Adherence to Antiretroviral Therapy in Sub-Saharan Africa and North America: A Meta-analysis

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JAMA. 2006;296(6):679-690 (doi:10.1001/jama.296.6.679)

http://jama.ama-assn.org/cgi/content/full/296/6/679

REVIEW

Adherence to Antiretroviral Therapy in Sub-Saharan Africa and North America

A Meta-analysis

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Context Adherence to antiretroviral therapy is a powerful predictor of survival for individuals living with human immunodeficiency virus (HIV) and AIDS. Concerns about incomplete adherence among patients living in poverty have been an important consideration in expanding the access to antiretroviral therapy in sub-Saharan Africa.

Objective To evaluate estimates of antiretroviral therapy adherence in sub-Saharan Africa and North America.

Data Sources Eleven electronic databases were searched along with major conference abstract databases (inclusion dates: inception of database up until April 18, 2006) for all English-language articles and abstracts; and researchers and treatment advocacy groups were contacted.

Study Selection and Data Abstraction To best reflect the general population, studies of mixed populations in both North America and Africa were selected. Studies evaluating specific populations such as men only, homeless individuals, or drug users, were excluded. The data were abstracted in duplicate on study adherence outcomes, thresholds used to determine adherence, and characteristics of the populations. A random-effects meta-analysis was performed in which heterogeneity was examined using multivariable random-effects logistic regression. A sensitivity analysis was performed using Bayesian methods.

Data Synthesis Thirty-one studies from North America (28 full-text articles and 3 abstracts) and 27 studies (9 full-text articles and 18 abstracts) from sub-Saharan Africa were included. African studies represented 12 sub-Saharan countries. Of the North American studies, 71% used patient self-report to assess adherence; this was true of 66% of the African assessments. Studies reported similar thresholds for adherence monitoring (eg, 100%, >95%, >90%, >80%). A pooled analysis of the North American studies (17 573 patients total) indicated a pooled estimate of 55% (95% confidence interval, 49%-62%; I^2, 98.6%) of the populations achieving adequate levels of adherence. Our pooled analysis of African studies (12 116 patients total) indicated a pooled estimate of 77% (95% confidence interval, 68%-85%; I^2, 98.4%). Study continent, adherence thresholds, and study quality were significant predictors of heterogeneity. Bayesian analysis was used as an alternative statistical method for combining adherence rates and provided similar findings.

Conclusion Our findings indicate that favorable levels of adherence, much of which was assessed via patient self-report, can be achieved in sub-Saharan African settings and that adherence remains a concern in North America.

JAMA. 2006;296:679-690 www.jama.com

ANTIRETROVIRAL THERAPY (ART) has improved the health of many human immunodeficiency virus (HIV) positive individuals who otherwise would have died. Treatment efficacy relies, however, on sustained adherence, which constitutes a serious challenge to those receiving ART.[1,2] The regimens are often complicated and can include varying dosing schedules, dietary restrictions, and adverse effects.[3] Consistently high levels of adherence are necessary for reliable viral suppression[4,5] and prevention of resistance,[6] disease progression,[7] and death.[8]

Access to ART is limited for the majority of individuals living with HIV/AIDS in sub-Saharan Africa. The World Health Organization's initiative to have 3 million individuals receiving ART by 2005 ("3 by 5") has yet to meet its planned provision of care timelines, leaving more than two thirds of the global number of individuals needing care worldwide without access to ART.[9]

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Although sub-Saharan Africa represents only 10% of the world's population, it represents 77% of women with HIV, 79% of AIDS deaths, and 92% of the world's AIDS orphans.[10] There has been concern that African patients, many of whom live in poverty and lack formal education, will have suboptimal adherence to ART, which could lead to the development and spread of drug resistence.[11,12]

Are concerns of poor adherence in Africans justified? No study has performed a systematic meta-analysis of adherence levels in Sub-Saharan Africa. We conducted a systematic review of available ART adherence data in both Africa and a resource-rich setting, North America, to determine the level of adherence in emerging African treatment programs relative to the more established North American programs.

METHODS

Eligibility Criteria

Prospective studies assessing adherence rates as a primary or secondary outcome (ie, noninterventional) in general HIV populations in North America and Africa were included. Studies had to have reported a threshold for adherence monitoring (eg, 100%, >95%, >90%, >80%). Studies were excluded if they reported adherence as a mean of all doses taken by the combined group of participants; were conducted in countries outside North America and Africa; contained experimental interventions to promote adherence because these studies do not reflect existing clinical settings[13]; or assessed only specific groups (eg, drug users, children, homeless individuals, homosexuals, men or women only)[14,15] because the focus was adherence rates in general populations of HIV-positive individuals.

Search Strategy

In consultation with an information specialist (Pearl Raju, PhD, Centre for International Health and Human Rights Studies, Toronto, Ontario), 3 of the authors (E.M., B.R., P.W.) developed search strategies. First, search terms that may indicate adherence (eg, *adherence, compliance, pill counts, Medication Event Monitoring System* [MEMS], *directly observed*) were identified. The searches combined these terms with Medical Subject Headings for HIV and were conducted from May 2005 to April 18, 2006, independently, in duplicate (B.R., P.W.). MEDLINE via PubMed, EMBASE, Cochrane CENTRAL, AIDSLINE, AMED, CINAHL, TOXNET, Development and Reproductive Toxicology Hazardous Substances Databank, Psych-info, and Web of Science were searched with the inclusion dates of the inception of the individual database up until April 18, 2006, except for AIDSLINE, which was searched from inception up until 2000 when its new citations ended. The Web sites of major HIV conferences also were searched, specifically all International AIDS Society conferences (up to Rio de Janeiro, Brazil, in July 2005) and all Conferences on Retroviruses and Opportunistic Infections (up to Denver in February 2006). Lay publications and Web sites were also searched including the Canadian AIDS Treatment Information Exchange publications, Médecins sans Frontières, AIDS Treatment News, and Google. Individual clinical researchers and AIDS cohort trial groups were contacted via e-mail and telephone (BC Centre for Excellence in HIV/AIDS, International AIDS Society, and Médecins sans Frontières) and asked if they were aware of any unpublished studies.

Study Selection

Using a predefined protocol (available from corresponding author on request), 2 investigators (E.M., P.W.), working independently, scanned all of the abstracts and obtained the full text of articles and reports from nongovernmental organizations that indicated or suggested a measurement of adherence had been achieved. After obtaining the full reports of the candidate studies (either a full peer-reviewed article, conference abstract, or non–peer-reviewed article), the same reviewers independently assessed eligibility. Reviewers were not blinded to study authors, study conclusions, and outcomes because blinding has been shown to have little effect on systematic reviews.[16] To obtain the full information regarding conference abstracts, the studies' authors were contacted via e-mail and telephone. After all potentially relevant full-text articles and abstracts were identified, 2 of the authors (E.M., P.W.) and a member of the study team (Dugald Seely, ND, MSc, University of Toronto, Toronto, Ontario) met to achieve consensus regarding eligibility.

Data Extraction

Between May 1, 2005, and April 23, 2006, data extraction was conducted independently, in duplicate, using a standardized form. Data abstractors collected information about the study country, study populations (age and sex), participant ethnicity (as classified in the original study), sample size, methods of adherence measurement, and outcomes. When more than 1 adherence measurement was used, data on all measures used were extracted and the most objective method was chosen for this analysis (eg, MEMS). Adherence measurements were defined in the studies as primary adherence thresholds. No studies reported exclusions of patients due to adherence levels prior to the study. However, in 8 studies, data are only reported for patients who completed the adherence assessments. In this case, only the data for study completers were used. Data on study settings (eg, nongovernmental organization clinic, specialist clinic) and predictors of ART adherence (eg, adherence threshold, use of MEMS, quality of assessment) were abstracted. Finally, where available, data were abstracted regarding whether patients receiving ART paid for it or received the therapy for free. Data on populations' disease state were not abstracted due to large heterogeneity of each study population. The data were entered into an electronic database such that duplicate entries existed for each study; when the 2 entries did not match, we reached consensus through discussion and if necessary requested third-

party arbitration. We considered study quality according to whether studies used multiple measurement tools to assess adherence (n=9) and when applicable considered loss to follow-up of greater than 20% of the study sample as being poor (n=10).

Data Analysis

To assess interrater reliability on inclusion of the articles and abstracts, the ϕ statistic, which provides a measure of interobserver agreement independent of chance, was used.[17] Descriptive analyses were used to compare the number of full-text articles published over time. To determine if complexity of regimens might yield differing adherence rates, a *z* test was used for the pooled North American adherence rates prior to and after 2002, the year when the African studies first appeared in print. Thresholds for adherence were considered as greater than or equal to the cutoff levels. To determine pooled proportions of study participants adherent to individual study measurement thresholds, the variances of the raw proportions (r/n) were stabilized using a Freeman-Tukey–type arcsine square root transformation[18,19]: $y=\arcsin[\sqrt{(r/(n+1)}]+\arcsin[\sqrt{(r+1)/(n+1)}]$, with a variance of $1/(n+1)$, where *n* is the denominator for population size. The I^2 statistic was calculated as a measure of the proportion of the overall variation in adherence that was attributable to between-study heterogeneity.[20] We anticipated large heterogeneity considering the varied populations, health care delivery systems, and course of the epidemic. The DerSimonian-Laird random-effects method was used to pool the transformed proportions,[21,22] which recognizes and anchors studies as a sample of all potential studies, and incorporates an additional between-study component to the estimate of variability. Random-effects logistic regression was used to explore this heterogeneity and to compare continents after adjusting for the potential confounding due to adherence thresholds (100%, >95%, >90%, >80%); assessment criteria (self-reported, pharmacy refills); whether the study participant paid for ART; loss to follow-up (>20%); and clinic settings (outpatient, nongovernmental organization). For any missing data on covariates, the authors of the articles were contacted and when there was no response, these studies were considered negative. A sensitivity analysis was also conducted to examine the impact of these negative studies on the meta-regression. The unadjusted and regression-adjusted estimates and odds ratios were calculated by continent. Separate pooled analyses were conducted of all studies using the same cutoff thresholds for adherence. For sensitivity analysis, we confirmed that a Mann-Whitney U test gave results consistent with those of the other methods used to compare continents. The sensitivity analysis was conducted using a Bayesian random-effects model with an alternative logit transformation in addition to Monte Carlo Markov Chain simulations of variability.[23] Forest plots were created for each continent, showing individual study proportions with Clopper-Pearson confidence intervals (CIs) and the overall DerSimonian-Laird pooled estimate. Each individual study in the forest plot represents the proportion of the study population meeting the threshold for appropriate adherence, as defined in the original studies. Results are reported as combined adherence proportions with 95% CIs. All *P* values are exact and $P<.05$ was considered significant. Analyses were conducted using StatsDirect version 2.5.2 (StatsDirect Ltd, Cheshire, England), which was developed by 1 of us (I.B.), Stata version 9.0 (StataCorp, College Station, Tex), and OpenBUGS version 2.1 (http://www.mathstat.helsinki.fi/openbugs/).

RESULTS

From the initial searches (May-November 2005), 136 relevant abstracts of full text articles were identified. Of these, 60 studies passed the first screening. There was near perfect agreement between the reviewers on the inclusion of 28 full-text articles and 2 abstracts addressing North American studies and 7 full-text articles and 15 abstracts addressing African studies ($\phi=0.91$). In a search update (April 18, 2006), 1 abstract addressing adherence in North American settings, 2 full-text African studies, and 3 abstracts addressing adherence in African settings were identified. Agreement on abstract inclusion was perfect. A flow diagram of studies included in the analysis is detailed in FIGURE 1.

The characteristics of the North American studies[3,4,24-52] appear in TABLE 1. All full-text articles and abstracts were published in English. Of the 28 full-text articles reporting on studies conducted in North American settings,[3,4,24-47] 26 were from the United States and 2 were from Canada.[48,49] Of the 3 abstracts reporting on studies conducted in North American settings, 2 assessed US populations[50,51] and 1 assessed a Canadian population.[52] The characteristics of the African studies[53-79] appear in TABLE 2. Of the 9 full-text articles reporting on studies conducted in Africa, 2 were from South Africa,[53,54] 2 were from Nigeria,[55,56] 1 was from Uganda,[57] 1 was from Senegal,[58] 1 was from Cameroon,[59] 1 was from Botswana,[60] and 1 was from Malawi.[61] Of the 18 abstracts reporting on studies conducted in African settings, 2 were from Nigeria,[62,63] 4 were from South Africa,[64-67] 5 were from Uganda,[68-72] 1 was from Malawi,[73] 1 was from Rwanda,[74] 1 was from the Democratic Republic of Congo,[75] 2 were from Burkina Faso,[76,77] 1 was from Cote d'Ivoire,[78] and 1 was from Tanzania.[79]

Study Characteristics

Full-text studies conducted in North America enrolled a median of 220 patients (interquartile range [IQR], 130-683). This was largely unchanged when combined with the 3 North American abstracts (median, 219 patients; IQR, 116-683). Full-text studies conducted in Africa enrolled a median of 109 patients (IQR, 60-263) and when the 18 African abstracts were included, the median was 100 patients (IQR, 60-270). Four abstracts were missing data[65,67,71,77]; 3 on loss to follow-up and 4 on payment of ART.

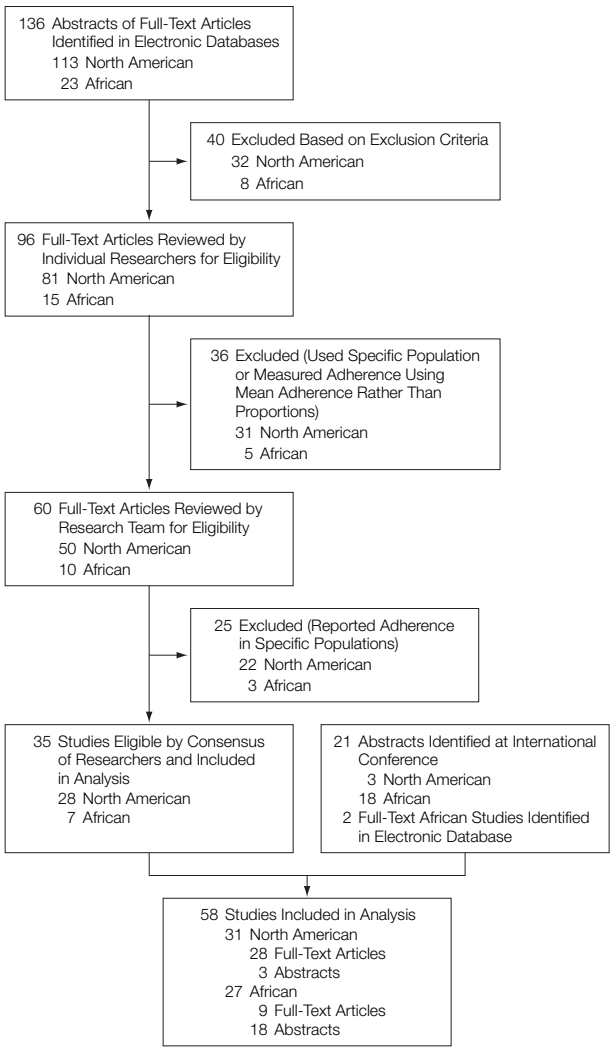
Twenty-two (71%) of the North American studies assessed adherence using patient-reported adherence levels over a specified period. Three studies (10%) used pharmacy claims. Three studies (10%) in North America used the MEMS to assess adherence. Two studies (6.5%) used a mix of patient reporting and clinician observations and 1 study (3%) used clinic staff reporting. Eighteen (66%) of the 27 studies assessing adherence in African settings used patient-reported adherence over a specified period. Three studies (11%) used pharmacy claims and 6 studies (22%) used a mix of patient reporting of pill counts and clinician observations.

Adherence Threshold Measurements

Fifteen North American studies defined adherence as 100% during the measurement period.* Nine North American studies assessed adherence as greater than 95%,† 4 as greater than 90%,[29,35,37,48] and 3 as greater than 80%.[25,28,31] Eleven African studies assessed adherence as 100%,‡ 11 as greater than 95%,§ 2 as greater than 90%,[53,78] and 3 as greater than 80%.[55,58,66] Thresholds defined to assess adherence were not systematically different across settings.

*References 3, 24, 26, 30, 32, 36, 38, 40, 42-47, 51.
†References 4, 27, 33, 34, 39, 41, 49, 50, 52.
‡References 56, 59, 61, 64, 71, 72, 74-77, 79.
§References 54, 57, 60, 62, 63, 65, 67-70, 73.

Figure 1. Flow Diagram of North American and African Studies Included in Analysis



Time Trends

Included studies assessing ART adherence in North America began in 1998 and continued to the present. There was no difference in the pooled effect size for North American studies between studies published prior to 2002 (n=4) and studies published since 2002 (n=27) (P=.52). We were unable to identify studies assessing ART adherence in Africa prior to 2002 that met our inclusion criteria.

Meta-analysis

Our primary meta-analyses aimed to determine the overall proportion of patients in each continent meeting the threshold measurements used in the specific studies. The combined continent analysis indicates adherence of 64% (95% CI, 59%-70%; I^2, 98.7%). FIGURE 2 displays a forest plot of all North American studies and FIGURE 3 displays a forest plot of all African studies. When we pooled abstracts with full-text articles, North American studies (31 studies; 17 573 patients total) yielded a pooled estimate of 55% (95% CI, 49%-62%; I^2, 98.6%) and African studies (27 studies; 12 116 patients total) yielded a pooled estimate of 77% (95% CI, 68%-85%; I^2, 98.4%), indicating a significantly (P<.001) higher level of ART adherence in Africa. North American full-text articles (28 studies) had a pooled proportion of 57% (95% CI, 49%-64%; I^2, 98.9%) and African full-text articles (9 studies) had a pooled proportion of 71% (95% CI, 62%-79%; I^2, 91.6%); the superior ART adherence rate in Africa remained (P=.02). The Bayesian sensitivity analysis provided an alternative statistical manner to evaluate pooled proportions and were largely similar to the pooled random-effects analysis of 55% (95% CI, 49%-62%) adherence in North America and 81% (95% CI, 72%-87%) adherence in Africa. The Mann-Whitney U analysis in case of scale transformation problems with arcsine

Table 1. Characteristics of North American Studies*

Source	No. of Participants	Characterisics of Study Population			Assessor	Adherence, %; Threshold for Measurement
		Female, %	Ethnicity, %	Age, y		
Acri et al,[24] 2005	106	29	Black, 26 Hispanic, 32	41 (13-69)†	Patient	100; Did not miss any doses over past month
Becker et al,[25] 2002	3788	31	NA	NA	Pharmacy claim	≥80; No. of days drug taken/365
Castillo et al,[48] 2004‡	788	18.1	NA	37 (30-45)†	Pharmacy claim	≥90; No. of months medication dispensed/No. of months of follow-up
Cook et al,[26] 2001	219	28	Black, 24 Hispanic, 15	NA	Patient	100; Did not miss dose in previous 24 h
Diamond et al,[27] 2005	874 (683 in Analysis)	12	Hispanic, 37 Black, 16	37 (21-73)†	Patient	≥95; No. of pills taken/pills prescribed in past week
Eldred et al,[28] 1998	244 (207 in Analysis)	37	Black, 85	NA	Medical record	≥80; Total dose of medication in previous week (total No. of capsules of medication taken in past week)
Ferguson et al,[3] 2002	149	12.8	Black, 34	39 (8.6)§	Patient	100; Missed <1 dose in the past 4 wk
Gebo et al,[29] 2003	196	32	Black, 78	37.5 (NA)§	Patient	≥90; No. of doses taken over past 2 wk
Gifford et al,[30] 2000	133	14	Black, 22 Hispanic, 11	NA	Patient	100; NA
Graney et al,[31] 2003	57	22.8	Black, 82.5	35 (23-46)‖	Patient	¶
Heckman et al,[32] 2004	329 (272 in Analysis)	92	Black, 18 Hispanic, 3 Native American, 1	40.9 (18-70)‖	Patient	100%; Based on past 7 d
Hinkin et al,[33] 2004	148	17	Black, 70 Hispanic, 9	44.2 (7.7)§	MEMS	#
Ingersoll and Heckman,[34] 2005	120 (46 in Analysis)	38	Black, 83 Native American, 2	40.4 (NA)§	Patient	≥95; Composite adherence score of 3
Johnson et al,[35] 2005	2765	24.4	Black, 49.4	42 (7.6)§	Patient	≥90; No. of pills taken/No. of pills prescribed over prior 3 d
Kalichman et al,[36] 2005	391 (255 in Analysis)	NA	Black, 71	41 (NA)§	Patient	100; Based on previous 7 d
Levine et al,[37] 2005	222	20	Black, 68	43.8 (7.2)§	MEMS	≥90; No. of the doses taken/No. of doses prescribed in 4-wk study period
Mohammed et al,[38] 2004	273	70.7	Black, 60.1	38.6 (19-66)‖	Patient	100; Based on past 7 d
Paterson et al,[4] 2000	99 (81 in Analysis)	NA	Black, 20.8	40 (21-62)†	MEMS	≥95; No. of doses recorded/total No. of doses prescribed
Penedo et al,[39] 2003	116	45	Black, 37 Hispanic, 33	39.2 (8.7)§	Patient	≥95; No. of doses taken/No. of doses prescribed in past 4 d
Power et al,[40] 2003	73	47	Black, 23	40.3 (6.9)§	Patient	100; Based on past 4 d
Russell et al,[41] 2004	130	3.8	Black, 15.4 Hispanic, 5.4	37.2 (7.2)§	Clinic staff	≥95; Based on a combined adherence regimen
Schneider et al,[42] 2004	554	15	Black, 14.5 Hispanic, 6.9	41.6 (7.7)§	Patient	100; Aggregate adherence score of 100 includes taking all medication in previous 7 d
Tesoriero et al,[43] 2003	435	48.6	Black, 47.9 Hispanic, 32.2	43.1 (NA)§	Patient	100; Based on past 3 d
Tucker et al,[44] 2003	1910	22	Black, 32	NA	Patient	100; Based on past 7 d
Wagner et al,[45] 2002	80 (40 in Analysis)	NA	Black, 35 Hispanic, 16 Native American, 3	39 (21-64)‖	Patient	100; Based on past 3 d
Weiss et al,[46] 2003	997	38.4	Black, 47.9 Hispanic, 32.9	NA	Patient	100; Based on past 3 d
Wilson et al,[47] 2001	454	28	Nonwhite, 37	42 (NA)§	Patient	100; Based on past 7 d
Wood et al,[49] 2003‡	1422	**	NA	37.1 (31.9-44.0)†	Patient or physician	≥95; Total amount of medication dispensed to patient would last to follow-up during first year
Montessori et al,[52] 2000‡,††	886	13.5	NA	NA	Pharmacy claims	≥95; No. of months prescriptions dispensed/No. of months of follow-up in first year
Robertson et al,[51] 2006††,‡‡	37	31	NA	NA	Patient	100; Based on past 4 d
Temoshok and Wald,[50] 2004††	131	44	Black, 91	42.4 (NA)§	Patient	≥95; NA

Abbreviations: MEMS, Medication Event Monitoring System; NA, data not available.
*Studies are from the United States unless otherwise indicated.
†Expressed as median (range).
‡Study is from Canada.
§Expressed as mean (SD).
‖Expressed as mean (range).
¶Adherence of 80 or greater on a scale of 100 coded for dosage.
#Adherence defined as 95% or greater of prescribed medication during a 4-week period.
**There were 224 females in this study.
††This study was published as an abstract.
‡‡Data missing on payment of antiretroviral therapy and on loss to follow-up.

remained significant ($P<.001$). The adjusted odds ratio of ART adherence in African studies in relationship to ART adherence in North America, independent of the thresholds used, is 3.0 (95% CI, 2.6-3.6). The odds ratio, adjusted for all other potential covariates, is 2.5 (95% CI, 1.9-3.3).

TABLE 3 displays the pooled proportions of each continent adjusted for thresholds. As anticipated, we found large heterogeneity across study analyses. In multivariable analyses (TABLE 4), heterogeneity was examined by continent, adherence threshold (100%, >95%, >90%), and use of more than 1 adherence measure. North American studies using MEMS to assess ART adherence had a reduced but nonsignificant level ($P=.08$) compared with other North American studies that did not use MEMS. Free access to care was not associated with higher ART adherence in Africa (16 studies; 74% [95% CI,

Table 2. Characteristics of African Studies

Source	Country	No. of Participants	Characteristics of Study Population		Assessor	Adherence, %; Threshold for Measurement
			Female, %	Age, y		
Byakika-Tusiime et al,[57] 2005	Uganda	304	53	39 (NA)[a]	Patient	≥95; No. of doses taken/No. of doses prescribed in last 3 d
Idigbe et al,[55] 2005	Nigeria	44	56	34.5 (30-60)[b]	Patient	≥80; Based on period between clinic visits
Iliyasu et al,[56] 2005	Nigeria	263	NA	NA	Patient	100; Based on previous 7 d
Laurent et al,[58] 2002	Senegal	58	44.8	41.5 (30-46)[b]	Patient	[c]
Laurent et al,[59] 2004	Cameroon	60	68	34.5 (29-40.5)[d]	Patient	100; Based on past 7 d
Orrell et al,[53] 2003	South Africa	289 (278 in Analysis)	43	33.4 (8.7)[a]	Pharmacy refill and pill count	≥90; Medication dispensed minus pills returned/ No. of pills prescribed over 48 wk
Nachega et al,[54] 2004	South Africa	66	71	36.1 (10.1)[a]	Patient	≥95; No. of pills taken/No. of pills prescribed in previous month
Weiser et al,[60] 2003	Botswana	109	50	NA	Patient or clinician	≥95; Based on previous year of missing <1 dose in 10-d period or 1 dose/wk
van Oosterhout et al,[61] 2005	Malawi	176	55	39 (22-71)[b]	Patient or file record	100; Did not miss any dose in prior day, week, or month
Adedayo et al,[62] 2005[e]	Nigeria	689	36	32 (NA)[b]	Patient	≥95; NA
Boileu et al,[77] 2005[e]	Burkina Faso and Mali	270	65.2	NA	Patient	100; Based on past 7 d
Brown et al,[64] 2004[e]	South Africa	50	NA	NA	Patient	100; Based on past 7 d
Byakika et al,[69] 2005[e]	Uganda	44 (28 in Analysis)	71.4[f]	29.5 (13.5)[a]	Pill count, patient, or VAS	≥95; Based on 3-d report
Daniel et al,[63] 2004[e]	Nigeria	53	60.4	40.5 (NA)[a]	Patient	≥95; Based on past 7 d
Darder et al,[67] 2004[e,g,h]	South Africa	192	NA	NA	Patient	[i]
Eholie et al,[78] 2004[e]	Cote d'Ivoire	308 (304 in Analysis)	47.4	NA	Pharmacy refill	≥90; Based on proportion of prescribed doses taken over 7 d
Ferris et al,[65] 2004[e,g]	South Africa	74	58.1[j]	37 (NA)[a]	Patient	≥95; Based on past 4 d
Hosseinipour et al,[73] 2004[e]	Malawi	141	52	NA	Patient	>95; NA
Karcher et al,[68] 2004[e]	Uganda	76	53.9[k]	NA	Patient	>95; NA
Muganzi et al,[70] 2004[e]	Uganda	530	NA	NA	Patient or pill count	>95; Based on majority of prescribed medication taken
Okongo et al,[71] 2004[e,g,h]	Uganda	100	58	33.4 (NA)[a]	Patient or pill count	100; Based on consistent medication regimen
Omes et al,[74] 2004[e]	Rwanda	95	NA	NA	Patient or VAS	100; Based on last 3 d (self-report) and the last month (VAS)
Nachega et al,[66] 2005[e]	South Africa	7812	56	NA	Pharmacy claim	≥80; No. of months patients submitted claims/No. of months since began taking antiretrovirals
Ramadhani,[79] 2006[e]	Tanzania	150	63	NA	Patient	100; NA
Shihab et al,[72] 2004[e]	Uganda	84	50	38.6 (8.2)[a]	Patient	100; Based on past 2 wk
Traore et al,[76] 2004[e]	Burkina Faso	120 (80 in Analysis)	NA	NA	Patient	100; Based on past month
Tu et al,[75] 2004[e]	Democratic Republic of Congo	30	NA	NA	Patient or pill count	100; Based on 3-mo period

Abbreviations: MEMS, Medication Event Monitoring System; NA, data not available; VAS, visual analog scale.
[a]Expressed as mean (SD).
[b]Expressed as median (range).
[c]Adherence based on 80% or greater of prescribed dose taken on the basis of the patients' statements to their physician at each monthly visit.
[d]Expressed as mean (range).
[e]This study was published as an abstract.
[f]Of the total population in this study, 14.3% were children; mean (SD) age, 1.5 (3.0) years.
[g]Data missing on payment of antiretroviral therapy.
[h]Data missing on loss to follow-up.
[i]Adherence based on 95% or greater dose taken at 1, 3, and 12 months.
[j]Of the total population in this study, 5.4% were Asian.
[k]Of the total population in this study, 6.6% were children.

64%-82%]) than North America (24 studies; 82% [95% CI, 67%-93%]) (P=.33).

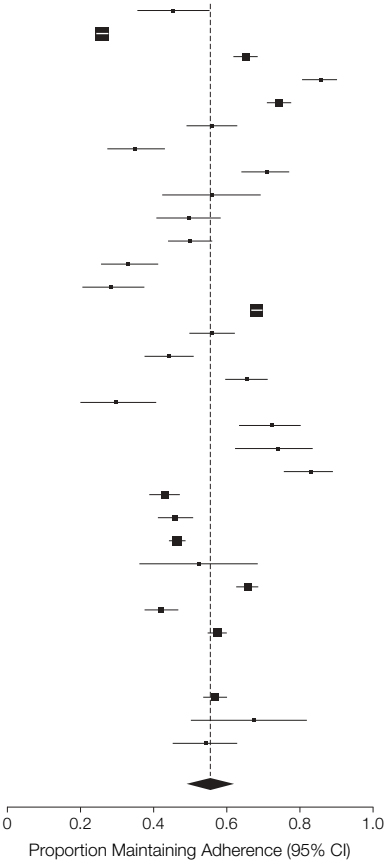
COMMENT

The findings from this systematic review and meta-analysis suggest that ART adherence among sub-Saharan African patients in early treatment programs are favorable, although it should be noted that the complexity of treatment regimens is potentially greater in North America, which should be considered when interpreting the data. This suggests that concerns about suboptimal adherence are not supported by the data and such concerns should not contribute to delayed access to treatment. While these data are promising, these relatively high levels of adherence may decline as treatment access expands. The African studies in these analyses were conducted in patients with early access to limited therapy and are possibly not generalizable to the larger HIV epidemic in Africa. Furthermore, most African studies include patients during early therapy when they are experiencing dramatic increases in health status and before they develop long-term adverse effects of therapy. While expectations of poor levels of adherence in Africa appear to be thus far unwarranted, efforts to sustain adherence in Africa and elsewhere remain important goals to optimize outcomes for individuals and global HIV treatment.

Strengths of this systematic review include explicit eligibility criteria and conduct of a comprehensive search that identified a number of eligible articles not published or available on electronic databases. We attempted to contact all of the articles' authors, however only 36 provided appropriate contact information. Thirty-two authors (89%) responded and clarified that adherence rates were correct as abstracted. Independent reviewers assessed eligibility and agreement was high. In keeping with the large heterogeneity across studies, we used the random-effects model to pool propor-

Figure 2. Pooled Proportion of Patients in North American Studies Adhering to Antiretroviral Therapy

Source	Country	No. Adherent/ Total No.	Proportion Adherent (95% CI)
Full-Text Articles			
Acri et al,[24] 2005	United States	48/106	0.45 (0.36-0.55)
Becker et al,[25] 2002	United States	985/3788	0.26 (0.25-0.27)
Castillo et al,[48] 2004	Canada	514/788	0.65 (0.62-0.69)
Cook et al,[26] 2001	United States	188/219	0.86 (0.81-0.90)
Diamond et al,[27] 2005	United States	508/683	0.74 (0.71-0.78)
Eldred et al,[28] 1998	United States	116/207	0.56 (0.49-0.63)
Ferguson et al,[3] 2002	United States	52/149	0.35 (0.27-0.43)
Gebo et al,[29] 2003	United States	139/196	0.71 (0.64-0.77)
Graney et al,[31] 2003	United States	32/57	0.56 (0.42-0.69)
Gifford et al,[30] 2000	United States	66/133	0.50 (0.41-0.58)
Heckman et al,[32] 2004	United States	136/272	0.50 (0.44-0.56)
Hinkin et al,[33] 2004	United States	49/148	0.33 (0.26-0.41)
Ingersoll and Heckman,[34] 2005	United States	14/46	0.30 (0.18-0.46)
Johnson et al,[35] 2005	United States	1887/2765	0.68 (0.66-0.70)
Kalichman et al,[36] 2005	United States	143/255	0.56 (0.50-0.62)
Levine et al,[37] 2005	United States	98/222	0.44 (0.38-0.51)
Mohammed et al,[38] 2004	United States	179/273	0.66 (0.60-0.71)
Paterson et al,[4] 2000	United States	24/81	0.30 (0.20-0.41)
Penedo et al,[39] 2003	United States	84/116	0.72 (0.63-0.80)
Power et al,[40] 2003	United States	54/73	0.74 (0.62-0.84)
Russell et al,[41] 2004	United States	108/130	0.83 (0.76-0.89)
Schneider et al,[42] 2004	United States	238/554	0.43 (0.39-0.47)
Tesoriero et al,[43] 2003	United States	200/435	0.46 (0.41-0.51)
Tucker et al,[44] 2003	United States	888/1910	0.46 (0.44-0.49)
Wagner et al,[45] 2002	United States	21/40	0.53 (0.36-0.68)
Weiss et al,[46] 2003	United States	655/997	0.66 (0.63-0.69)
Wilson et al,[47] 2001	United States	191/454	0.42 (0.37-0.47)
Wood et al,[49] 2003	Canada	816/1422	0.57 (0.55-0.60)
Abstracts			
Montessori et al,[52] 2000	Canada	504/886	0.57 (0.54-0.60)
Robertson et al,[51] 2006	United States	25/37	0.68 (0.50-0.82)
Temoshok and Wald,[50] 2004	United States	71/131	0.54 (0.45-0.63)
Combined			0.55 (0.49-0.62)



Size of data markers is proportional to sample size. The combined data marker indicates the DerSimmonian-Laird combined proportion of all North American studies. CI indicates confidence interval.

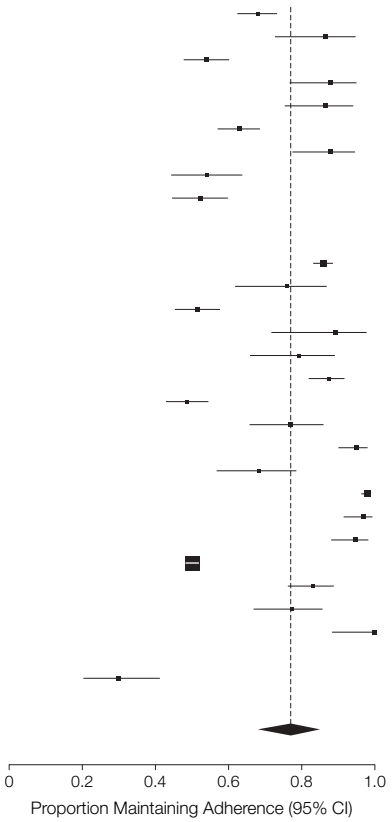
tions. We used random-effects logistic regression to account for the extent of differences between populations and examined a priori defined variables to explain the heterogeneity.

The main limitation of our review is in the quality of the studies. There is no gold standard for evaluating adherence to medication.[80] Patient recall and pill counts have inherent biases in their measurement.[81] However, proportionately, both continents used a similar number of patient recall and pill counts to evaluate adherence, thereby making our analysis as valid as the policies to provide care in North America. There were only 3 studies that assessed adherence using the MEMS and these were in North America.[4,33,37] These studies reported a nonsignificant pooled reduction in ART adherence compared with self-reported studies of 19%, which is in keeping with expectations that self-report may exaggerate adherence. We found large heterogeneity across the meta-analyses as we had expected. We were able to explain heterogeneity across several outcomes. There are unidentified factors either related to populations, drug regimens, or methodological features that may have a large impact on either apparent or real adherence. Setting aside the pooled estimates, all but 2 African studies had more than 50% of all patients meeting the threshold for appropriate ART adherence. Furthermore, despite our extensive searching and contact with organizations providing care in North America and Africa, as well as reviewing other review articles,[82,83] which have addressed several of our included studies,‖ it is possible that we have missed some unpublished studies assessing ART adherence. We cannot know the extent to this limitation because funnel plots do not apply in nonintervention-based studies. Finally, our analysis was based on studies across a great spectrum of geographical and economic locations. It is possible that political or sociodemographic status can affect adherence rates. These data were rarely available in the included studies and while a more detailed analysis comparing regions would be informative in determining which factors within Africa influence ART adherence, it

‖References 54, 57-60, 63-65, 67, 68, 70, 73-76, 84.

Figure 3. Pooled Proportion of Patients in African Studies Adhering to Antiretroviral Therapy

Source	Country	No. Adherent/ Total No.	Proportion Adherent (95% CI)
Full-Text Articles			
Byakika-Tusiime et al,[57] 2005	Uganda	207/304	0.68 (0.63-0.73)
Idigbe et al,[55] 2005	Nigeria	38/44	0.86 (0.73-0.95)
Iliyasu et al,[56] 2005	Nigeria	142/263	0.54 (0.48-0.60)
Laurent et al,[58] 2002	Senegal	51/58	0.88 (0.77-0.95)
Laurent et al,[59] 2004	Cameroon	52/60	0.87 (0.75-0.94)
Orrell et al,[53] 2003	South Africa	175/278	0.63 (0.57-0.69)
Nachega et al,[54] 2004	South Africa	58/66	0.88 (0.78-0.95)
Weiser et al,[60] 2003	Botswana	59/109	0.54 (0.44-0.64)
van Oosterhout et al,[61] 2005	Malawi	92/176	0.52 (0.45-0.60)
Abstracts			
Adedayo et al,[62] 2005	Nigeria	593/689	0.86 (0.83-0.89)
Brown et al,[64] 2004	South Africa	38/50	0.76 (0.62-0.87)
Boileu et al,[77] 2005	Burkina Faso and Mali	139/270	0.51 (0.45-0.58)
Byakika et al,[69] 2005	Uganda	25/28	0.89 (0.72-0.98)
Daniel et al,[63] 2004	Nigeria	42/53	0.79 (0.66-0.89)
Darder et al,[67] 2004	South Africa	168/192	0.88 (0.82-0.92)
Eholie et al,[78] 2004	Cote D'Ivoire	148/304	0.49 (0.43-0.54)
Ferris et al,[65] 2004	South Africa	57/74	0.77 (0.66-0.86)
Hosseinipour et al,[73] 2004	Malawi	134/141	0.95 (0.90-0.98)
Karcher et al,[68] 2004	Uganda	52/76	0.68 (0.57-0.79)
Muganzi et al,[70] 2004	Uganda	519/530	0.98 (0.96-0.99)
Okongo et al,[71] 2004	Uganda	97/100	0.97 (0.91-0.99)
Omes et al,[74] 2004	Rwanda	90/95	0.95 (0.88-0.98)
Nachega et al,[66] 2005	South Africa	3908/7812	0.50 (0.49-0.51)
Ramadhani,[79] 2006	Tanzania	125/150	0.83 (0.76-0.89)
Shihab et al,[72] 2004	Uganda	65/84	0.77 (0.67-0.86)
Tu et al,[75] 2004	Democratic Republic of Congo	30/30	1.00 (0.88-1.00)
Traore et al,[76] 2004	Burkina Faso	24/80	0.30 (0.20-0.41)
Combined			0.77 (0.68-0.85)



Size of data markers is proportional to sample size. The combined data marker indicates the DerSimmonian-Laird combined proportion of all African studies. CI indicates confidence interval.

would not change the primary finding that treatment programs in Africa have thus far had relatively high levels of adherence even accounting for this heterogeneity.

Recognizing these limitations, the consistent difference of ART adherence in North America and Africa raises the question as to why early opinions may have underestimated adherence among Africans. This sentiment was expressed at high levels of international agency decision making.[85] Reports indicate that individuals living in poverty in North America had suboptimal adherence in the range of 56% to 67%.[86,87] These data may have been interpreted to mean that poverty is a risk factor for incomplete adherence and that individuals living in extreme poverty would then have lower levels of adherence. The barriers to adherence among impoverished individuals in North America appear, however, to be due to poor patient-clinician relationships, untreated depression, substance abuse, and other factors that are common among poor individuals in the North American setting rather than poverty itself.[5] It appears that the interactions between such factors and ART adherence in Africa may be quite different. Specific factors that can correlate with poverty are at play in reduced adherence and poverty itself is not the only determinant.

To date, the most important and prevalent factors that have been reported to negatively affect adherence in sub-Saharan Africa are cost,[54,59,88,89] not disclosing HIV status to a loved one or fear of being stigmatized,[54,60] alcohol abuse,[90] and difficulty in following complex drug regimens.[59,91] Studies report that the majority of patients receiving ART have disclosed their HIV status to family or friends[92,93] and that those who have not appear to do worse with therapy.[54,60] Such patients are likely to have frequent treatment interruptions due to the fact that tablets must be hidden and therefore not taken in the presence of others. Encouraging voluntary HIV status disclosure in a community with access to ART may result in improved uptake of voluntary counseling and testing, help decrease the stigma, and improve adherence.

The findings of this analysis have implications for clinicians in both continents. We have shown that there are patients in both settings that have suboptimal adherence and that factors beyond poverty play an important role. Clinicians should therefore proactively inquire with patients about current barriers or facilitators of adherence to HIV medications. We have previously identified that important barriers to ART adherence in both the developed and developing world included forgetfulness, a lack of understanding of treatment benefits, severity of adverse events, and the level of complexity of the drug regimen.[90] Although the success of interventions to improve adherence is modest to

Table 3. Pooled Adherence Rates Across Thresholds for North American and African Studies

	No. of Studies Pooled	Summary Proportion, % (95% CI)*	I^2, %	*P* Value†
Adequate adherence for full-text articles only				
North America	28	57 (49-64)	98.9	.02
Africa	9	71 (62-79)	91.6	
Adequate adherence for full-text articles and abstracts				
North America	31	55 (49-62)	98.6	<.001
Africa	27	77 (68-85)	98.4	
Adequate adherence for abstracts only				
North America	3	57 (54-60)	4.3	<.001
Africa	18	80 (68-89)	98.9	
100% Adherence				
North America	15	56 (49-63)	95.8	.004
Africa	11	76 (62-87)	96.7	
>95% Adherence				
North America	9	55 (45-65)	96.7	<.001
Africa	9	82 (73-90)	96.3	
>90% Adherence				
North America	4	63 (54-70)	90.9	.41
Africa	2	56 (42-69)	91.6	
>80% Adherence				
North America	3	45 (22-70)	97.9	.15
Africa	3	75 (44-96)	97.1	
>1 Adherence measure				
North America	5	65 (55-75)	95.8	.003
Africa	5	91 (72-100)	97.0	

Abbreviation: CI, confidence interval.
*All summary proportions use a random-effects pooled model.
†A *z* test of the pooled estimate was used to test for differences between continents.

Table 4. Multivariable Random-Effects Logistic Regression*

Variable	Coefficient (95% CI)	OR (95% CI)	*P* Value
Africa	0.91 (0.64 to 1.19)	2.5 (1.9 to 3.3)	<.001
100% Adherence	0.85 (0.16 to 1.54)	2.3 (1.2 to 4.7)	.02
>95% Adherence	0.94 (0.26 to 1.63)	2.6 (1.3 to 5.1)	.006
>90% Adherence	0.90 (–0.13 to 1.94)	2.5 (0.9 to 7.0)	.87
>1 Adherence measure	0.68 (0.29 to 1.08)	2.0 (1.3 to 2.9)	.001
Clinic setting	0.37 (–0.09 to 0.85)	1.5 (0.9 to 2.3)	.12
Paying for treatment	0.19 (–0.05 to 0.45)	1.2 (0.9 to 1.6)	.13
Loss to follow-up	–0.41 (–0.66 to 0.16)	0.7 (0.3 to 1.4)	.10
MEMS	–1.00 (–1.93 to –0.08)	0.4 (0.2 to 0.7)	.03

Abbreviations: CI, confidence interval; MEMS, Medication Event Monitoring System; OR, odds ratio.
*A priori defined covariates were used. Four abstracts[65,67,71,77] included in the analyses were missing data (3 on loss to follow-up and 4 on payment of ART).

date,[94] the use of patient-directed interventions and innovative reminder systems may be desirable for some patients.

Although the World Health Organization's "3 by 5" initiative aims to increase access to ART throughout sub-Saharan Africa, the goal is far from being achieved. In all of the sub-Saharan African countries included in our analyses, estimates of access to ART remain severely limited. For example, the World Health Organization estimates indicate that as of June 2005, the proportion of patients requiring urgent access to ART and currently receiving therapy was 56% in Botswana, 10% in Burkina Faso, 15.8% in Cameroon, 5.4% in Cote d'Ivoire, 3.2% in the Democratic Republic of Congo, 13.6% in Malawi, 8% in Nigeria, 26.5% in Rwanda, 12.5% in South Africa, 3.2% in Tanzania, and 56% in Uganda.[95,96]

Given the apparent relatively high level of ART adherence in Africa, one of the most controversial program components in developing countries is whether there is a need for intensive interventions such as directly observed therapy of ART (DOT-ART). Through observation of a patient actually taking a dose, by a close family member or friend to whom the patient has voluntarily disclosed their HIV status, DOT-ART is proposed to influence patient outcomes. Indeed, in settings with high HIV status disclosure rates, community-based DOT-ART with a patient-nominated treatment *accompagnateur* or supporter[97-99] has been reported to be feasible and helps to improve or maintain high levels of ART adherence. However, because patient outcomes may be confounded by a constellation of services provided by the program, community support, or other factors, the effectiveness of community-based DOT-ART still needs to be confirmed in well-conducted randomized trials, which are under way in several African countries. Alternatively, long-term, clinic-based DOT-ART is not likely to be feasible due to the lifelong nature of HIV treatment and long transportation distances in rural settings. Patients who do not disclose their HIV status due to fear of stigma, discrimination, or violence will need other adapted and culturally sensitive innovative adherence support if they prove to be poorly adherent to ART.

The findings of this analysis have important policy implications. First, the expectation of poor adherence in Africa is not an evidence-based rationale for delaying the expansion of ART programs in resource-poor settings. Second, given the average relatively high levels of adherence in resource-poor settings documented in this analysis, the focus (or priority) must now be to maintain these ART adherence rates by increasing access to affordable ART and establishing reliable drug supply and distribution networks from the pharmacy to the individual patient. Third, understanding culturally specific barriers to adherence will be important in developing evidence-based interventions targeted at the individuals with poor ART adherence.

HIV/AIDS is the most difficult public health challenge the world currently faces. However, adherence to ART in Africa may not be the challenge that many predicted. Policies designed to combat this pandemic must be based on sound and timely evidence. Formulating policies based on assumptions, without seeking evidence, may leave millions of individuals without effective interventions.

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Acquisition of data: Mills, Nachega, Rachlis, Wu, Bangsberg.
Analysis and interpretation of data: Mills, Nachega, Buchan, Singh, Rachlis, Wu, Cooper, Thabane, Guyatt, Bangsberg.
Drafting of the manuscript: Mills, Nachega, Buchan, Orbinski, Attaran, Singh, Rachlis, Cooper, Guyatt, Bangsberg.
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Obtained funding: Mills.
Administrative, technical, or material support: Mills, Singh, Rachlis, Guyatt, Bangsberg.
Study supervision: Mills, Nachega, Orbinski, Wilson, Guyatt, Bangsberg.
Financial Disclosures: Dr Nachega received grant support or funding, honoraria (including honoraria for continuing medical education), travel grants, and lecture sponsorships from GlaxoSmithKline, Bristol-Myers Squibb, and Aspen Pharmaceuticals.
Funding/Support: Dr Mills is supported by the Ontario HIV Treatment Network and the Canadian Institutes for Health Research. Dr Nachega is supported by grants AI005535901 and K23A106858201 from the US National Institutes of Health. Dr Wilson is supported by the Canadian Institutes for Health Research. Dr Bangsberg is supported by grants AA015287, MH54907, and AI27763 from the US National Institutes of Health and by the Doris Duke Charitable Foundation. The Ontario HIV Treatment Network provided financial support for this study.
Role of the Sponsor: The agencies had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
Acknowledgment: We thank Pearl Raju, PhD (Centre for International Health and Human Rights Studies, Toronto, Ontario), and Dugald Seely, ND, MSc (University of Toronto, Toronto, Ontario), for assistance with searching and arbitration. They did not receive compensation for their work. We also thank the authors of the original studies for assistance and clarifications.

REFERENCES

1. Mannheimer SB, Matts J, Telzak E, et al. Quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence. *AIDS Care*. 2005; 17:10-22.
2. Altice FL, Mostashari F, Friedland GH. Trust and the acceptance of and adherence to antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2001;28:47-58.
3. Ferguson TF, Stewart KE, Funkhouser E, et al. Patient-percieved barriers to antiretroviral adherence: associations with race. *AIDS Care*. 2002;14:607-617.
4. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133: 21-30.
5. Bangsberg DR, Hecht FM, Charlebois ED, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS*. 2000;14:357-366.
6. Bangsberg DR, Charlebois ED, Grant RM, et al. High levels of adherence do not prevent accumulation of HIV drug resistance mutations. *AIDS*. 2003;17:1925-1932.
7. Bangsberg DR, Perry S, Charlebois ED, et al. Nonadherence to highly active antiretroviral therapy pre-

dicts progression to AIDS. *AIDS*. 2001;15:1181-1183.
8. Wood E, Hogg RS, Yip B, et al. Is there a baseline CD4 cell count that precludes a survival response to modern antiretroviral therapy? *AIDS*. 2003;17:711-720.
9. Predicting the failure of 3 by 5. *Lancet*. 2005;365:1597.
10. Joint United Nations Program on HIV/AIDS. Uniting the world against AIDS. http://www.unaids.org/epi/2005/doc/report_pdf.asp. Accessed July 15, 2006.
11. Harries AD, Nyangulu DS, Hargreaves NJ, et al. Preventing antiretroviral anarchy in sub-Saharan Africa. *Lancet*. 2001;358:410-414.
12. Liechty CA, Bangsberg DR. Doubts about DOT. *AIDS*. 2003;17:1383-1387.
13. Vist GE, Hagen KB, Devereaux PJ, et al. Systematic review to determine whether participation in a trial influences outcome. *BMJ*. 2005;330:1175.
14. Palepu A, Tyndall M, Yip B, et al. Impaired virologic response to highly active antiretroviral therapy associated with ongoing injection drug use. *J Acquir Immune Defic Syndr*. 2003;32:522-526.
15. Samet JH, Horton NJ, Meli S, et al. Alcohol consumption and antiretroviral adherence among HIV-infected persons with alcohol problems. *Alcohol Clin Exp Res*. 2004;28:572-577.
16. Berlin JA; University of Pennsylvania Meta-analysis Blinding Study Group. Does blinding of readers affect the results of meta-analyses? *Lancet*. 1997;350:185-186.
17. Meade MO, Guyatt GH, Cook RJ, et al. Agreement between alternative classifications of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2001;163:490-493.
18. Stuart A, Ord JK. *Kendall's Advanced Theory of Statistics.* 6th ed. London, England: Arnold Publishers; 1994.
19. Jaynes ET. Confidence intervals vs Bayesian intervals. In: Harper WL, Hooker CA, eds. *Foundations of Probability Theory, Statistical Inference, and Statistical Theories of Science.* Dordrecht, the Netherlands: Reidel; 1976:175.
20. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539-1558.
21. Fleiss JL. The statistical basis of meta-analysis. *Stat Methods Med Res*. 1993;2:121-145.
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
23. Robert CP, Casella G. *Monte Carlo Statistical Methods.* 2nd ed. New York, NY: Springer-Verlag; 2004.
24. Acri T, Coco A, Lin K, et al. Knowledge of structured treatment interruption and adherence to antiretroviral therapy. *AIDS Patient Care STDS*. 2005;19:167-173.
25. Becker SL, Dezii CM, Burtcel B, et al. Young HIV-infected adults are at greater risk for medication nonadherence. *MedGenMed*. 2002;4:21.
26. Cook RL, Sereika SM, Hunt SC, et al. Problem drinking and medication adherence among persons with HIV infection. *J Gen Intern Med*. 2001;16:83-88.
27. Diamond C, Richardson JL, Milam J, et al. Use of and adherence to antiretroviral therapy is associated with decreased sexual risk behavior in HIV clinic patients. *J Acquir Immune Defic Syndr*. 2005;39:211-218.
28. Eldred LJ, Wu AW, Chaisson RE, Moore RD. Adherence to antiretroviral and pneumocystis prophylaxis in HIV disease. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;18:117-125.
29. Gebo KA, Keruly J, Moore RD. Association of social stress, illicit drug use, and health beliefs with nonadherence to antiretroviral therapy. *J Gen Intern Med*. 2003;18:104-111.
30. Gifford AL, Bormann JE, Shively MJ, et al. Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. *J Acquir Immune Defic Syndr*. 2000;23:386-395.
31. Graney MJ, Bunting SM, Russell CK. HIV/AIDS medication adherence factors. *Tenn Med*. 2003;96:73-78.
32. Heckman BD, Catz SL, Heckman TG, et al. Adherence to antiretroviral therapy in rural persons living with HIV disease in the United States. *AIDS Care*. 2004;16:219-230.
33. Hinkin CH, Hardy DJ, Mason KI, et al. Medication adherence in HIV-infected adults. *AIDS*. 2004;18(suppl 1):S19-S25.
34. Ingersoll KS, Heckman CJ. Patient-clinician relationships and treatment system effects on HIV medication adherence. *AIDS Behav*. 2005;9:89-101.
35. Johnson MO, Charlebois E, Morin SF, et al. Perceived adverse effects of antiretroviral therapy. *J Pain Symptom Manage*. 2005;29:193-205.
36. Kalichman SC, Cain D, Fuhrel A, et al. Assessing medication adherence self-efficacy among low-literacy patients. *Health Educ Res*. 2005;20:24-35.
37. Levine AJ, Hinkin CH, Castellon SA, et al. Variations in patterns of highly active antiretroviral therapy (HAART) adherence. *AIDS Behav*. 2005;9:355-362.
38. Mohammed H, Kieltyka L, Richardson-Alston G, et al. Adherence to HAART among HIV-infected persons in rural Louisiana. *AIDS Patient Care STDS*. 2004;18:289-296.
39. Penedo FJ, Gonzalez JS, Dahn JR, et al. Personality, quality of life and HAART adherence among men and women living with HIV/AIDS. *J Psychosom Res*. 2003;54:271-278.
40. Power R, Koopman C, Volk J, et al. Social support, substance use, and denial in relationship to antiretroviral treatment adherence among HIV-infected persons. *AIDS Patient Care STDS*. 2003;17:245-252.
41. Russell J, Krantz S, Neville S. The patient-provider relationship and adherence to highly active antiretroviral therapy. *J Assoc Nurses AIDS Care*. 2004;15:40-47.
42. Schneider J, Kaplan SH, Greenfield S, et al. Better physician-patient relationships are associated with higher reported adherence to antiretroviral therapy in patients with HIV infection. *J Gen Intern Med*. 2004;19:1096-1103.
43. Tesoriero J, French T, Weiss L, et al. Stability of adherence to highly active antiretroviral therapy over time among clients enrolled in the treatment adherence demonstration project. *J Acquir Immune Defic Syndr*. 2003;33:484-493.
44. Tucker JS, Burnam MA, Sherbourne CD, et al. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. *Am J Med*. 2003;114:573-580.
45. Wagner GJ, Remien RH, Carballo-Dieguez A, Dolezal C. Correlates of adherence to combination antiretroviral therapy among members of HIV-positive mixed status couples. *AIDS Care*. 2002;14:105-109.
46. Weiss L, French T, Finkelstein R, et al. HIV-related knowledge and adherence to HAART. *AIDS Care*. 2003;15:673-679.
47. Wilson IB, Tchetgen E, Spiegelman D. Patterns of adherence with antiretroviral medications. *J Acquir Immune Defic Syndr*. 2001;28:259-263.
48. Castillo E, Palepu A, Beardsell A, et al. Outpatient pharmacy care and HIV viral load response among patients on HAART. *AIDS Care*. 2004;16:446-457.
49. Wood E, Montaner JS, Yip B, et al. Adherence and plasma HIV RNA responses to highly active antiretroviral therapy among HIV-1 infected injection drug users. *CMAJ*. 2003;169:656-661.
50. Temoshok L, Wald RL. Transmission risk behavior and suboptimal adherence among disadvantaged HIV patients in Baltimore. Presented at: XV International AIDS Conference; July 11-16, 2004; Bangkok. Abstract TuPeB4680.
51. Robertson K, Parsons T, Chauhan S, et al. Cognitive function and adherence in individuals receiving ART. Presented at: 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract WeP70-363.
52. Montessori V, Heath KV, Yip B, et al. Predictors of adherence with triple combination antiretroviral therapy. Presented at: 7th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2000; San Francisco, Calif. Abstract A72.
53. Orrell C, Bangsberg DR, Badri M, Wood R. Adherence is not a barrier to successful antiretroviral therapy in South Africa. *AIDS*. 2003;17:1369-1375.
54. Nachega JB, Stein DM, Lehman DA, et al. Adherence to antiretroviral therapy in HIV-infected adults in Soweto, South Africa. *AIDS Res Hum Retroviruses*. 2004;20:1053-1056.
55. Idigbe EO, Adewole TA, Eisen G, et al. Management of HIV-1 infection with a combination of nevirapine, stavudine, and lamivudine. *J Acquir Immune Defic Syndr*. 2005;40:65-69.
56. Iliyasu Z, Kabir M, Abubakar IS, et al. Compliance to antiretroviral therapy among AIDS patients in Aminu Kano Teaching Hospital, Kano, Nigeria. *Niger J Med*. 2005;14:290-294.
57. Byakika-Tusiime J, Oyugi JH, Tumwikirize WA, et al. Adherence to HIV antiretroviral therapy in HIV+ Ugandan patients purchasing therapy. *Int J STD AIDS*. 2005;16:38-41.
58. Laurent C, Diakhate N, Gueye NF, et al. The Senegalese government's highly active antiretroviral therapy initiative. *AIDS*. 2002;16:1363-1370.
59. Laurent C, Kouanfack C, Koulla-Shiro S, et al. Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon. *Lancet*. 2004;364:29-34.
60. Weiser S, Wolfe W, Bangsberg D, et al. Barriers to antiretroviral adherence for patients living with HIV infection and AIDS in Botswana. *J Acquir Immune Defic Syndr*. 2003;34:281-288.
61. van Oosterhout JJ, Bodasing N, Kumwenda JJ, et al. Evaluation of antiretroviral therapy results in a resource-poor setting in Blantyre, Malawi. *Trop Med Int Health*. 2005;10:464-470.
62. Adedayo A, Modupeola A, Timothy A. Scaling up antiretroviral therapy use for HIV-positive adults in southwestern Nigeria. Presented at: 12th Conference on Retroviruses and Opportunistic Infections; February 22-25, 2005; Boston, Mass. Abstract A623.
63. Daniel O, Ogun SA, Odugsoga OL, et al. Adherence pattern to ARV drugs among AIDS patients on self-purchased drugs and those on free medications in Sagamu, Nigeria. Presented at: XV International AIDS Conference; July 11-16, 2004; Bangkok. Abstract e276.
64. Brown S, Friedland GH, Bodasing U. Assessment of adherence to antiretroviral therapy in HIV-infected South African adults. Presented at: XV International AIDS Conference; July 11-16, 2004; Bangkok. Abstract B12223.
65. Ferris D, Dawood H, Chiasson MA, et al. Self-reported adherence to antiretroviral therapy and virologic outcomes in HIV-infected persons in Durban, KwaZulu Natal, South Africa. Presented at: XV International AIDS Conference; July 11-16, 2004; Bangkok. Abstract WePeB5829.
66. Nachega J, Hislop M, Lo M, et al. Adherence to antiretroviral therapy assessed by pharmacy claims and survival in HIV-infected South Africans. Presented at: 12th Conference on Retroviruses and Opportunistic Infections; February 22-25, 2005; Boston, Mass. Abstract.
67. Darder M, Michaels D, Boulle A, et al. Determinants of short and long-term adherence to antiretroviral treatment in resource-poor settings. Presented at:

XV International AIDS Conference; July 11-16, 2004; Bangkok. Abstract B11852.
68. Karcher H, Moses A, Weide AL, et al. Evaluation of antiretroviral treatment in Fort Portal, Western Uganda. Presented at: eJournal of the International AIDS Society Meeting; July 11-16, 2004. Abstract B12706.
69. Byakika J, Oyugi J, Musoke P, et al. Adherence approaches 100% with excellent viral load suppression when all HIV-infected Ugandan household members receive antiretroviral treatment. Presented at: 12th Conference on Retroviruses and Opportunistic Infections; February 22-25, 2005; Boston, Mass. Abstract A626.
70. Muganzi A, Bondo MC, Draru J, Biryeri J. Adherence to HAART in a rural resource limited country HIV/AIDS treatment program. Presented at: XV International AIDS Conference; July 11-16, 2004; Bangkok. Abstract WePeB5760.
71. Okongo B, Kerr A, Namagala E, et al. Lessons learned from an antiretroviral access initiative in rural Uganda (UGANDA CARES). Presented at: XV International AIDS Conference; July 11-16, 2004; Bangkok. Abstract ThPeB7278.
72. Shihab H, Spacek LA, Mwesigire D, et al. Health beliefs and behaviors of HIV infected people treated with antiretroviral therapy in the resource-limited setting of Kampala, Uganda. Presented at: XV International AIDS Conference; July 11-16, 2004; Bangkok. Abstract TuPeD5193.
73. Hosseinipour MC, Kanyama C, Nkhalamba T, et al. Safety and efficacy of D4T/3Tc/NVP among HIV positive adults in Lilongwe, Malawi. Presented at: eJournal of the International AIDS Society Meeting; July 11-16, 2004. Abstract TuPeB4522.
74. Omes C, Schuman M, Kamesigwa J, et al. Adherence to antiretroviral (ARV) therapy among advanced-stage, indigent patients in the funded ESTHER programme in Kigali, Rwanda. Presented at: XV International AIDS Conference; July 11-16, 2004; Bangkok. Abstract B12315.
75. Tu D, Kos N, Culbert H, Migabo K, Amisi T. ARV selection criteria and innovative group adherence counseling in Bukavu, Democratic Republic of Congo-Program implementation in the context of chronic war and a failing healthcare system. Presented at: XV International AIDS Conference; July 11-16, 2004; Bangkok. Abstract B12702.
76. Traore A, Nguyen VK, Fakoya A, et al. Barriers to adherence to ARV therapy in a community-based cohort in Burkina Faso. Presented at: XV International AIDS Conference; July 11-16, 2004; Bangkok. Abstract WePeB5824.
77. Boileu C, Aboubacrine SA, Niamba P, et al. Inadequate adherence to antiretroviral treatment and prevention in hospital and community sites in Burkina Faso and Mali. Presented at: 12th Conference on Retroviruses and Opportunistic Infections; February 22-25, 2005; Boston, Mass. Abstract A628.
78. Eholie E, Bissagnene Emmanuel BE, Ouiminga Maryam OM, et al. Adherence to HAART and its principal determinants in the HIV infected adults in Abidjan (Cote d'Ivoire). Presented at: XV International AIDS Conference; July 11-16, 2004; Bangkok. Abstract WePeB5790.
79. Ramadhani HO. Predictors of maladherence among patients receiving fixed dose combination Stavudine/Lamivudine/Nevirapine in Northern Tanzania. Presented at: 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colo. Abstract WeP91-553.
80. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487-497.
81. Liu H, Golin CE, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med*. 2001;134:968-977.
82. Akileswaran C, Lurie MN, Flanigan TP, Mayer KH. Lessons learned from use of highly active antiretroviral therapy in Africa. *Clin Infect Dis*. 2005;41:376-385.
83. Gill CJ, Hamer DH, Simon JL, Thea DM, Sabin LL. No room for complacency about adherence to antiretroviral therapy in sub-Saharan Africa. *AIDS*. 2005; 19:1243-1249.
84. Akam A. Anti-retroviral adherence in a resource poor setting. Presented at: XV International AIDS Conference; July 11-16, 2004; Bangkok. Abstract B12311.
85. Attaran A, Freedburg KA, Hirsch M. Dead wrong on AIDS. *Washington Post.* June 15, 2001;A33.
86. Moss AR, Hahn JA, Perry S, et al. Adherence to highly active antiretroviral therapy in the homeless population in San Francisco: a prospective study. *Clin Infect Dis*. 2004;39:1190-1198.
87. Wood E, Montaner JS, Chan K, et al. Socioeconomic status, access to triple therapy, and survival from HIV-disease since 1996. *AIDS*. 2002;16:2065-2072.
88. Bangsberg DR, Ware N, Simoni JM. Adherence without access to antiretroviral therapy in sub-Saharan Africa? *AIDS*. 2006;20:140-141.
89. Crane JT, Kawuma A, Oyugi JH, et al. The price of adherence: qualitative findings from HIV positive individuals purchasing fixed-dose combination generic HIV antiretroviral therapy in Kampala, Uganda [published online ahead of print April 25, 2006]. *AIDS Behav*. doi: 10.1007/s10461-006-9080-z. Accessibility verified July 17, 2006.
90. Mills E, Nachega J, Bangsberg D, et al. Adherence to antiretroviral therapy. Presented at: Ontario HIV Treatment Network Research Day; November 24-25, 2005; Toronto, Ontario. Abstract Ab 249.
91. Laniece I, Ciss M, Desclaux A, et al. Adherence to HAART and its principal determinants in a cohort of Senegalese adults. *AIDS*. 2003;17(suppl 3):S103-S108.
92. Nachega JB, Lehman DA, Hlatshwayo D, et al. HIV/AIDS and antiretroviral treatment knowledge, attitudes, beliefs, and practices in HIV-infected adults in Soweto, South Africa. *J Acquir Immune Defic Syndr*. 2005;38:196-201.
93. Orrell C. Antiretroviral adherence in a resource-poor setting. *Curr HIV/AIDS Rep*. 2005;2:171-176.
94. Rueda S, Park-Wylie L, Glazier R, Bayoumi A, Tynan A, Rourke S. Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS. Presented at: Ontario HIV Treatment Network Research Conference; October 26-28, 2005; Toronto, Ontario. Abstract A207.
95. World Health Organization Web site. 3 by 5 Initiative: country profiles. http://www.who.int/3by5/countryprofiles/en/index1.html. Accessibility verified July 7, 2006.
96. Braitstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy. *Lancet*. 2006;367:817-824.
97. Farmer P, Leandre F, Mukherjee JS, et al. Community-based approaches to HIV treatment in resource-poor settings. *Lancet*. 2001;358:404-409.
98. Severe P, Leger P, Charles M, et al. Antiretroviral therapy in a thousand patients with AIDS in Haiti. *N Engl J Med*. 2005;353:2325-2334.
99. Nachega JB, Knowton AR, deLuca A, et al. Treatment supporter to improve adherence to antiretroviral therapy in HIV-infected South African adults. Presented at: State of the Science Meeting on Research to Improve Antiretroviral Therapy Adherence; November 11-12, 2005; New Haven, Conn. Abstract 14.

