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ORIGINAL ARTICLE

Self-Report Measures of Antiretroviral Therapy Adherence: A Review with Recommendations for HIV Research and Clinical Management

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Abstract A review of 77 studies employing self-report measures of antiretroviral adherence published 1/1996 through 8/2004 revealed great variety in adherence assessment item content, format, and response options. Recall periods ranged from 2 to 365 days (mode = 7 days). The most common cut-off for optimal adherence was 100% (21/48 studies, or 44%). In 27 of 34 recall periods (79%), self-reported adherence was associated with adherence as assessed with other indirect measures. Data from 57 of 67 recall periods (84%) indicated self-reported adherence was significantly associated with HIV-1 RNA viral load; in 16 of 26 (62%), it was associated with CD4 count. Clearly, the field would benefit from item standardization and a priori definitions and operationalizations of adherence. We conclude that even brief self-report measures of antiretroviral adherence can be robust, and recommend items and strategies for HIV research and clinical management.

Keywords HIV/AIDS · Antiretroviral · Medication adherence · Self-report · Viral load

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Introduction

An abundance of convergent empirical evidence has confirmed that strict adherence to medication regimens is key to the successful treatment of HIV infection with antiretroviral therapy or ART (Bangsberg *et al*., 2000; Hogg *et al*., 2002; Paterson *et al*., 2000). However, there is decidedly less agreement on the best strategy for assessing ART adherence. An ideal assessment instrument would be reliable, valid, and logistically practical, with low participant and staff burden.

The search for an adherence assessment "gold standard" is not unique to the field of HIV (Geletko *et al*., 1996; Martin *et al*., 2001; Rudd, 1979; Rudd, Ahmed, Zachary, Barton, & Bonduelle, 1990; Straka, Fish, Benson, & Suh, 1997; Waterhouse, Calzone, Mele, & Brenner, 1993). Across multiple clinical conditions, researchers have examined a range of methodologies for capturing medication adherence. These have been categorized as either direct or indirect methods (Liu *et al*., 2001; Miller & Hays, 2000; Paterson, Potoski, & Capitano, 2002; Turner, 2002; Wutoh *et al*., 2003). Direct methods such as biological assays of active drug, metabolite or other markers in blood, urine, or other bodily fluids confirm active drug ingestion. Indirect methods, which do not measure the presence of the drug in the individual, include self-report, clinician assessment, medical chart review, clinic attendance, behavioral observation such as directly observed therapy, pill count (PC), pharmacy

refill (PR) records, electronic drug monitoring (EDM), and therapeutic impact such as HIV-1 RNA viral load (VL), CD4 lymphocyte count, Centers for Disease Control-defined stage of disease progression, and mortality. These assessment methods have advantages and disadvantages (Gao, Nau, Rosenbluth, Scott, & Woodward, 2000), with the trade-off generally assumed to be financial and logistical cost versus psychometric and epidemiologic accuracy (Gordis, 1979).

The present study focused on the most widely used indirect method of assessing ART adherence: self-report measures. The practicality of self-report makes this approach a likely candidate for continued widespread use in clinical and research settings, including in resource-poor countries just gaining access to ART.

Patient self-report measures in the form of personal interviews or written questionnaires have many advantages, including low cost, minimal participant burden, ease and speed of administration, flexibility in terms of mode of administration and timing of assessment, and the potential to yield specific information about the timing of doses and adherence to food requirements (Wagner & Miller, 2004). Additionally, the specificity of self-report measures is high, i.e., patients' acknowledgment of nonadherence is generally credible (Bangsberg *et al*., 2001). Moreover, a recent meta-analysis found that despite significant study heterogeneity, the pooled association between self-reported ART adherence and VL was statistically significant, adjusted OR = 2.31, 95% CI = 1.99–2.68 (Nieuwkerk & Oort, 2005).

On the other hand, self-report is susceptible to recall bias and inaccurate memory and potentially to social desirability bias; indeed, self-report does tend to produce estimates of adherence that are 10–20% higher than those from EDM (Arnsten *et al*., 2001; Wagner & Miller, 2004). Because of these limitations, some researchers have suggested that EDM or other less subjective methods may be preferable to self-report for adherence assessment in intervention trials (Miller & Hays, 2000). Others have noted practical limitations of EDM (Bova *et al*., 2005) and that adherence may be underestimated by EDM and overestimated by self-report and pill count, thus warranting the use of several adherence measures (Liu *et al*., 2001). This strategy, though, may be impractical for ongoing clinical use. Despite the perceived limitations, many clinicians and researchers alike continue to rely extensively on self-report adherence measures, probably because they continue to be the least costly and burdensome way to assess ART adherence.

For the present report, we conducted a review of the literature with the goals of identifying (a) the variety of self-report measures used in ART adherence research, (b) the pattern of associations between self-report and other adherence assessment strategies such as pill count and EDM, and (c) the relation between self-report and clinical indicators such as VL and CD4 lymphocyte count. Our aim was to determine best practices with respect to selecting self-report measures for both research purposes and clinical monitoring.

Selection of studies for review

We conducted an extensive search of PsycINFO, AIDS Line, and MEDLINE for articles published in refereed journals from January 1996 through August 2004 that contained some combination of the terms (a) *HIV* or *human immunodeficiency virus* or *AIDS* or *acquired immunodeficiency syndrome* and (b) *adherence* or *compliance*. Additionally, we scanned bibliographies of relevant articles and consulted with experts in the field for other references. From the resulting list of over 600 articles, we selected the English-language publications describing studies of individuals at least 18 years of age that utilized a self-report measure of ART adherence and reported its association with at least one other adherence assessment method (such as pill count or pharmacy refill records) or with an indicator of clinical impact (such as VL or CD4 count). We excluded the few early studies examining adherence to ART monotherapy, resulting in 77 published articles that met the a priori selection criteria.

Review strategy

From each article we extracted information on the study setting, location, and sample size; details regarding the self-report measure (including its source, number, and wording of items, and how adherence was operationalized for analysis); the recall period; and the measure's associations with other adherence measures and clinical indicators. These are presented as a reference source in Table 1. Although not noted in the Table, we also recorded eligibility criteria, sample characteristics, and study purpose and design.

After summarizing key descriptive information about the studies, we focused on describing the self-report adherence measures in detail and use χ^2 tests to assess the association between self-report and other adherence measures. Our examination of the reported associations between self-reported adherence and clinical outcomes such as VL include a forest plot graph to visually summarize reported association effect sizes (Fig. 1). In a sub-analysis, we examined the effect of recall period length on the association between self-reported adherence and VL using χ^2 tests of proportions and logistic regression.

Table 1 Studies reporting the association of self-reported antiretroviral adherence with adherence as measured by other indirect measures or with clinical indicators

Source	Study	Self-report measure	Recall period	Association with other indirect adherence measures	Association with clinical indicators
	Setting; location; sample size	Source/items/(nonadherence operationalization) (CO: continuous, CT: categorical, DI: dichotomous)		electronic data monitoring; pharmacy refills (PR); pill count (PC); other	HIV-1 RNA viral load (VL); CD4; other (adherent vs. nonadherent)
Alcoba *et al*. (2003)	2 HIV clinics; Spain; $N = 106$	N/R; N/R; DI: <90% of prescribed doses for at least one drug	4 days		VL detectable (*NS*); plasma indinavir levels (*NS*)
Aloisi *et al*. (2002)	57 ID hospital units; Italy; $N = 366$	N/R; 3 items; DI: "Yes" to all three items vs. <3	6 months		VL undetectable*** 68% vs. 40% @ 12 mo
Altice, Mostashari, and Friedland (2001)	4 prison HIV clinics; CT, US; $N = 164$	Ickovics '97; N/R; DI: 80% of pills taken/prescribed	7 days	PR $r = 0.82$ (significance N/R)	CD4 count (*NS*)
Ammassari *et al*. (2004)	11 clinical centers; Italy; $N = 135$	Murri '00; 1 forced-choice item on timing of last missed dose; DI: missed ≥ 1 dose over last 7 days	7 days		CD4 higher mean (*SD*)* 637 (341) vs. 509 (362)
Antinori *et al*. (2004)	Study cohort; Italy; $N = 238$	Murri '00; N/R; DI: missed ≥ 1 dose over last 7 days	7 days		VL rebound > 500 copies/mL (*NS*)
Arnsten *et al*. (2001)	Hospital study cohort; Bronx, NY, US; $N = 67$	N/R; N/R; CO: % of prescribed doses taken	1 day; 7 days	EDM; 1-day $r = 0.49$***; 7-day $r = 0.46$***	VL <500; 1-day $r = 0.43$***; 7 day $r = 0.52$***
Bangsberg *et al*. (2000)	Community cohort; San Francisco, US; $N = 34$	N/R; 3 items; CO: Mean value of 3 measures of % prescribed doses	3 days		VL $r = -0.60$***
Bangsberg *et al*. (2001)	Community cohort; San Francisco, US; $N = 45$	N/R; Day-by-day review of doses; CO: % prescribed doses, DI: >80%	3 days	PC $r = 0.85$***; PC $\kappa = 0.65$***; provider estimate (*NS*)	
Bangsberg *et al*. (2002)	Private clinic and county hospital; San Francisco, US; $N = 110$	AACTG (Chesney '00); Day-by-day review of doses on computer; DI: 90 and 80%	3 days	Provider estimate*** (test statistic NR)	VL detectable ≥500; <80% OR 3.0 (95% CI 1.1–8.1)
Barroso *et al*. (2003)	HIV reference center; Rio de Janeiro, Brazil; $N = 64$	N/R; 1 item; DI: taking as prescribed >80% days	30 days		VL<400; OR 7.2 (95% CI 1.6–31.9) in semen; OR_A 8.2 (95% CI 1.2–56.7) in plasma
Brigido *et al*. (2001)	Public AIDS clinic; São Paulo, Brazil; $N = 168$	N/R; 5 items; CT: Reg: all doses taken, qReg: miss up to 4 doses or 1 full day/mo, Ireg: all other irregular	30 days		VL median $\log_{10}$*; Reg 2.0 (1.6–5.6); qReg 2.0 (1.6–5.5); Ireg 3.6 (1.6–6.2); CD_4 median gain*; (test statistic N/R); AIDS development or death* (test statistic N/R)
Carrieri *et al*. (2001)	Routine clinical sites; France; $N = 436$	AACTG; 5 items for each drug; CT: 100%, 80–99%, <80%	4 days		VL undetectable at 4**; 12**, and 20 months** (test statistic N/R)

Table 1 Continued

Source	Study	Self-report measure	Recall period	Association with other indirect adherence measures	Association with clinical indicators
Carrieri *et al*., 2003	Routine clinical sites; France; $N = 360$	AACTG; 5 items for each drug; CT: 100%, 80–99%, <80%	4 days		VL suppression at 3 years: Highly adherent OR 3.4 (95% CI 1.4–7.9); Mod adherent *NS*; CD4 increase >200 by 3 years: highly adherent OR 2.4 (95% CI 1.0–5.5); Mod adherent *NS*
Catz, Kelly, Bogart, Benotsch, and McAuliffe (2000)	Outpatient ID clinic; Milwaukee, US; $N = 72$	N/R; 2 items; CT: missed doses daily, weekly, monthly, or never	3 months		VL <400* (test statistic N/R)
Cederfjall, Langius-Eklof, Lidman, and Wredling (2002)	Outpatient HIV clinic; Stockholm, Sweden; $N = 99$	N/R; 1, 7, 30 days = % missed in 1 month; DI: 95%	1 month		VL <50 71% vs. 45%*; CD4 <200 8% vs. 32%***
Cingolani *et al*. (2002)	Tertiary care ID department; Italy; $N = 127$	Murri '00; 1 item, timing of last missed dose; DI: missed before 2–4 weeks (adherent) vs. yesterday, last week	N/A		VL <500 at 3 mo* (test statistic NR); nonadherent OR 0.37 (95% CI 0.1–0.95)*; CD4 change; 3 mo + 50 vs. − 12**; 6 mo + 62 vs. − 13**
Cohn, Kammann, Williams, Currier, and Chesney (2002)	AACTG sites; 29 sites in US; $N = 643$	AACTG; 2 items; DI: 100%	48 hr		VL>500 nonadherence over 56 weeks; OR 2.3 (95% CI N/R); 70% vs. 50%***
Dorz *et al*. (2003)	2 ID departments; Padua and Verona, Italy; $N = 109$	N/R; 1 item; CO: # pills/ # prescribed, DI: 80%	7 days		VL mean 10,854 vs. 34,149*; CD4 mean 6899 vs. 379***
Duong *et al*. (2001)	AIDS outpatient clinic; Dijon, France; $N = 149$	PMAQ (Paterson '99); 4 items; DI: 100% (nonadherent score<4)	Combined: 4 days and 4 weeks		VL reduction; OR_A 2.9 (95% CI 1.2–7.1); Did not miss any PI last 4 days $r = .18$*
Duran *et al*. (2001)	Study cohort; France; $N = 277$	AACTG; 5 items; DI:100%	Combined: 4 days and weekend		VL undetectable 4 months after ART initiation 59.4% vs. 41.6%**
Duran *et al*. (2001)	Study cohort; France; $N = 57$	N/R; 1 item; CT: 100%, 99–80%, <80%	1 week		VL median $\log_{10}$** 100%: 2.3 (2.3–3.5); 80%–99%: 2.3 (2.3–3.6); <80%: 3.8 (2.6–5.04); VL undetectable** 100%: 73.1%; 80%–99%: 69.2%; <80%: 22.2%; CD4 (*NS*, $p = 0.06$); drug level***
Duran *et al*. (2003)	47 hospitals; France; $N = 642$	N/R; 5 items; CT: 100%, 99%–80%, <80%	4 days		VL detectable; 100%: OR 1.0; 99%-80%: OR 1.5 (95% CI 1.0–2.3); <80%: OR 2.3 (95% CI 1.3–4.1)
Eldred, Wu, Chaisson, and Moore (1998)	Hospital HIV clinic; Baltimore, MD, USA; $N = 244$	N/R; 1 item for each time frame; DI: 80%	7 days; 14 days	Medical record kappa 71%; 7 day: 60% vs. 56% (*NS*); 14 day: 74% vs. 67%**	

Fong *et al*. (2003)	HIV clinic; Hong Kong; $N = 161$	N/R; Number missed doses; DI: 100%	Since last visit		VL<500; OR_A 4.2 (95% CI 1.8–12.3)
Gao *et al*. (2000)	3 clinics; West Virginia, US; $N = 72$	Samet '92; N/R, assessed doses; CO: prescribed – missed/prescribed	2 days		Disease severity*
Garcia de Olalla *et al*. (2002)	HIV hospital unit; Barcelona, Spain; $N = 1219$	N/R; N/R; DI: 90%	1 month		Mortality: Non adherent; Relative hazard 1.5 (95% CI 1.2–1.99)
Gifford *et al*. (2000)	Community practices; San Diego CA, US; $N = 133$	CASQ (Berry '00) 4 items per drug taken; CT: 100%, 80–99%, <80%	7 days		VL $\log_{10}$ Each increase in adherence category associated with 1.3 $\log_{10}$ decrease**
Giordano, Guzman, Clark, Charlebois, and Bangsberg (2004)	Participants' usual place of residence; San Francisco, CA, US; $N = 84$	AACTG and Visual Analog Scale – VAS (Walsh '98); 4 items/drug (3 day), VAS-1; CO: Mean adherence over three visits	3 days (AACTG) 3 or 4 weeks (VAS)	Unannounced PC and VAS: $r = 0.76$ (95% CI 0.65–0.84); 3-day $r = 0.71$ (95% CI 0.59–0.80); (sig. N/R; *NS* diff betw VAS and 3 day)	VL; VAS: $r = -.49$ (95% CI -0.64–0.31); 3-day $r = -.34$ (95% CI -0.51–0.13); (sig. N/R; *NS* diff betw VAS and 3 day)
Godin, Gagne, and Naccache (2003)	4 HIV clinics; Montreal, Quebec City; $N = 256$	Researcher-created; 9 items, # pills missed/# prescribed; DI: 95%	1, 2, 7, 30 days		VL increase over 6 months; Nonadherent 1, 2, 30 day (*NS*); 7 days OR 1.9 (95% CI 1.0–3.6)
Golin *et al*. (2002)	3 public HIV clinics; N/R; $N = 117$	Composite score with EDM, PC, SR interview (Liu '01) 1 item CO: #doses taken/# prescribed	7 days	EDM $r = 0.38$ (sig. N/R); PC $r = 0.62$ (sig. N/R)	
Gordillo, del Amo, Soriano, and Gonzalez-Lahoz (1999)	HIV reference center; Madrid, Spain; $N = 366$	N/R; N/R; DI: 90%	Last week		CD4 at enrollment and good adherence; >500 OR_A 2.4 (95% CI 1.3–4.4); 200–499 OR_A 2.8 (95% CI 1.4–5.5)
Goujard *et al*. (2003)	Hospital centers; France; $N = 326$	AACTG, PMAQ, and 3 items re: instructions (Metcalf '98) 13 items; CO: Nonadherence score 0–26	N/R		VL lower (test statistics N/R)*** CD4 higher (test statistics N/R)*
Guaraldi *et al*. (2003)	8 tertiary centers; Northern, Central Italy; $N = 175$	MOS-HIV Health Survey N/R; 85% (>1 dose in 7 days)	7 days	Morphologic alterations; OR_A 2.36 (95% CI 1.1–5.0)	
Haubrich *et al*. (1999)	5 university HIV clinics; CA, US; N = 164 @ 2 months, 119 @ 6 months	N/R 24 items; assessed % prescribed doses taken; CT: 100%, 99–95%, <95–80%, <80%	4 weeks	Provider estimate kappa = 0.02 (*NS*)	VL $\log_{10}$ reduction (*SD*) @ 2 months* 100%, 99–95%, <95–80%, <80%; 0.95 (2.2); 0.79 (2.0); 0.57 (1.8); 0.04 (2.0); VL $\log_{10}$ increase (*SD*) @ 6 months* 100%: -1.1 (2.2); <80%: 0.2 (1.2); CD4 cells @ 6 months** 100%, 99–95%, <95–80%, <80% 72 (162); +87 (154); +54 (162); -19 (74)

Table 1 Continued

Source	Study	Self-report measure	Recall period	Association with other indirect adherence measures	Association with clinical indicators
Ho *et al.* (2002)	Clinic; Hong Kong; $N = 161$	Doung '01 1 item, % prescribed doses taken CT: 100%, 99–95%, 94–90%, <90%	4–6 weeks		VL detectable** $\leq$99% vs. 100% OR 4.2 (95% CI 1.8–12.3) Disease progression**
Horne *et al.* (2004)	Outpatient clinic; Brighton, UK; $N = 109$	VAS 1 item, correct dose timing; DI: 7 pt scale 0–6: cutoff $\geq$ 5	N/R		VL>400; 18% vs. 26% (*NS*); CD4 (*NS*)
Hugen *et al.* (2002)	University centre; Nijmegen and Arnhem Netherlands; $N = 26$	N/R; VAS; Multiple items; CT: 3 groups and range 1–10	N/R	EDM % taken on time*** $\rho = .73$; % taken** $\rho = .55$	N/R
Ickovics *et al.* (2002)	21 AACTG sites; Multisites, US; $N = 93$	AACTG 1 item for each drug DI: 95%	4 days		VL>50 @ 24 weeks <95% adherent OR 2.6 (95% CI 1.1–6.1) CD4 change (*NS*)
Ingersoll (2004)	University ID clinic; Virginia; $N = 120$	Medication Adherence Form (Ingersoll '99) Multiple items; DI: 95% PIs taken; DI: Adherence score 1–3, cutoff >2	1 week		VL undetectable 77% vs. 23%* CD4 <200 54% vs. 46%*
Kimmerling *et al.* (2003)	Clinics, community; Los Angeles, US; $N = 58$	N/R # doses taken q.d. of last 3; CO: score	3 days	EDM: $r = 0.47$*** Subset reporting missed doses (*NS*)	
Kleeberger *et al.* (2001)	Research cohort; Baltimore, Chicago, Pittsburgh, LA, US; $N = 393$	Modified AACTG; multiple items; DI: 100%	4 days		VL undetectable <50 copies; 53.3% vs. 37.4%** CD4 $\geq$ 400 (*NS*); 64.4% vs. 58.3%
Knobel *et al.* (2001)	University HIV clinic; Barcelona, Spain; $N = 679$	N/R; N/R; DI: 90%	1 month		VL <500; Adherent OR 3.1 (95% CI 2.2–4.2)***; nonadherent OR_A 0.4 (95% CI 0.2–0.7)**; CD4 mean increase 171 vs. 107**
Knobel *et al.* (2001)	69 hospitals; Spain; $N = 2528$ @ 3, 2127 @ 6, and 1797 @ 12 months	SMAQ (from Morisky '86); 6 items; DI: 95% (missed >2days in 3 mos; 2 doses 7 days or yes to 1/4 items)	Combined 1 weekend; 1 week; 3 months	EDM: sensitivity 72%; specificity 91%; PPV 91%; NPV 80%	VL <500; @ 3 months OR 2.2 (95% CI 1.8–2.6)***; @ 6 months OR 2.6 (95% CI 2.2–3.1)***; @ 12 months OR 2.5 (95% CI 2.0–3.1)***; VL >500; Nonadherent OR_A 1.7 (95% CI 1.4–2.1)
Knobel *et al.* (2004)	2 hospitals; Barcelona, Spain; $N = 85$	SMAQ (from Morisky '86); 6 items; DI: 90%	1 weekend; 1 week; 3 months		VL >500 @ first year: Nonadherent OR 5.2 (95% CI 2.1–13.3); OR_A 4.4 (95% CI 1.6–12.3)
Laniece *et al.* (2003)	3 health clinics; Dakar, Senegal; $N = 158$	N/R; N/R; # taken: #prescribed; DI: 90%	30 days		VL mean difference nonadherent; Month 18: 1.7 $\log_{10}$ copies*; Month 24: 1.8 $\log_{10}$ copies*
Le Moing *et al.* (2001)	47 clinical centers; Paris/France; $N = 750$	N/R; N/R; DI: 100%	4 days		VL <500: 84% vs. 73%***; OR 2.0 (95% CI 1.3–3.0)
Le Moing *et al.* (2002)	47 clinical centers; France; $N = 1129$	N/R; 5 items; categorical:100%, 80–99%, <80%	4 days		VL rebound = VL>500; 27% high adher. HR = 0.4 (95% CI 0.3–0.6)***; 34% moderate adher. HR = 0.6 (95% CI 0.4–0.8)**; 53% low adher. HR = 1.0

Liu *et al.* (2001)	Public HIV clinic; N/R; $N = 108$	N/R; 2 items, composite adherence score; CO: mean	1 week	EDM $r = 0.38^{***}$; PR: $r = 0.62^{***}$	VL <400 vs. VL>400 mean adherence 8 week (*NS*), 24 week* 0.97 (0.85–0.96) vs. 0.90 (0.85 − 0.96)
Lopez-Suarez, Fernandez-Gutierrez del Almo, Perez-Guzman, and Giron-Gonzalez (1998)	N/R; Cadiz, Spain; $N = 65$	N/R; N/R; DI: 80%	N/R		VL $\log_{10}$, 2 drug/3 drug regimen; 3 months: 2.9 vs. 4.4***/3.6 vs. 4.9*; 6 months: 3.1 vs. 4.5***/3.3 vs. 4.8*; CD4, 2 drug/3 drug regimen; 3 months: 550 vs. 356***/405 vs. 333*; 6 months: 567 vs. 416***/540 vs. 400*
Lucas, Cheever, Chaisson, and Moore (2001)	Johns Hopkins AIDS Service; Baltimore, MD, US; $N = 533$	N/R; N/R; DI: missed >2 doses in 2 weeks	2 weeks		VL $\log_{10}$ difference 0.4 (0.2–0.7); CD_4 cell difference − 12 (-40–15) (sig. N/R)
Maggiolo *et al.* (2002)	Outpatient clinic; Bergamo, Italy; $N = 597$	Modified AACTG (Chesney '00); N/R; DI: 100%	90 days		VL<50; 75.6 vs. 55.3%***
Mannheimer *et al.* (2002)	18 CPCRA Sites; US; $N = 1095$	CPCRA (Form 646, '02); N/R; CT: 100%, 80–99%, <80%	7 days		VL $\log_{10}$ decrease***; 100%: 2.8, 80–99: 2.3, <80%: 0.7; CD4 increase***; 100%: 179, 80–99: 159, <80%: 53
Martin *et al.* (2001)	Hospital HIV unit; Madrid, Spain; $N = 242$	N/R; 4 items, # of pills delivered/prescribed	6 days	SR vs. PR; 80% adherence cutoff: sens = 25%, spec = 86%, PPV = 49%, positive likelihood ratio (LR) = 1.8; 90% adherence: sens = 19%, spec = 84%, PPV = 58%, positive LR = 1.2	
Martin-Fernandez *et al.* (2001)	HIV unit; Madrid, Spain; $N = 283$	Tuldra '99; 2 items: Capable (1–5, cutoff <4); Effort (100 pt scale, cutoff <= 36); Pharmacy refill = gold standard; DI: 95%	N/R	Area under curve of measure; Capable 0.61 (0.54–0.67); Effort 0.64 (0.57–0.70). Concordance between negative response on 2 SR to PR kappa 0.25 (0.13–0.36)	
Mathews *et al.* (2002)	University HIV Clinic; San Diego, CA, US; $N = 175$	Modified AACTG (Chesney '00); 5 items; DI: Score 0–33 cutoff 5	30 days	EDM $\rho = -0.40$ (sig. N/R)	VL $\log_{10}$ difference*; 1 month: .04, 3 month: 1.1, 6 month: 1.3; VL undetectable*; CD4*; plasma level $\rho = -0.48$ (sig. N/R)
Melbourne *et al.* (1999)	Physician offices; Providence, RI, US; $N = 44$	N/R; N/R; CO: mean %	1 month	SR (*SD*) vs. EDM (*SD*) ; 1 month: 98% (3.6) vs. 90% (14)*; 2 month: 96% (5) vs. 90% (12.6)*	
Moatti *et al.* (2000)	Hospitals; Marseilles, Avigon, Nice, Paris, France; $N = 164$	N/R; N/R; DI: 80%	7 days		VL median $\log_{10}$ (range)**; 2.7 (2.3–5.6) vs. 3.9 (2.3–5.8); VL undetectable or decrease >1 $\log_{10}$ 57% vs. 40.3%*; CD4 median increase (*NS*); disease progression (*NS*)

Table 1 Continued

Source	Study	Self-report measure	Recall period	Association with other indirect adherence measures	Association with clinical indicators
Murri *et al*. (2001)	University HIV clinic; Rome, Italy; $N = 140$	Researcher-created; 16 items; DI: forgot 1 dose vs. >1 dose in 3 days	1 day; 3 days		VL detectable; nonadherent 3 days; OR 2.2 (95% CI 1.0–4.7); Plasma level PI 1 day: OR 15.9 (95% CI 4.9–50.7), 3 day: OR 4.4 (95% CI 1.7–11.9)
Nieuwkerk *et al*. (2001)	14 hospitals; The Netherlands, Belgium; $N = 160$	Researcher-created 3 items; DI: 100%	7 days	PC measure for saquinivir*; PC measure for ritonavir (*NS*)	VL>400 @ 48 weeks; nonadherent 40%, adherent 15%*
Nieuwkerk *et al*. (2001)	22 hospitals; The Netherlands; $N = 224$	Researcher-created 4 items; DI: 100%	7 days		VL>500; nonadherent OR 2.1 (95% CI 0.9–4.9); nonadherent OR_A 4.0 (95% CI 1.4–11.6); drug level median concentration (range) 1.1 (0.6–1.4) vs. 0.8 (0.51.1)***
Oyugi *et al*. (2004)	Research-affiliated clinics and hospitals; Kampala, Uganda; $N = 34$	AACTG (Chesney '00) and Visual Analogue Scale (VAS); N/R; CO: Mean	3 days (AACTG); 30 day (VAS)	EDM 3 day $r = 0.87$***; VAS 0.77***; PC 3 day $r = 0.89$***; VAS 0.86***; 3 day and VAS $r = 0.82$***	VL < 400 @ 12 weeks; 3-day $r = -0.42$**; 30-day VAS $r = -.036$*
Palepu, Horton, Tibbetts, Meli, and Samet (2004)	Medical and methadone clinics, respite facility; Boston, MA, US; $N = 194$	N/R; N/R; DI: 95%; CO: Mean	30 days		VL $\log_{10}$ mean (*SD*); 1.8 (1.8) vs. 2.7 (1.9)***; CD4 mean (*SD*); 414 (254) vs. 375 (216) (*NS*)
Pinheiro *et al*. (2002)	Public clinic; Pelotas, Brazil; $N = 195$	Researcher-created; N/R; DI: 95%	2 days		VL <500; 67.5% vs. 31.5%***; CDC disease stage (*NS*)
Pradier *et al*. (2001)	Research cohort: 12 outpatient hospitals in Marseilles, Avigon, Nice, and Paris, France; $N = 119$	N/R; 1 item for each medication; DI: 100% 3 groups: (1) no VL change or <0.5 decrease, (2) > 0.5 decrease but still detectable, (3) undetectable	7 days		VL $\log_{10}$; G3 vs. G2 = OR_A 5.8 (95% CI 1.5–22.1); G3 vs. G1 = OR_A 5.6 (95% CI 1.3–24.7)
Raboud *et al*. (2002)	N/R; Italy, The Netherlands, Canada, and Australia; $N = 311$	INCAS, AVANTI 2 and 3 studies; N/R; DI: Adherence from 3 different studies which each dichotomized differently 92.3, 75, 75%	28 days	PC (N/R)	Virologic failure; RR 3.0 (95% CI 1.4–6.1); Test statistics NR for the following: Virologic suppression**; Triple drug**, double drug (*NS*); VL undetectable *
Schuman *et al*. (2001)	Research cohort; Baltimore, Chicago, Detroit, New York, LA, Wash. DC, US; $N = 371$	N/R; 1 item; DI: 75%	2 weeks		VL undetectable; OR 3.9 (95% CI 1.8–8.5); CD4 ≥ 200; OR 2.1 (95% CI 1.0–4.3)*
Silveira *et al*. (2002)	HIV/AIDS service; Pelotas, Brazil; $N = 244$	N/R; 1 item (# tablets taken); CT: ≥ 95%, 94–80%, 79–60%, <60%	48 hr		VL <80 across groups OR ≥ 95%: OR 5.5 (95% CI 2.6–11.9); 60–79%: OR 4.2 (95% CI 1.3–13.3); 80%–94%: OR 5.6 (95% CI 2.2–14.1); <60%: 1.0

Spire *et al.* (2002)	Research cohort, 47 hospitals, France; $N = 445$	N/R; 3 items; DI: 100%	4 days		VL $\log_{10}$ median decrease @ 4 months; 1.7 vs. 1.3***; VL ≤ 500 77% vs. 60%***
Trotta *et al.* (2003)	Research cohorts; Rome and other sites, Italy; $N = 596$	Murri '00; 16 items; DI: 86% (missed ≥ 1 dose last 7 days)	7 days		VL ≤ 500; nonadherent OR 0.7 (95% CI 0.5–0.9); CD4 <200/mm; OR 0.6 (95% CI 0.3–1.0, $p = .06$)
Vincke and Bolton (2002)	N/R; Belgium; $N = 86$	PI attitude scale (Weiss N/R) 3 items Ordinal: scale (1–5, 5: excellent)	4 weeks	Clinician: $r = -0.25$ (*NS*); Significant other: $r = -0.42$**	VL; $R = 0.30$ (sig. N/R)
Wagner *et al.* (2001)	3 VA Medical Centers; Cleveland, OH, Houston, TX, Manhattan, NY, US; $N = 793$	N/R; 4 items; CT: 0 (poor), 1, 2 (perfect)	4 days	SR and provider agreement; kappa −.03, (−.09,.03) (*NS*)	VL <400; 55% vs. 36% vs. 22%***; OR_A 0.9 (95% CI 0.8–1.3); VL median 141 vs. 393 vs. 1679***; OR_A 0.04 (95% CI −0.2–0.1)
Wagner, 2002	CBOs, clinics; Los Angeles, USA; $N = 180$	Modified AACTG (Chesney '00) N/R; CO: Mean	3 days	4-week EDM: $r = 0.34$**	
Wagner *et al.*, 2003	Mental health community; LA, CA, US; $N = 47$	N/R; N/R; CO: Means	3 days; 2 weeks	EDM 3 days*** $r = 0.61$; 2 weeks*** $r = 0.63$	VL $\log_{10}$ $r = -0.39$* (recall period N/R); VL $\log_{10}$ mean (*SD*); 3 day: 2.3 $\log_{10}$ (1.0) vs. 3.5 $\log_{10}$ (1.2)**; CD4 3 days (NS); 14 days (NS)
Walsh *et al.* (2001)	Publicly funded clinic; N/R; $N = 178$	Researcher-created; N/R; CO: Median	30 day and VAS (30 days)	PR $\rho = 0.19$**; Nurse rating $\rho = 0.51$**; MD rating $\rho = 0.33$**¶	
Walsh *et al.* (2002)	Public HIV clinic; London, England; $N = 78$	AACTG (Chesney '00), Hecht '98, Fletcher '79; 6 items: 3 –3day; 1–2 week, 1 last missed; VAS 30 day (0–100%); CO: Mean	3 day; 2 weeks; 30 day (VAS)	EDM: Univariate linear regression; 3 day $r = 0.32$; 0.68 (95% CI 0.23–1.13)**; 2 week $r = 0.62$; 1.21 (95% CI 0.86–1.56)***; VAS $r = 63$; 1.09 (95% CI 0.78–1.39)***	VL<50; 3 day (*NS*); 14 day $\rho = -0.30$**; VAS $\rho = -0.28$**
Weiser *et al.* (2003)	3 private clinics; Gaborone, Francistown, Botswana; $N = 93$–109	Modified AACTG (Chesney '00); N/R; DI: 95%	1 year	SR and provider agreement; Kappa = .35, $x^2 = 11.13$***	
Wutoh *et al.* (2001)	2 large HIV clinics; Washington DC, US; $N = 100$	N/R; N/R; CO: Mean	7 days		VL mean; $\rho = .-312$**

Notes. N/R: Not reported, *NS*: Non-significant, ID: Infectious disease, *SD*: Standard deviation, PI: Protease inhibitor.

[a] Odds ratios, hazard ratios, and relative risks are unadjusted unless denoted by subscript "A"; 95% confidence intervals denote significance unless only a *p*-value is given.

[b] Correlation statistics are Pearson's *r* or Spearman's ρ.

[c] Significance level was calculated from data provided in the article using a 1 sample test of proportion.

[d] Significance level was calculated from data provided in the article using a 1 sample *t*-test.***

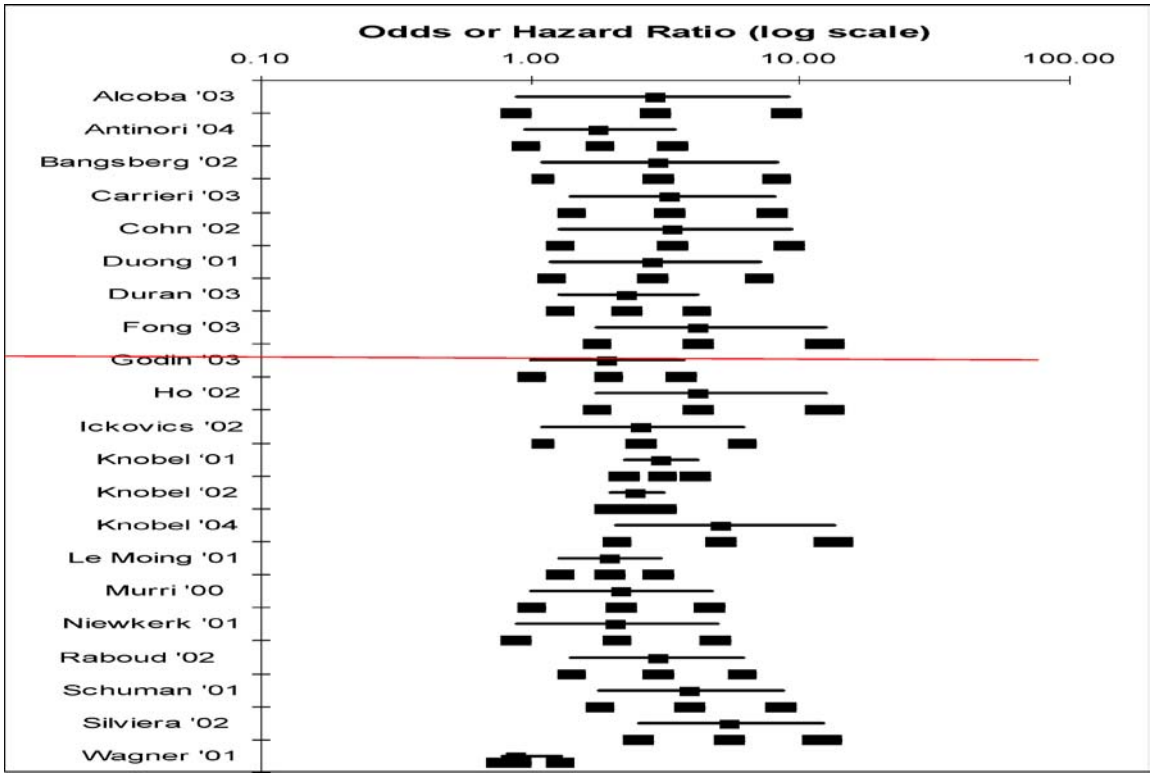


Fig. 1 Association is between (a) adherence and VL suppression or (b) nonadherence and VL increase or rebound. Excludes 4 studies that showed statistically significant associations due to overly-wide confidence intervals (Barroso *et al.,* 2003) or because the association was reported differently (e.g., nonadherence as protective from VL suppression) and could not be re-calculated from published data (Cingolani *et al.,* 2002; LeMoing *et al.,* 2002; Trotta *et al.,* 2003)

Findings from the review

Study description

Study date, location, and setting

The number of publications peaked in the years 2001–2002 (1997 $n=1$; 1998 $n=1$; 1999 $n=3$; 2000 $n=6$; 2001 $n=22$; 2002 $n=22$; 2003 $n=14$; and through August 2004 $n=8$). The vast majority of studies were conducted in the United States (US, $n=26$) and Europe ($n=38$), mainly France ($n=12$), Spain ($n=9$), or Italy ($n=9$). There were two from Asia, both from Hong Kong (Fong *et al*., 2003; Ho, Fong, and Wong, 2002), four from South America, all from Brazil (Barroso *et al*., 2003; Brigido *et al*., 2001; Pinheiro, de-Carvalho-Leite, Drachler, and Silveira, 2002) and only three recent reports from Africa, in Uganda (Oyugi *et al*., 2004); Botswana (Weiser *et al*., 2003); and Senegal (Laniece *et al*., 2003). Most studies ($n=61$) occurred in hospital-based outpatient clinics, either offering HIV primary care or specializing in infectious diseases.

Eligibility criteria and sample characteristics

Eligibility criteria varied greatly across studies. Some studies enrolled any adult patients on ART, while others had extensive inclusion and exclusion criteria that created highly specific samples. Most studies referred to at least one of the following as part of their eligibility criteria: Disease status or clinical status as measured by CD4 count and VL; coexisting problems such as substance use; type of regimen (most required inclusion of a protease inhibitor); treatment experience (many studies required participants to be ART-naïve or on ART for no more than a specified amount of time); and pregnancy status (some studies excluded pregnant women).

Study sample size ranged from 26 (Hugen *et al*., 2002) to 2528 (Knobel *et al*., 2002); only five studies had fewer than 50 participants. The majority of participants in almost every study was male (range = 29 to 100% male). Specifically, in the 71 studies reporting sex of participants, 62 included samples that had at least 60% males; two studies had no female participants, and two studies had no male participants. Most studies did not include sufficient numbers of women

to conduct analyses by sex. Where reported, these generally indicated that there were no sex differences in adherence levels and no interactions by sex among the adherence measures and other factors. Most participants in the US studies were members of racial/ethnic minority groups; in European samples, race/ethnicity was rarely reported. Some studies provided data on baseline disease stage, VL, or CD4 count.

Study design and purpose

Eighteen studies employed cross-sectional survey designs, often including chart-extracted reports of VL and CD4 counts. The earlier studies generally aimed to identify predictors of nonadherence and often were embedded within clinical trials; later studies often involved sub-analyses of intervention trials. Six studies set out specifically to evaluate adherence measures (i.e., Martin-Fernandez, Escobar-Rodriguez, Campo-Angora, & Rubio-Garcia, 2001; Martin *et al*., 2001; Murri *et al*., 2001; Vincke & Bolton, 2002; Wagner *et al*., 2001; Walsh, Mandalia, & Gazzard, 2002).

Self-report adherence measures

The most common self-report measure consisted of a single item querying the number of prescribed doses the participant had missed in a specified time period ($n = 22$). There was great heterogeneity among other assessment measures, which included items assessing missed doses on the weekends and adherence to dietary restrictions. Apart from the Adult AIDS Clinical Trials Group (AACTG) adherence measurement form and its variations, which were used in 15 studies, a visual analog scale (six studies), and the Simplified Medication Adherence Questionnaire (two studies), no other single instrument was used in more than one study.

Twenty-five studies did not provide important details about the adherence assessment strategy they employed. Those that did described measures ranging from one item to the lengthy AACTG measure that addresses each medication over each of the last 3 days in terms of number of doses taken per day, number of pills taken per dose, and adherence to any special dietary instructions (Chesney *et al*., 2000). Measures varied with respect to recall period (from 2 to 365 days); item response format (i.e., closed-ended, open-ended, Likert-type, visual analogue); and whether introductory statements normalizing nonadherence were included. Psychometric properties such as internal consistency of multi-item scales were reported in only three studies.

Most self-report interview modalities appeared to involve paper instruments, although this information was not always explicitly provided. Two studies employed computer-assisted self-interviews (Bangsberg, Bronstone, & Hofmann, 2002; Pinheiro *et al*., 2002); two were conducted over the telephone (Silveira, Draschler Mde, Leite, Pinheiro, & da Silveira, 2002; Wagner, Kanouse, Koegel, & Sullivan, 2003); and none involved the internet. Few studies reported whether providers, study staff, or the patients themselves administered the interviews.

The construct of adherence was operationalized for the data analyses in a variety of ways–sometimes multiple ways in the same study. A continuous measure of percentage of doses taken was calculated often as

$$\frac{\text{Prescribed doses} - \text{missed doses}}{\text{Prescribed doses}} \times 100.$$

Other researchers created a summary score based on some combination of multiple items. Frequently, adherence data were converted to dichotomous indicators of adherent versus nonadherent patients, with thresholds, often apparently assigned post hoc, of 80% ($n = 6/48$ or 13% of recall periods assessed), 90% ($n = 7/48$, 15%), 95% ($n = 11/48$, 23%), or 100% ($n = 21/48$, 44%) or less of prescribed doses taken.

Association of self-report and other measures of adherence

As seen in Table 2, 27 of the studies reported data on the association between self-reported adherence and adherence as assessed with another indirect measure of adherence, including EDM ($n = 11$); pharmacy refill records ($n = 9$); clinician assessments ($n = 7$); pill counts ($n = 3$, of which two were unannounced); chart review (patient report of adherence to provider; $n = 1$); and morphologic alterations ($n = 1$). In 27 of the 34, or 79%, of the recall periods examined in these studies, associations were significant or resulted in moderately strong kappa values. Sample sizes were insufficient to compare the level of association by assessment technique.

Association of self-reported adherence and clinical indicators

Most of the studies (60 of 77 or 78%) assessed VL, although the types of tests and their detection thresholds (e.g., Roche Amplicor, 50 copies/μL) were not uniformly described. Many were taken from a review of medical records instead of based on blood samples drawn on the same day adherence was assessed. Analyses of the relation between self-reported adherence and VL most often involved bivariate tests of association such as Pearson product moment correlations. These rarely controlled for confounders or assessed potential effect modifiers such as previous experience with ART. When they did, the association between self-reported adherence and VL usually remained statistically significant (e.g., Alcoba *et al*., 2003; Nieuwkerk, Gisolf, Sprangers, & Danner, 2001).

Table 2 Association of self-reported antiretroviral adherence with adherence as measured by other indirect measures or with clinical indicators, by recall period

	Self-reported adherence recall period (days)											
	1	2	3	4	7	14	28	30	30 (VAS)	90, 180, or 365	Combined time periods or "last missed"	Total
Clinical impact												
HIV-1 RNA viral load (VL)	1/3[2–4]	3/4[3, 5–7]	4/6[4, 8–12]	9/10[13–22]	13/16[2, 3, 23–35]	3/3[11, 12, 36]	3/3[37–39]	10/11[3, 10, 12, 40–47]	2/2[10, 12]	3/3[48, 4950]	6/6[51–56]	57/67
Plasma Rx level	1/1[4]		1/1[4]	0/1[22]	2/2[24, 35]			1/1[40]				5/6
CD4 count			0/1[11]	1/4[14, 16, 17]	7/11[23, 24, 26, 28, 29, 32, 34, 57–59]	2/3[36, 60]	1/1[54]	4/5[41, 42, 44, 46, 47]			1/1[51]	16/26
Disease progression/mortality		1/1[61]	0/1[6]		0/1[29]		1/1[39]	2/2[41, 62]				4/6
Other indirect measure of adherence												
Electronic data monitoring	1/1[2]		4/4[11, 12, 63, 64]		2/2[2, 27]	2/2[11, 12]		2/2[65]	2/2[10, 12]			13/13
Pill count			1/1[66]	1/1[43]	1/2[30]				2/2[10, 43]			5/6
Pharmacy refill					1/1[27, 67]				1/1[68]			2/2
Provider estimate			0/2[9, 66]	0/1[21]			0/1[69]		2/2[68]	1/1[70]		3/7
Other					1/2[37, 71]	1/1[71]	1/2[37, 69]					3/5
Significance not reported			VL[43]				PC[38] VL[46, 69]	PL[46] EDM[72]	VL[43]			

Notes. Fractions indicate the proportion of associations that were statistically significant (i.e., $p < 0.05$ or 95% confidence intervals excluding 1.0). Unadjusted results are reported where available. Superscripted numbers refer to citations that are marked with an asterisk in the References section. Note that some studies provided data on more than one recall period. Not represented in this table: Goujard *et al*., 2003; Horne *et al*., 2004; Hugen *et al*., 2002; Lopez-Suarez *et al*., 1998; Martin-Fernandez *et al*. 2001, as self-report recall period could not be determined. Results for mean VL, detectable VL, and different VL outcome categories (e.g., >500 cells, 200–499) were entered individually if separate analyses were conducted. 'Other' = medical record, morphologic alterations, or significant other.

In 57 of 67 (85%) of recall periods assessed (note that some studies reported data on more than one recall period), self-reported adherence was significantly related to VL (see Table 2). The magnitude of the significant correlations ranged from 0.30 to 0.60. Across different recall periods, odds ratios and hazard ratios of the association between self-reported adherence and VL were on the order of 2.0, with 95% confidence bounds generally excluding 1.0 (see Fig. 1). Findings from analyses of the proportion of patients with good adherence (with viral suppression as the outcome) and of the proportion of patients with poor adherence (with higher VL as the outcome) were comparable.

As seen in Table 2, fewer studies found a positive correlation between self-reported adherence and CD4 count (16/26 or 62%) of recall periods. Five studies (Brigido *et al*., 2001; Gao *et al*., 2000; Ho *et al*., 2002; Moatti *et al*., 2000; Pinheiro *et al*., 2002) reported associations of self-reported adherence with disease progression as defined by development of a new opportunistic infection or disease staging; three were significant. Two studies assessed mortality as the outcome; in both, the association with self-report was significant (Brigido *et al*., 2001; Garcia de Olalla *et al*., 2002).

Association of length of recall period and VL

As seen in Table 2, there was some suggestion of an effect of the length of the self-report adherence assessment recall period on the relation with VL: Adherence was associated with VL in 88% of recall periods that were greater than 3 days and in 64% of those that were 3 days or less, χ^2 $(N = 63) = 4.16$, $p = 0.04$. However, an unadjusted bivariate logistic regression included 1.0 (crude odds ratio 0.25, 95% confidence interval 0.06–1.0, $p = 0.05$).

Conclusions and implications

A review of the literature on self-report measures of ART adherence identified 77 published articles meeting eligibility criteria. Most were published in 2000–2001 and were based on data from hospital-based clinic samples of predominantly men from the US and Europe. The most common assessment strategy involved asking patients about the number of missed doses over a specified recall period; otherwise, there was great variability in the content of the items, the response format, and the recall period. The lack of widespread use of standardized measures made it difficult to evaluate any particular measure or to compare measures across studies.

Nonetheless, self-reported adherence was significantly related to adherence as assessed by other indirect measures such as EDM and pill count in 79% of studies comparing measurement approaches. Although we were not able to statistically examine these issues in this review, it would be helpful to know which techniques are most closely associated with VL and whether any socio-demographic indicators moderate these relationships. Self-report measures may not be feasible with some individuals (such as the cognitively impaired); therefore, data on which other methods are appropriate options would be useful.

We observed a robust pattern of association between self-reported adherence and VL: In 84% of recall periods, self-reported adherence was associated with VL based on odds ratios or simple measures of correlation. The association was statistically significant across a variety of self-report measures, administration modalities, and recall periods. These findings are consistent with the conclusions of a recent meta-analysis of adherence studies (Nieuwkerk & Oort, 2005). These results may provide some reassurance to practitioners and researchers employing self-reported adherence strategies.

There was some suggestion that longer recall periods may be more likely than shorter ones to yield estimates of adherence that are significantly correlated with VL, although this was not statistically conclusive in our review or in the previously published meta-analysis (P. Nieuwkerk, personal communication April 21, 2005). The association between self-report and CD4 was less consistent, a finding that is not entirely unexpected, as viral load and CD4 count generally correlate but discordant results are common. Furthermore, CD4 response can be somewhat delayed following initial ART initiation. For this reason, many experts believe that VL is the best measure of therapeutic response to ART, though CD4 remains the best clinical prognostic indicator (Bartlett & Gallant, 2004).

These findings are limited by several factors. Because most of the studies were conducted in the West, results may not be generalizable to resource-poor settings. The lack of data on refusal rates and the preponderance of non-probability samples of patients who were largely in care, participants in cohort studies, or volunteers receiving monetary incentives further limit the generalizability of these findings to other HIV populations. Relatedly, we were not able to determine whether self-report measures have differential validity for groups varying in socio-demographic or disease factors, because these variables, if assessed and reported, were not usually included in the analyses and small sample sizes limited the ability to conduct subgroup analyses. The possibility of publication bias—that studies with non-significant associations between adherence and VL are

less likely to be published—also cannot be definitively ruled out.

Lack of information about the interviewer's relationship to the participant and mode of interview administration (DiMatteo, 2004; Rudd *et al*., 1990), as well as the lack of any systematic manipulation of these two variables in the studies we reviewed, limits the extent to which we can comment on their relevance to our findings. It is worth exploring whether audio computer-assisted self-interviews (ACASI) can contribute to the quality and validity of ART self-reporting, as has been seen with respect to sex and other sensitive behaviors (Schroder, Carey, & Vanable, 2003). An example of the visual analog scale as presented in a handheld computer can be viewed at http://faculty.washington.edu/wcurioso/emulator/emulator.htm.

Finally, the timing of the adherence assessment may affect the strength of its association with clinical outcome. We would not expect perfect agreement between assessment of self-reported adherence over a brief, recent recall period and current VL, given all the other potential effect modifiers such as co-morbidity and earlier periods of nonadherence that may have resulted in resistance (Bangsberg *et al*., 2003). Most studies examined the association of adherence and VL cross-sectionally, but adherence over time (serial measurements within patients) may better predict VL prospectively. Longitudinal HIV studies increasingly include tests for genotypic or phenotypic resistance, parameters that may be useful in future ART adherence evaluations.

Obtaining accurate data on the association between assessed ART adherence and relevant outcomes requires methodologically precise studies. Future research in this area should report baseline characteristics that may confound or modify (Raboud, Harris, Rae, & Montaner, 2002) the association between self-reported adherence and health outcomes, including CD4 count nadir, baseline VL, class and duration of previous ART experience, and possibly, evidence of specific ART viral resistance. This precision will enable more accurate estimations of the quality of assessment methods, although given the complex and dynamic nature of HIV disease, no single adherence assessment measure can be expected to correlate perfectly with clinical indicators or clinical outcomes.

Recommendations for best practices in HIV research and clinical management

Our findings suggest that both researchers and clinicians may proceed with the use of self-report measures of ART adherence with some confidence in their validity at least in terms of their associations with other indirect measures of adherence and VL, a reliable surrogate marker of clinical impact. Some experts have advocated the use of multiple adherence measures (Caplan, Harrison, Wellons, & Frech, 1980; Ickovics, 1997; Konkle-Parker, 2000; Samet, Sullivan, Traphagen, & Ickovics, 2001). Our findings suggest this may not be routinely required in clinical arenas, where VL and other biological markers are often readily available and funds for additional assessments are limited. However, there are at least two situations in which further assessment may be warranted.

First, in intervention trials, the use of less subjective methods such as EDM or unannounced pill counts may be worthwhile because of the potential reporting bias with self-report strategies in the intervention conditions. Second, although patient reports of nonadherence can generally be believed, clinicians may be at a loss to interpret individual patient reports of perfect (100%) adherence. Pharmacy refill data, where accessible, may be useful in validating self-reported "perfect" adherence. In one study, adherence as measured by time-to-pharmacy refill was able to distinguish VL impact among self-reportedly perfect adherers (Grossberg, Zhang, & Gross, 2004). Other strategies to mitigate the ceiling effect of reportedly perfect adherence include calculating the proportion of times across multiple interviews that 100% adherence was reported and supplementing the standard 3-day missed dose item with another item assessing the timing of the last missed a dose or whether any doses were missed in the last 30 days (Mannheimer, Friedland, Matts, Child, & Chesney, 2002). These approaches may assist clinicians in identifying patients claiming to be adherent who, in fact, need ART adherence support.

When employing self-report strategies, researchers and clinicians alike should capitalize on the flexibility of self-report methodologies and inquire beyond the assessment of missed doses, gathering information on other aspects of adherence such as knowledge of medication names and prescribed dosing regimens, attention to special dietary instructions, and patterns of nonadherence on weekends, mid-day, or when daily schedules change. Barriers to adherence and facilitators are also important factors that are inaccessible with other adherence assessment methodologies.

Adherence experts have developed guidelines for assessment that are geared toward minimizing social desirability. These include using self-administered measures with open-ended and forced choice items; broaching the topic with a preamble acknowledging the low prevalence and difficulty of perfect adherence; wording items in such a way that nonadherence is presented as expected and accepted; querying reasons for nonadherence; focusing on recent behavior; specifying a time frame; aiding recall when possible using medication lists and diagrams of pills; anchoring reports to salient events; embedding threatening with non-threatening items; using authority to justify and normalize the behavior; and ending with a reliability check of the accuracy of responses (Miller & Hays, 2000).

Fig. 2 Recommended items for assessing self-reported antiretroviral adherence

[a] Many patients find it difficult to take all their HIV medications exactly as prescribed.

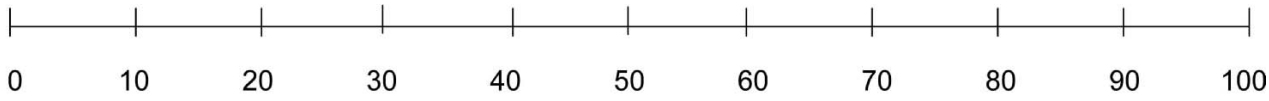
How many doses of your HIV medication did you miss in the last 7 days? (# doses)

[b] Put a mark on the line below at the point that shows your best guess about how much of your prescribed HIV medication you have taken in the last month. We would be surprised if this were 100% for most people.

Examples: 0% means you have taken no medication

50% means you have taken half your medication

100% means you have taken every single dose of your medication



[c] Do you ever forget to take your HIV medications? (Yes or No)

[c] Sometimes if you feel worse, do you stop taking your HIV medications? (Yes or No)

[c] Did you not take any of your HIV medications over the past weekend? (Yes or No)

What makes it difficult to take your HIV medications regularly? (Write in response)

Notes: [a]Based on Golin *et al*. (2002); [b]Based on Wash, Mandalia, and Gazzard (2002). An exact percentage can be calculated by measuring the distance from 0 to mark in cm or inches; [c]Based on Knobel *et al*. (2002).

Researchers designing statistical analyses and clinicians seeking guidance for advising patients could benefit from recommendations regarding an appropriate threshold of adherence necessary for favorable clinical outcomes. In the studies we reviewed, thresholds appeared to be often determined post hoc, increasing the probability of Type I error. In some instances, a threshold was predetermined but analyses were conducted with a continuous measure of adherence. Generally speaking, parametric tests of continuous variables will have more power than nonparametric analyses of dichotomous variables but will not define a clinically relevant cutoff. Given that continuous measures of self-report are highly skewed and non-normal, it may be most valid to dichotomize at 100% for statistical analyses. However, as a clinical goal, this level may be unreasonable for patients in the long term. Optimal virologic success declines rapidly in patients taking fewer than 95% of their prescribed doses (Paterson *et al*., 2000). Nonetheless, one study using pharmacy refill data among 923 HIV-positive patients showed that there was no difference in the risk of disease progression between those with moderate (70–90%) and high (>90%) levels of adherence compared to those with low (<70%) adherence (Kitahata *et al*., 2004). It is worth exploring whether patients can reliably make fine distinctions about their adherence behavior, such as judging it as either less than 80% or less than 85% (Bangsberg, Moss, & Deeks, 2004).

Which recall period is best to use is an open question. Patients do report more accurately over briefer time periods, with accuracy dropping off as rapidly as beyond 24 hr (Turner & Hecht, 2001; Wagner & Miller, 2004; Walsh, Horne, Dalton, Burgess, & Gazzard, 2001). It is worth considering, however, whether somewhat longer recall periods may yield more useful data as the increasing use of once-daily ART dosing may now result in too few dosing times in a very brief (i.e., 1–3 day) recall period to provide sufficient variability in adherence (Paterson *et al*., 2000). A very short interval may not allow for differentiation between patients whose good adherence is consistent and those who report good adherence over a recent brief time period but who are generally less adherent. A particular advantage of a 7-day recall period is that it will always include a weekend, during which adherence is often problematic.

Recommended self-report measures are presented in Fig. 2. These items are drawn both from the literature and from clinical experience and incorporate use of normalizing language, 7-day recall, and exploration of barriers to adherence (Morisky, Green, & Levine, 1986). Many different self-report measures appear to have an association with VL. Researchers and clinicians may choose single or multiple items based on their needs, weighing the need to assess inaccurate dosing or dietary adherence with the desire to reduce respondent burden. Longitudinal use of the increasingly utilized visual analog scale may be enhanced by measuring the exact distance from zero to the patient's mark. We suggest use of the term "dose" over "pills" as patients generally do not take partial doses (G. Wagner, personal communication March 2, 2005) and it is easier to calculate the number of missed doses than the exact number of pills missed across missed doses. Exploring the reasons why patients "forget" to take their medications may uncover important issues that can be addressed with subsequent potential problem-solving (Bartlett, 2002). More consistent use of items such as these

would allow comparison of self-report measure psychometric and clinical performance across populations.

The ability to make more definitive recommendations regarding precise measurement strategies will be enhanced with further research that explicitly addresses some of the issues we have raised. In the meantime, results from this extensive literature review offer some direction for HIV researchers and clinicians in their critically important work attempting to address and enhance ART adherence.

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(Numbered asterisks indicate studies cited in Fig. 1)

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