

Pharmacy Adherence Measures to Assess Adherence to Antiretroviral Therapy: Review of the Literature and Implications for Treatment Monitoring

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Prescription or pill-based methods for estimating adherence to antiretroviral therapy (ART), pharmacy adherence measures (PAMs), are objective estimates calculated from routinely collected pharmacy data. We conducted a literature review to evaluate PAMs, including their association with virological and other clinical outcomes, their efficacy compared with other adherence measures, and factors to consider when selecting a PAM to monitor adherence. PAMs were classified into 3 categories: medication possession ratio (MPR), pill count (PC), and pill pick-up (PPU). Data exist to recommend PAMs over self-reported adherence. PAMs consistently predicted patient outcomes, but additional studies are needed to determine the most predictive PAM parameters. Current evidence suggests that shorter duration of adherence assessment (≤ 6 months) and use of PAMs to predict future outcomes may be less accurate. PAMs which incorporate the number of days for which ART was prescribed without the counting of remnant pills, are reasonable minimum-resource methods to assess adherence to ART.

Since the introduction of combination antiretroviral therapy (ART) in the mid-1990s, human immunodeficiency virus (HIV)-1 infected patients have experienced decreasing levels of morbidity and mortality in both high-income countries (HICs) and low- and middle-income countries (LMICs) [1–3].

Successful HIV treatment largely depends on patient adherence to ART. Suboptimal adherence predicts virological failure [4–7], the development of HIV drug resistance [8–10], and death [11–13]. Standardized,

simple, and routine cost-effective monitoring of adherence is necessary to identify patients at risk of poor outcomes who would benefit from targeted adherence support [14]. Two simple methods for assessing adherence are patient self-report or prescription- or pill-based adherence measures, referred to in this review as “pharmacy adherence measures” (PAMs). Unlike patient self-reported adherence, which can be affected by recall or social desirability bias, PAMs are objective and may be calculated from information routinely available in medical and pharmacy records [14].

The World Health Organization (WHO) recommends the assessment of adherence to ART with every patient contact [15]. Despite these recommendations, there is no consensus regarding the optimal method to estimate individual- and population-level adherence to ART [15, 16]. This review summarizes currently available knowledge on PAMs, identifies their strengths and limitations, proposes factors to consider when selecting

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a PAM to monitor adherence and predict treatment outcomes, and identifies areas for future research.

DEFINITIONS AND SEARCH STRATEGY

PAMs are prescription- or pill-based adherence estimates calculated using dates of prescription refills and/or pill counts performed during routine clinic visits. Importantly, PAMs do not include self-reported measures, PCs performed outside of routine clinic visits (eg, unannounced PCs), monitoring of antiretroviral drug levels or monitoring with electronic devices (eg, electronic pill bottle [MEMS] caps). For purposes of clarity, we define the period of time over which individual patient adherence is estimated as “the duration of adherence assessment.” In addition, we identify 3 broad categories of PAMs: MPR, PC, and PPU. Definitions and formulae used to calculate these adherence estimates are provided in Table 1.

We searched PubMed, the Cochrane Database of Systematic Reviews, and the ISI Scientific Citation Index databases, using the terms “HIV” and “adherence” or “compliance,” together with “pharmacy,” “prescription,” “pill count,” “medication possession,” or “pick-up,” for articles published from inception until April 2010. We also searched reference lists of all included studies. All English-language publications investigating associations between PAMs and the following outcomes of interest were included: virological failure or suppression (ie, viral load greater or less than a defined threshold), change in viral load, immunological failure, HIV drug resistance, or mortality. Studies in which the outcome of interest occurred before the estimation of patient adherence or in which estimates were calculated by combining a PAM with an additional adherence measure were excluded.

If different adherence analyses were published using data from a single cohort, we selected the publication that provided the most information. Because of marked study heterogeneity, meta-analyses were not performed.

ASSOCIATION BETWEEN PAMs AND PATIENT OUTCOMES

In total, we identified 36 studies that met our inclusion criteria: 12 from LMICs (Table 2) [4, 13, 17–26] and 24 from HICs (Table 3) [10, 11, 27–48]. All LMIC studies were from sub-Saharan Africa. Eight LMIC studies used MPR [4, 13, 17, 19–23], 3 used PC [18, 25, 26], and 1 used PPU [24]. HIC studies included 18 studies from North America, 5 from Europe, and 1 from Australia. Sixteen studies from HICs estimated adherence using MPR [10, 11, 27, 29–32, 34, 36–39, 41, 45, 47, 48], 5 used PC [28, 33, 35, 40, 43], and 3 used PPU [42, 44, 46].

Association with Virological Outcomes

Twenty-seven (75%) of 36 studies reported virological outcomes; 19 were from HICs [27–37, 39–45, 48], and 8 were from LMICs [4, 17, 18, 22–26]. PAMs predicted virological failure in 14 (88%) of 16 studies, virological suppression in 8 (89%) of 9 studies, and viral load change in 3 (60%) of 5 studies. Studies conducted in LMICs generally assessed ART-naive populations receiving nonnucleoside reverse transcriptase inhibitor (NNRTI)-containing regimens and demonstrated that PAMs were predictive of either virological failure or virological suppression. In contrast, all studies demonstrating no association between PAMs and virological outcome were conducted in HICs and assessed ART-experienced patients using smaller sample sizes (≤ 115 subjects; range, 40–115 subjects) [30, 31, 43,

Table 1. Pharmacy-Based Adherence Measure (PAM) Categories

PAM category	Definition	Formulae
Medication or drug possession ratio	Measures the amount of time an individual is in possession of ≥ 1 ARV or prescriptions for the ARVs as a proportion of the time between 2 ARV pick-ups or prescriptions	Number of days ARV prescribed or dispensed/number of days in the interval
Pill count	Measures the quantity of ARV pills an individual has used between 2 ARV pickups as a proportion of the number of pills dispensed or as a proportion of time between pick-ups	1. (Number of ARV pills dispensed – number of ARV pills returned)/number of ARV pills dispensed 2. (Number of days ARV pills dispensed – number of days ARV pills returned)/number of days in the interval
Pill pickup	Measures whether an individual picks up all or a majority of their prescribed ARVs and expresses the adherence estimate in a dichotomous fashion (some measures require that ARVs be picked up on or before the date the previous ARV supply finishes).	1. Where “Adherent” = (ARV refills picked up/ARV refills prescribed) > predefined value 2. Where “Adherent” = (ARV refills picked up prior to previous refill finishing/ARV refills prescribed) > predefined value

Note. ARV, antiretroviral

Table 2. Reported Associations with Pharmacy-Based Adherence Measures (PAMs) in Low- and Middle-Income Countries

Study (year)	Design	Type of care	Region	ART naive	ART regimen (%) ^a	PAM category	PAM definition in study	PAM months ^b	Sample size, no. of persons	Key findings ^c
Nachega et al [13] (2006)	Retrospective cohort	Private	Sub-Saharan Africa (multiple countries)	Yes	NNRTI (82), PI	MPR	Months ART claims submitted (entire regimen)/ months from start to death, withdrawal or censor	Variable; median, 22	6288	1. PAM <80% predicted death and death + LTFU ($P < .01$) 2. compared with PAM adherence of 100%, decreasing PAM strata increasingly predicted death ($P < .01$), except for PAM adherence of 80%–99%
						MPR	Months ART claims submitted (entire regimen)/ Months in the interval	12 (0–12)	3267	PAM <80% in first 12 months predicted death ($P < .01$)
Weidle et al [26] (2006)	Clinical trial	Home based	Uganda	Yes	NNRTI (100)	PC ^f	(Days 3TC delivered - days 3TC returned) /days in the interval	3 (3–6) 3 (9–12)	913 894	1. PAM <95% predicted VF ^d at 6 or 12 months ($P < .01$) 2. self-report predicted VF at 12 ($P < .05$) but not 6 months
						PC	(3TC Pills delivered – 3TC pills returned)/3TC pills delivered	3 (3–6) 3 (9–12)	913 894	PAM <95% predicted VF ^d at 6 or 12 months ($P < .05$)
Nachega et al [4] (2007)	Retrospective cohort	Private	Sub-Saharan Africa (multiple countries)	Yes	NNRTI (100)	MPR	Months ART claims submitted (all ARVs)/months from start to death/leaving/ censor	Variable median, 26	2821	PAM strata >50% increasingly predicted sustained VL suppression ($P < .01$), shorter time to VL suppression ($P < .05$), and increased time to viral rebound ^e ($P < .05$)
Bisson et al [17] (2008)	Retrospective cohort	Private	Sub-Saharan Africa (multiple countries)	Yes	NNRTI (100)	MPR	Months ART claims submitted (all ARVs)/months from start to study endpoint	6 (0–6) 12 (0–12)	958 872	1. PAM <90% predicted VF ^c at 6 and 12 months ($P < .01$) 2. it was better than changes in the CD4 cell count at predicting VF ^d at 6 and 12 months ($P < .01$)
								Variable median, 20	1101	1. PAM <90% predicted viral rebound ^e ($P < .05$) 2. not different than changes in the CD4 cell count from maximum on-treatment value in predicting viral rebound ^e

								3 (0–3) 3 (6–9)	958 872	PAM was no better than changes in the CD4 cell count over first 6 or 12 months in predicting VF ^c at 6 or 12 months
Bisson et al [18] (2008)	Case-control	Public	Botswana	No	NNRTI (100)	PC	Sum of (days ART prescribed – remnant days ART) between last and 3 prior fills/days between last and 3 prior fills	3 (varied)	302	1. Decreasing PAM rates (90%-95%, 80%-90%, and <80%) 2. ($P < .05$) and PAM <95% ($P < .01$) in 3 months prior to recruitment predicted VF ^d compared with PAM >95%
Goldman et al [23] (2008)	Retrospective cohort (all clinical or IF)	Public	Zambia	Yes	NNRTI (100)	MPR	100% - [(days late to pharmacy visits – 3)/days on ART] ^g	Variable median, 24	913	1. Lower PAM (<80%, 80%-94%, and >95%) more likely to predict VF ^d at time of the VL test ($P < .05$) 2. Self-reported adherence did not predict VF ^d
San Lio et al [25] (2008)	Prospective cohort	NGO, free	Mozambique	No	NNRTI (100)	PC	(Days pills prescribed – days pills returned)/days between appointments	12 (varied)	394	PAM <95% predicted VF ^h after 12 months of follow-up ($P < .05$)
Toure et al [20] (2008)	Retrospective cohort	Public, private and NGO	Cote d'Ivoire	Yes	NNRTI (96), PI, 3NRTI	MPR	Days ART given to patient/days since ART start to last visit, or censor if last visit was after censor date	Variable median, 8	10211	1. PAM <80% predicted increases in the CD4 cell count of <50 cells after 6 months ($P < .01$) 2. PAM <80% predicted LTFU ($P < .01$) but not death over a period of 16 months
Chi et al [19] (2009)	Retrospective cohort	Public	Zambia	Yes	NNRTI (100)	MPR	100% - [(days late to pharmacy visits – 3) ^g /days on ART]	12 (0–12)	27115	1. PAM <80% predicted lower CD4 cell counts after 18–36 months ($P < .01$) 2. decreasing PAM adherence rates (>95%, 80%-94%, and <80%) predicted LTFU after 12-36 months of ART ^h ($P < .01$) PAM <80% predicted death ($P < .01$) at 12–36 months but higher strata (80%-94% and >95%) did not
Danel et al [22] (2009)	Clinical trial (one or both of VF or IF)	Free	Cote d'Ivoire	Yes	NNRTI (87), PI	MPR	Days ART delivered/days in the interval	6 (0–6)	208	PAM of >90% did not predict CD4 cell counts of >350 cells/ μ L plus VL suppression at 36 months

								30 (6–36)	208	PAM >90% predicted either or both of the following: a CD4 cell count >350 cells/ μ L and VL suppression at 36 months ($P < .01$)
Rougemont et al [24] (2009)	Prospective cohort	Private	Cameroon	Yes	NNRTI (99), PI	PPU	“Nonadherent” was defined as being >2 weeks late to pick-up medication or as “abandoned ART” on phone tracing	6 (0–6)	194	“Nonadherent” status predicted VF ^d ($P < .01$); no different than CD4 cell count change over 6 months at predicting VF ^d ; day 30 Self-reported adherence did not predict 6-month VF ^d
Ross-Degnan et al [21] (2010)	Retrospective cohort	Public, private, and NGO	Sub-Saharan Africa (multiple countries)	Yes	NNRTI, PI (NR)	MPR	Days with ART/days since ART start	Variable median, 6	409	1. PAM <80% (but not 80%-90% or 90%-100%) predicted lower CD4 cell counts (at 4-9 months), compared with PAM 100% ($P < .05$) 2. PAMs were not directly compared with self-reported adherence
						MPR	“Nonadherent” was defined as >30 days without receipt of ART	Variable Median, 6	409	“Nonadherent” status predicted lower CD4 cell counts at 4-9 months ($P < .05$)

NOTE. ART, antiretroviral therapy; ARV, antiretroviral; IF, immunological failure; LTFU, lost to follow-up; MPR, medication possession ratio; NGO, nongovernmental organization; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NR, not reported; PC, pill count; PI, protease inhibitor; 3NRTI, triple nucleoside reverse-transcriptase inhibitor; 3TC, lamivudine; VF, virological failure; PPU, pill pick-up; VL, viral load.

^a Data are ART regimens for that study. Number in parentheses represents percentage of subjects receiving the predominant regimen.

^b Duration of adherence assessment, with the months over which assessed in parentheses. If there was a variable duration of adherence assessment, than the median, mean, or range is listed.

^c Number after PAM is the percentage adherence.

^d Single viral load above threshold.

^e Single viral load above threshold after previous VL suppression.

^f Because remnant pills were counted to determine adherence, this measure comes under the PC category despite being referred to as medication possession ratio in the study.

^g Subjects not late to pharmacy visit until after 3 days, to account for routine provision of 3 days extra ART.

^h Statistical significance for association was not reported, so we determined statistical significance using raw data with the χ^2 test.

Table 3. Reported Associations with Pharmacy-Based Adherence Measures (PAMs) in High-Income Countries

Study (year)	Design	Type of care	Region	ART naive (%)	ART regimen (%) ^a	PAM category	PAM description in study	PAM duration, months ^b	Sample size	Key findings ^c
Maier et al [42] (1999)	Retrospective cohort	VA, minor costs	USA	No (26)	PI (100)	PPU	Adherence occurred if the patient consistently filled 4 prescriptions on time "non-adherent did not do this"	4 (varied)	205	Adherent status predicted VL suppression ($P < .01$) and CD4 cell count increase ($P < .01$), whereas "non-adherent" status predicted VL suppression ($P < .05$) but not CD4 increase over 5–9 months of follow-up
Singh et al [46] (1999)	Prospective cohort	VA, private	USA	No (7)	NR	PPU	Adherence occurred if refills picked-up/refills prescribed was >90%	6 (varied)	123	Adherence predicted greater change in the CD4 cell count ($P < .05$)
Descamps et al [33] (2000)	Case-control study in an RCT	Free	France	Yes	PI, 2NRTI ^f	PC	(Pills prescribed – remnant pills)/pills to cover the interval	6 (0–6)	116	Mean PAM for zidovudine and indinavir predicted VL rebound ^e ($P < .05$)
Low-Beer et al [41] (2000)	Retrospective cohort	Public	Canada	Yes	NNRTI, PI (NR)	MPR	Months ART prescribed/months follow-up in 1 st year	12 (0–12)	886	Increasing PAM strata (<70%, 70%-80%, 80%-90%, 90%-95%, and 95%-100%) predicted VL suppression during follow-up (median duration of follow-up, 19 months; $P < .01$)
Liu et al [40] (2001)	Prospective cohort	Private	USA	Yes	NNRTI, PI (NR)	PC	1 – [(actual pills – expected pills)/pills per dose/prescribed doses for the period]	2 (0–2) 6 (0–6)	108	1. Increasing PAM strata predicted VL suppression at 2 and 6 months ($P < .01$) 2. no difference was shown between PC and MEMS at predicting VL at 2 and 6 months, but both were superior to self-reported adherence at 2 months ($P < .01$)
McNabb et al [43] (2001)	Prospective cohort	Private	USA	No	PI (63), NNRTI, 2NRTI	PC	(1) doses taken/doses prescribed, OR if return after 30 days, then (2) doses taken/doses required for interval	3 (varied)	40	PAM and self-report changes were not associated with VL change, whereas increasing MEMS adherence was associated with decreasing VL ($P < .05$) and VL suppression ($P < .01$)

Hogg et al [38] (2002)	Retrospective cohort	Public	Canada	Yes	PI (73), NNRTI	MPR	Months ART prescribed/ months follow-up in first year	12 (0–12)	1282	PAM adherence of <75% predicted mortality, or mortality plus new AIDS diagnosis, over maximum follow-up of 50 months ($P < .01$)
Alcoba et al [30] (2003)	Retrospective cohort	NR	Spain	No	PI (100)	MPR	Patient was “nonadherent” if (days in the interval – days dispensed)/ days in the interval is >10%	3 (varied)	106	“Nonadherent” status, self-report, and ARV plasma levels were not associated with VL
Wood et al [48] (2003)	Retrospective cohort	Public	Canada	Yes	NNRTI, PI (NR)	MPR	Months ART prescribed/ months follow-up in 1 st year	12 (0–12)	1422	PAM adherence of >95% predicted time to VL suppression and time to VL rebound ^e over follow-up, which was NR but variable and maximum of 67 months ($P < .01$)
Grossberg et al [37] (2004)	Retrospective cohort	VA, costs	minor USA	No(35)	NNRTI, PI, 3NRTI (NR)	MPR	(Total pills/ daily number of pills)/days between refills	3 (varied)	110	Self-reported adherence and increasing PAM strata predicted VL reductions ($P < .01$), apart from self-report in ART naive
Kitahata et al [39] (2004)	Retrospective cohort	Free ART	USA	Yes	PI (78), NNRTI	MPR	Mean for all ARVs of [(1 – days without ARV)/days in the interval]	6 (0–6)	212	1. Increasing PAM strata (<70%, 70%–90%, and >90%) predicted viral rebound ^h ($P < .01$) and higher CD4 cell counts over 12–24 months ($P < .05$) 2. PAM adherence <70% predicted new AIDS or death, compared with PAM adherence of >70%, over 24 months ($P < .01$) (but PAM adherence of 70%–90%, compared with >90%, did not)
Wood et al [47] (2004)	Retrospective cohort	Public	Canada	Yes	PI (69), NNRTI	MPR	Months ART prescribed/ months follow-up in 1 st year	12 (0–12)	1522	PAM adherence <75% predicted a lower increase in the CD4 cell count over 24 months ($P < .01$), whereas PAM strata >75% increasingly predicted increases in the CD4 cell count over 24 months ($P < .01$)

Fairley et al [34] (2005)	Retrospective cohort	Public	Australia	No	NNRTI, PI (NR)	MPR	Days ART prescribed/days in the interval	Variable range, 12-44	752	Increasing PAM and self-reported adherence predicted VL suppression ($P < .01$)
Fletcher et al [35] (2005)	RCT (Prior VF on PI regimen)	Free ART	USA	No	NNRTI + PI (100)	PC	(doses dispensed – doses returned)/doses dispensed	1(0–1)	220	PAM did not predict VL changes at 4 months; self-reported adherence ($P < .05$) ($n = 244$) and ARV plasma levels ($P < .05$) ($n = 180$) predicted VL changes at 4 months, whereas MEMS did not ($n = 62$)
Harrigan et al [10] (2005)	Retrospective cohort	Public	Canada	Yes	PI (74), NNRTI	MPR	Months ART prescribed/months follow-up in 1 st year	12 (0–12)	1191	PAM adherence of 80%-90% is the highest predictor of single and multiple category HIVDR over 24 months, compared with PAM adherence of 0%-20% ($P < .01$)
King et al [28] (2005)	RCT	Free ART	Multi-continent	Yes	PI (100)	PC	Pills consumed/pills expected to be consumed	Variable range, 2 – 3	590	Decreasing PAM strata increasingly predicted VF ^g ($P < .01$); the mean PAM adherence rate was lower in persons with detectable HIVDR to PI and/or 3TC ($P < .01$)
Inciardi et al [29] (2005)	Retrospective cohort	Private	USA	No	NNRTI (56), PI	MPR	Sum of (interval days – ARV days) for all ARVs/sum of interval days for all ARVs ⁱ	Variable ^h	94	Decreasing PAM adherence was associated with VL increase ($P < .01$)
Gross et al [36] (2006)	Retrospective cohort	Public	Canada	No	NNRTI, PI (NR)	MPR	(Days ART [any ARV] dispensed between 3 refills +30)/days between 3 refills	Variable range, 2-6	1634	Decreasing PAM strata (<70%, 70%-95%, and >95%) in a 2-6 observed interval, predicted a higher proportion with VF ^d ($P < .01$)
				Yes	NNRTI, PI (NR)	MPR	(Days ART [any ARV] dispensed +30)/days between refills	Variable median, 29	1634	PAM adherence <95% (treated as a time-varying variable, with or without a 30-day grace period) predicted viral rebound ^e over the period of observation ($P < .05$)
Braithwaite et al [27] (2007)	Retrospective cohort	VA, minor costs	USA	Yes	PI (58), NNRTI, 3NRTI	MPR	Days ART prescribed/days in interval	12 (0–12)	6394	Increasing PAM strata increasingly predicted VL change, VL suppression, or changes in the CD4 cell count at 12 months

Townsend et al [31] (2007)	Retrospective cohort	VA, minor costs	USA	No	PI(50), NNRTI, NRTI	MPR	Days ART prescribed/days in the interval	6 (varied)	58	PAM was not associated with VL; PAM adherence <70% was associated with changes in the CD4 cell count ($P < .05$), but PAM adherence of 70%-90%, compared with >90%, was not
Saberi et al [45] (2008)	Retrospective cohort	Private	USA	No	NNRTI (100)	MPR	(Pills dispensed/pills prescribed per day)/days between refills	Variable range, 3-18	151	PAM adherence >85% maintained VL suppression in 8 of 10 patients between 2 VL measurements
Lima et al [11] (2009)	Retrospective cohort	Public	Canada	Yes	PI (64), NNRTI	MPR	Days ART prescribed/days of follow-up	Variable maximum, 30	903	PAM adherence <95% predicted mortality over follow-up period (maximum, 55 months) ($P < .05$)
Nellen et al [44] (2009)	Retro- and Prospective cohort	NR	Holland	No	NNRTI (58), PI, 3NRTI	PPU	ART dispensed/ART prescribed	6 (varied)	115	PAM adherence <85% did not predict VF ^g (but did for an ART-naïve subgroup; $P < .01$) over 24 months; self-reported adherence and ARV plasma levels did not predict VF ^g over 24 months
Cambiano et al [32] (2010)	Retrospective cohort	Public	England	No	PI(47), NNRTI, NRTI	MPR	Days with ≥ 3 ARV prescriptions/study interval	6 (varied)	1632	PAM strata <95% predicted ($P < .01$) viral rebound, but PAM adherence of 95%-99% did not, ^h over the subsequent 9 months, compared with PAM adherence of 100%

NOTE. ART, antiretroviral therapy; ARV, antiretroviral; HIVDR, HIV drug resistance; MEMS medication event monitoring system; MPR, Medication possession ratio; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NR, not reported; PC, pill count; PI, protease inhibitor; PPU, pill pick-up; RCT, randomized control trial; 3NRTI, triple nucleoside reverse-transcriptase inhibitor; 3TC, lamivudine; 2NRTI, double nucleoside reverse-transcriptase inhibitor; VA, veterans affairs hospital; VF, virological failure; VL, viral load.

^a Data are ART regimens for that study. The numbers in parentheses represent the percentages of subjects receiving the predominant regimen.

^b Duration of adherence assessment, with the months over which assessed in parentheses. If there was a variable duration of adherence assessment, then the median, mean, or range is listed.

^c The number after "PAM" is the percentage adherence.

^d Two viral loads separated in time above threshold.

^e Two viral loads above threshold after previous VL suppression.

^f All patients received triple-drug PI regimens for 3 months and were then randomized to receive double-NRTI (50%) or 1 PI plus 1 NRTI (36%) or to continue the PI regimen (14%).

^g Single viral load above threshold.

^h Single viral load above threshold after previous VL suppression.

ⁱ "Interval days" was the sum of multiple 3-month periods prior to VL tests performed over a 2-year period, and "ARV days" was the sum of ARVs prescribed over these same periods.

44] or estimated adherence over shorter durations of assessment (4 weeks) [35].

Given the importance of PAMs in predicting virological failure or suppression, we considered 2 important sources of study heterogeneity: the duration of adherence assessment and the temporal relationship between the adherence assessment and viral load testing.

The duration of adherence assessment was most commonly the first 6 months [17, 22, 24, 31–33, 39, 40, 44] or 12 months [17, 27, 41, 48] after ART initiation but ranged widely (range, 1–44 months). All studies with a duration of adherence assessment greater than 6 months demonstrated association with virological failure or suppression [4, 17, 22, 23, 25, 27, 34, 36, 41, 48]. However, only 11 (79%) of 14 studies demonstrated an association when the duration of adherence assessment was 2–6 months. Notably, associations were maintained over shorter durations of assessment (2–6 months) when larger sample sizes were used (>115 subjects) [17, 18, 24, 26, 28, 32, 36, 42, 46, 49], suggesting that studies that involved shorter durations of adherence assessment or smaller sample sizes lack power to detect statistically significant associations.

The time at which viral load was assessed varied and occurred either at the end of the period of adherence assessment or at a future time point. Fourteen (88%) of 16 studies demonstrated an association between PAMs and virological failure or suppression at the end of adherence assessment [4, 17, 18, 22–28, 30, 31, 33, 34, 36, 40], whereas in 5 (63%) of 8 studies, PAMs were predictive of future outcomes (range, 1–55 months after adherence assessment) [17, 22, 32, 39, 41, 42, 44, 48]. In 2 studies, PAMs were found to be more predictive of virological outcomes at the end of the period of adherence assessment than at a future time point. However, the duration of adherence assessment used to predict the future outcome was shorter in both studies, making it difficult to draw further conclusions [17, 22].

Association with Nonvirological Outcomes

All studies that assessed the association between PAMs and CD4 cell count response demonstrated that lower levels of adherence were associated with a poorer CD4 cell count responses [19–22, 27, 31, 39, 42, 46, 47]. Of the 6 studies documenting association between PAMs and mortality [11, 13, 19, 20, 38, 39], all but 1 [20] demonstrated increasing mortality with lower levels of adherence. In addition, 2 large studies that assessed African treatment programs showed an association between lower individual adherence and subsequent classification as lost-to-follow-up during the first 12 months after ART initiation [19] or after a median of 7.7 months [20]. Importantly, authors of the study in which PAMs were associated with loss to follow-up and not with mortality acknowledge that many subjects who were lost to follow-up were likely to have died [20].

Data regarding the association between poor adherence to ART, as estimated by PAMs and HIV drug resistance, were limited. However, 2 studies that involved ART-naïve patients receiving NNRTI- or protease inhibitor (PI)-based regimens [10, 28] demonstrated an association between adherence and acquired HIV drug resistance.

Studies Assessing Pharmacy and Nonpharmacy Adherence Measures

Ten studies documented PAMs and self-reported adherence and their associations with virological outcomes. Both PAMs and self-report measures were associated with virological outcomes in 3 studies; however, the superiority of one measure over the other could not be inferred [26, 34, 37]. In 4 studies, PAMs predicted virological outcomes, whereas self-reported adherence did not [23, 24, 26, 37]. In 1 study that compared PAMs with self-reported adherence using receiver operating characteristic curves, the PAM was superior to self-reported adherence ($P < .001$) [40]. In contrast, self-reported adherence was superior to a PAM in 1 study [35] in which a 4-week PC assessment failed to predict change in viral load 12 weeks later, whereas improved self-reported adherence measured at the later time point was predictive of a viral load reduction. In 3 additional studies, neither the PAMs nor self-reported adherence predicted virological outcome [30, 43, 44].

Three studies compared PAMs with use of MEMS caps [35, 40, 43]. Better adherence by both measures predicted virological suppression in 1 study [40], neither predicted viral load change in a second study [35], and only use of MEMS cap predicted viral load change in the third [43].

In 3 studies [30, 35, 44] in which PAMs were not predictive of virological outcome, antiretroviral plasma levels were also determined and found to be predictive in only one [35].

Studies Assessing Different PAMs

Only 1 study compared different PAMs by investigating 2 different PC measures—one incorporating time into the denominator and the other without. Lower estimates of adherence by both PC measures predicted virological failure at 6 and 12 months [26]. The ability of the 2 PAMs to predict virological failure was not directly compared; thus, superiority could not be established. Interestingly, the PC measure using time in the denominator classified more individuals as nonadherent and provided greater variability in adherence estimates.

PAM THRESHOLDS AND RELATIONSHIP TO TREATMENT OUTCOMES

To identify patients at risk for suboptimal clinical or virological response using PAMs, an understanding of the relationship between adherence and outcomes, including potential adherence thresholds or cutoffs, is essential. Studies commonly report

adherence estimates dichotomously or across ≥ 3 strata. All studies that stratified adherence estimates were reviewed to identify potential threshold effects.

PAM Thresholds and Virological Outcomes

Historically, $>95\%$ patient adherence to ART has been cited as the threshold to achieve virological suppression. This threshold was based on a single study of ART-experienced patients receiving unboosted-PI regimens [7]. Subsequent studies have suggested that adherence levels of $<95\%$ are associated with virological suppression in a considerable proportion of patients receiving NNRTI or boosted-PI regimens [6, 28, 50]. Seven studies using PAMs with stratified adherence estimates [4, 23, 28, 32, 36, 39, 41] failed to detect a threshold effect. Interestingly, in 2 studies, when 100% adherence was used as the highest stratum, no significant difference in the rate of viral rebound was observed, compared with levels of adherence of 95%–99% [32] and 90%–99% [4]; however, both studies reported decreased risk of viral rebound for every 10% increase in adherence across all strata. The ability of some studies to detect a threshold effect may have been limited by the fact that patients received different ART regimens [32, 36, 39, 41]. However, 2 studies that assessed only NNRTI-based regimens [4, 23] reported virological failure rates of 29% at 80%–95% adherence [23] and of $\sim 25\%$ at 80%–99% adherence [4]. These observations are consistent with studies using self-reported adherence, unannounced PCs, and use of MEMS caps for patients receiving NNRTI regimens in which the majority of individuals had virological suppression in adherence strata below 95% [6, 50].

PAM Thresholds and Mortality

Four studies reported adherence across ≥ 3 strata and observed a threshold effect for mortality. For individuals receiving predominantly NNRTI [13, 19] or unboosted-PI regimens [38, 39], ≥ 2 adherence strata above 70% [39], 75% [38], or 80% [13, 19] did not differ in their ability to predict mortality, but lower adherence strata did predict increased mortality. Importantly, investigators attempted to account for “reverse causation” (ie, cessation of ART because of reasons related to poor survival) by using prolonged durations of adherence assessment before observing subjects for survival outcomes. On the basis of these data, a threshold effect predicting increased mortality among patients with a level of adherence of $<80\%$ noted by use of PAMs may serve as a potential target for adherence interventions, especially if available resources are limited.

PAM Thresholds and HIV Drug Resistance

Two studies described entirely [28] or predominantly (74% of subjects) [10] ART-naive populations who had received unboosted-PI regimens, with those who had adherence rates of 75%–90% having the highest risk for developing resistance. Because of these limited findings, we were unable to draw

conclusions about adherence thresholds for the emergence of HIV drug resistance. Importantly, no studies examined the relationship between PAMs and drug resistant HIV in patients exclusively receiving NNRTI or boosted-PI regimens.

USE OF PAMs TO MONITOR ADHERENCE AND TREATMENT OUTCOMES

PAMs are ideally suited to monitoring adherence because they are objective and can be easily derived from data routinely collected for other purposes, such as clinical care, medication billing, fulfillment of legal requirements, or drug supply management. Importantly, PAMs may overestimate actual pill taking if individuals discard or share pills and, therefore, estimate maximum possible adherence. In addition, PAMs do not provide information on patterns of nonadherence known to be associated with the development of resistance to NNRTIs [51, 52].

Despite their limitations, in settings in which frequent routine viral load monitoring is not available, PAMs can play an important role in monitoring individual and population-level adherence to ART. Although prospective studies of adherence interventions and viral load testing targeted at patients with lower levels of adherence, as determined by PAMs, have not been reported, findings from 2 studies are optimistic [17, 36]. In a study conducted in sub-Saharan Africa, PAMs were superior to CD4 cell count criteria in predicting virological failure, and when PAMs were performed before determinations of viral load and CD4 cell count, PAMs were as accurate as CD4 cell count changes in predicting virological failure. These results support the use of PAMs for potential identification of patients at risk of future virological failure [17]. In a second study, which was from Canada, analysis of repeated measures of adherence, which account for changes in adherence over time, predicted future viral rebound [36], suggesting that routine surveillance of patient adherence with PAMs can be used to alert clinicians to possible future virological failure.

Use of PAMs to monitor adherence requires the following minimum data: ART regimen dispensed, date of dispensing, and number of days of ART dispensed. Selection of a PAM will depend on available resources at a site or in a program, as well as a local assessment of the strengths and limitations of different PAMs. MPR estimates are the most studied and incorporate time in the denominator (Table 1); thus, patients need to return to the dispensary before their medication finishes if taken as prescribed, to be considered 100% adherent. PC and PPU measures that do not incorporate time in the denominator (Table 1) may overestimate adherence, because patients may use all dispensed ART but do so over longer periods than intended. PC measures are limited by the increased resources required to routinely count and record remnant pills at each clinic or pharmacy visit. In

addition, if patients do not bring all remnant pills for counting or share or lose pills, the rate of adherence will be overestimated. Although PC measures may provide a more accurate assessment of adherence by accounting for unused ART, to our knowledge, no data comparing PC to non-PC PAMs are available. PPU measures are the least studied PAM. Unlike MPR and PC measures, PPU estimates are dichotomous and, therefore, do not provide a range of adherence, limiting their ability to identify individuals in need of increased adherence support.

In the absence of data suggesting an advantage of PC over non-PC measures, and considering the extra resources required to count remnant pills, we do not suggest using PC measures. Furthermore, measures incorporating the number of days for which ART was prescribed in their definition, such as MPR and some PPU, measures are likely to be the most informative. Available data suggest that shorter durations of adherence assessment (≤ 6 months) may be less accurate at predicting virological outcome. Moreover, PAMs are more likely to accurately predict outcomes at the end of a period of adherence assessment than at future time points. Not surprisingly, the balance of studies suggests that PAMs are superior to self-reported adherence in predicting virological outcome. Finally, a threshold effect for mortality is observed at adherence levels of 70%–80%, in contrast to virological outcomes, for which no adherence thresholds were observed.

PAM-based adherence estimates can be used by pharmacists and other health care providers to promote ART adherence. Although the literature on pharmacist-directed interventions is limited, pharmacy-based adherence interventions have successfully combined adherence education [53–55], tailoring regimens to patient lifestyles [54, 56], and the management of adverse drug reactions [55, 56], resulting in improved adherence [53, 54, 56] and improved virological [53, 55] and immunological [55] response. Further investigation of these interventions is warranted in HICs and in LMICs where similar interventions have not been reported.

FUTURE RESEARCH NEEDS

Although many studies have assessed various PAMs and their associations with clinical and virological outcomes, significant gaps in our understanding remain. Research is needed to compare different PAMs in the same population and against other adherence measures and biomarkers, such as antiretroviral levels in hair. In addition, the optimal duration of adherence assessment remains to be clarified for different clinical and virological outcomes. Also, because the relationship between adherence and virological outcomes varies over time [57] and by regimen [6, 50], studies should investigate the predictive value of PAMs in both ART-naive and ART-experienced patients receiving different regimens.

The potential benefit of PAMs includes the identification of individuals at risk for virological failure and undesirable treatment outcomes. Prospective studies incorporating PAMs with interventions designed to improve adherence, clinical outcome, and virological outcome have not been reported but are necessary if PAMs are to be used to optimize clinical care. Researchers attempting to design such studies will face multiple challenges, such as calculating accurate adherence estimates, devising tools for clinicians to easily interpret PAM results, and correctly applying interventions to at-risk patients.

CONCLUSIONS

Pharmacy-based methods for estimating adherence during routine clinical care are heterogeneous, yet they predict virological and other clinical outcomes in the majority of studies. Limited comparative data suggest that PAMs are likely superior to self-reported adherence measures. Nevertheless, additional studies are needed to clarify this finding and to identify which PAM parameters are most predictive of clinical or virological outcomes and which measure is best suited to each treatment setting. Available evidence suggests that PAMs are more accurate in predicting current rather than future outcomes and that PAMs applied over shorter durations of adherence assessment (≤ 6 -months) are likely to be less predictive of outcome than PAMs estimated over longer durations. In conclusion, available data suggest that MPR and PPU estimates, which include the number of days for which ART was prescribed, are appropriate minimum-resource methods to assess patient adherence to ART.

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