunisations. J Clin Epidemiol 11: 1101–1108.
102. Mills E, Wilson K, Rachlis B, Griffith L, Wu P, et al. (2006) Barriers to participation in HIV drug trials: A systematic review. Lancet Infect Dis 1: 32–38.
103. Mills EJ, Seely D, Rachlis B, Griffith L, Wu P, et al. (2006) Barriers to participation in clinical trials of cancer: A meta-analysis and systematic review of patient-reported factors. Lancet Oncol 2: 141–148.
104. Devereaux PJ, Choi PT, El-Dika S, Bhandari M, Montori VM, et al. (2004) An observational study found that authors of randomized controlled trials frequently use concealment of randomization and blinding, despite the failure to report these methods. J Clin Epidemiol 12: 1232–1236.
105. Urquhart J, Vrijens B (2005) New findings about patient adherence to prescribed drug dosing regimens: An introduction to pharmionics. Eur J Hosp Pharm Sci 55: 103–106.
106. Liechty CA, Bangsberg DR (2003) Doubts about DOT: Antiretroviral therapy for resource-poor countries. AIDS 9: 1383–1387.
107. Farmer P, Leandre F, Mukherjee J, Gupta R, Tarter L, et al. (2001) Community-based treatment of advanced HIV disease: Introducing DOT-HAART (directly observed therapy with highly active antiretroviral therapy). Bull World Health Organ 12: 1145–1151.
108. Johnston-Roberts K, Mann T (2003) Adherence to antiretroviral medications in HIV/AIDS care: A narrative exploration of one woman's foray into intentional nonadherence. Health Care Women Int 24: 552–564

Editors' Summary

Background. The World Health Organization has estimated that in 2005, about 38 million people worldwide were living with HIV/AIDS; the mortality caused by HIV/AIDS is very high. Antiretroviral drugs are effective at controlling the disease and extending life span. However, it is important for people to stick to the drug regimens exactly in order to keep levels of HIV low, prevent it from becoming resistant to drugs, and stop the illness from progressing. However, many people find it very difficult to take antiretroviral drugs precisely as they should. There is already some evidence from research studies on the reasons why this is the case. There are two different research approaches taken by these studies: "qualitative" methods, which try to find out about attitudes and behaviors using focus groups, interviews, or other techniques; and "quantitative" methods, which try to find out about peoples' opinions and experience using surveys with set questions for the participants to answer, and then count the different responses.

Why Was This Study Done? The investigators wanted to put together all of the available evidence from published research studies (called doing a "systematic review") on which factors affected people's adherence to antiretroviral drugs. They wanted to do a systematic review because it is thought to be a very rigorous way of appraising all the available evidence (although there is considerable debate about the value of using such a method to analyze the results of qualitative research).

What Did the Researchers Do and Find? The study team searched biomedical literature databases as well as conference abstracts and research registries using a defined set of search queries. They screened all the scientific papers they found; those reporting results of original research into factors affecting antiretroviral adherence were then analyzed in more detail. 84 relevant studies were identified, of which 37 used "qualitative" methods (focus groups, interviews, open-ended questioning) and 47 used "quantitative" methods (surveys). Most of these studies had been carried out in the developed world. Then, the researchers extracted the factors affecting adherence from the original studies, which could be either "positive" factors (helping adherence) or "negative" ones (making adherence more difficult). They classified the factors into four key themes: "patient related" (e.g., seeing positive results, fear of disclosure, being depressed); "beliefs about medication" (e.g., faith in how well the drugs worked, side effects); "daily schedules" (e.g., using reminder tools, disruptions to routine); and "interpersonal relationships" (e.g., trusting relations with health-care provider; social isolation).

Many barriers to adherence were common to both developed and developing settings. Some factors were unique to the studies conducted in the developing world, such as financial constraints and problems with traveling to get access to treatment. Fear of disclosure was an important barrier identified in many of the studies.

What Do These Findings Mean? The researchers combined the results of many different studies and identified factors that help or obstruct adherence to antiretroviral treatment. By identifying influences common to the different settings, greater weight can be placed on the factors that were identified. Only 12 of the studies included in this research were from the developing world, where the majority of HIV/AIDS patients live; hence more work is needed to examine and address the factors influencing antiretroviral adherence in these parts of the world. This study provides researchers and health policy makers with a starting point for changes that might help to ensure greater adherence to antiretroviral treatment.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.0030438.

- Medline Plus information on AIDS medicines (Medline Plus is a service of the US National Library of Medicine and the National Institutes of Health)
- Joint United Nations Programme on HIV/AIDS has information about the state of the HIV/AIDS epidemic worldwide
- The World Health Organization has an HIV/AIDS program site providing comprehensive information on the HIV/AIDS epidemic worldwide
- The World Health Organization pages on antiretroviral therapy