INTERVIEW WITH:

Seth Kalichman, PhD
Correcting mistakes and misperceptions in managing antiretroviral adherence

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Abstract: Over the past two decades, high-level adherence improved steadily in five North American and European cohorts representing a diverse sociodemographic array of people with HIV. Several individual studies and meta-analyses confirm the intuitive idea that once-daily regimens promote adherence better than twice-daily combinations, and that single-tablet regimens bolster adherence more than multitab combinations. But research also shows that missing one or two doses of a once-daily regimen can allow virologic failure more readily than missing one or two doses of a twice-daily combination. Large cohort studies provide evidence that suboptimal antiretroviral adherence can boost chances of virologic failure, emergency department visits, longer hospital stays, and death. Adolescents who dump antiretrovirals before pill counts appear to run a higher risk of virologic failure.

Is poor antiretroviral adherence a worry of the past? With six once-daily single-tablet regimens available, almost as many two-pill combinations in hand, and once-monthly injected antiretroviral maintenance in phase 3 trials, will problems taking antiretrovirals evaporate?

Not likely. For starters, four of the six single-tablet regimens must be taken with food, one (Atripla) must be taken on an empty stomach, and only one (Triumeq) can be taken with or without food—a tally leaving plenty of room for incorrect dosing. And if once-monthly or every-2-months injected antiretrovirals get licensed, no one knows how regularly people will get their shots outside clinical trials. For example, a study of a quarter-million US women taking contraceptives found stopping injected agents within 3 months much more likely than stopping oral pills.

Just forgetting to take antiretrovirals remains the leading cause of faulty adherence among adults and adolescents, and people can just forget a once-daily tablet as easily as a twice-daily dose. With almost everyone starting antiretroviral therapy (ART) feeling better as a result, factors related to better health may assume greater importance as reasons for imperfect adherence: being away from home, changing one's daily routine, being busy.

But of course the more convenient, less toxic regimens that surged to the fore in the past decade inevitably improved adherence, as the next section of this article makes clear. Still, the clinical threats of wavering adherence—viral rebound, resistance, disease progression, death—remain a cautionary tale clinicians should be sure their patients understand, as the final section of this article details. The remaining articles in this issue attempt to spell out the major reasons for poor adherence (page 21), offer clear advice on adherence assessment (page 36), and explain which adherence strategies work (page 41). Almost all research cited in these reviews appeared within the past 10 years; even so, a caveat deserves stressing: Older studies reflect adherence to more toxic and cumbersome regimens,
including those featuring lopinavir/ritonavir, efavirenz, tenofovir disoproxil fumarate (TDF), and other even more compromising agents. So adherence in a 2017 report does not mean what it meant in a 2007 report.

**Adherence improving with newer regimens**

Five large cohort studies in the North America and Europe chart improving adherence over the past two decades,6-10 with study years ranging from 1996-2009 to 2006-2013 (Table 1). A study of 682 drug injectors in Vancouver, Canada determined that adherence of at least 95% during the first year of treatment, based on pharmacy refill records, climbed steadily from 19.3% in 1996 to 65.9% in 2009.9 Linear regression analysis linked every year after 1996 with 8% higher odds of good adherence (adjusted odds ratio [aOR] 1.08, 95% confidence interval [CI] 1.03 to 1.13, \( P < 0.001 \)).

### Table 1. Improving adherence in large North American and European cohorts

<table>
<thead>
<tr>
<th>Author</th>
<th>Group, n, % women</th>
<th>Study years</th>
<th>Adherence measure</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mann6</td>
<td>Vancouver drug injectors, n = 682, 36% W</td>
<td>1996-2009</td>
<td>≥95% adherence (days dispensed/days eligible in first year of ART)</td>
<td>Rose from 19.3% in 1996 to 65.9% in 2009; rose 8% per year after 1996</td>
</tr>
<tr>
<td>Viswanathan8</td>
<td>MACS (n = 1215, 0% W) and ALIVE (n = 337, 31% W) cohorts</td>
<td>2001-2011</td>
<td>≥95% self-reported in last 4 days</td>
<td>Rose from 84% to 90% in MACS and from 87% to 92% in ALIVE; every 2 years average adherence rose 11% in MACS and 14% in ALIVE</td>
</tr>
<tr>
<td>Glass9</td>
<td>SHCS, n = 6709, 30% W</td>
<td>2003-2009</td>
<td>Self-reported 0 missed doses in last 4 weeks</td>
<td>Rose from 70% in 2003 to 83% in 2009</td>
</tr>
<tr>
<td>Hanna10</td>
<td>WIHS, n = 1727, 100% W</td>
<td>2006-2013</td>
<td>≥95% self-reported adherence in last 6 months</td>
<td>Rose from 78% in 2006 to 85% in 2013</td>
</tr>
</tbody>
</table>

ALIVE, AIDS Linked to the Intravenous Experience; ART, antiretroviral therapy; MACS, Multicenter AIDS Cohort Study (men who have sex with men); SHCS, Swiss HIV Cohort Study; WIHS, Women's Interagency HIV Study.
At London’s Royal Free HIV Clinic, a study of 2060 HIV patients tracked for a median of 4.5 years from 1999-2002 through 2007-2008 used generalized estimating equation models to determine that chances of better than 95% adherence improved 2% every year (aOR 1.02, 95% CI 1.01 to 1.04, \( P = 0.0053 \)).\(^7\) A US study of 1215 men who have sex with men (MSM) in the Multicenter AIDS Cohort Study (MACS) and 337 drug injectors in the AIDS Linked to the Intravenous Experience (ALIVE) cohort figured that at least 95% self-reported adherence in the last 4 days rose from 84% to 90% in MACS and from 87% to 92% in ALIVE from 2001 through 2011.\(^8\) Every 2 years average adherence improved 11% in MACS and 14% in ALIVE.

Swiss HIV Cohort Study (SHCS) investigators tracked self-reported adherence from 2003 through 2009 in 6709 cohort members.\(^9\) Through a median follow-up of 4.5 years, the proportion reporting no doses missed in the last 4 weeks climbed from 70% in 2003 to 83% in 2009. In the US Women’s Interagency HIV Study (WIHS), the rate of 95% or better self-reported adherence improved from 78% in 2006 to 85% in 2013 (\( P < 0.001 \)).\(^10\) Increased use of single-tablet regimens (from 7% in 2006 to 27% in 2013) accounted for much of the improved adherence (adjusted risk ratio [aRR] 1.05, 95% CI 1.03 to 1.08), and single-tablet therapy raised chances of virologic suppression (aRR 1.06, 95% CI 1.01 to 1.11).

The consistency of these five studies reassures that no single HIV risk group, gender group, or nationality explains improving adherence in recent years.\(^6\)\(^-\)\(^10\) The studies include drug injectors,\(^6\)\(^-\)\(^8\) men who have sex with men,\(^7\)\(^-\)\(^9\) heterosexual men,\(^6\)\(^-\)\(^9\) and women (100% of the WIHS study\(^10\) and 22% to 36% of other cohorts that include women). There were 682 people from Canada, 2060 from Britain, 3279 from the United States, and 6709 from Switzerland.

**Adoption and impact of once-daily and single-tablet combos**

The surging adherence rates cataloged over recent across countries and risk groups\(^6\)\(^-\)\(^10\) reflect the ever-improving convenience, tolerability, and activity of newer antiretrovirals. Several individual studies and meta-analyses confirm the intuitive ideas that once-daily regimens are easier to take than twice-daily combinations, and that single-tablet regimens have an adherence advantage over multitabllet medleys.

A 2009 meta-analysis compared adherence with once- versus twice-daily regimens in 11 randomized controlled trials involving 3029 participants.\(^11\) All studies used pills counts or electronic MEMS pill bottle caps to measure adherence, defined as total number of doses taken over total doses prescribed. Adherence proved significantly better with once-daily regimens in the overall analysis (+2.9%, 95% CI 1.0% to 4.8%, \( P < 0.003 \)) and in 11 sensitivity analyses, each of which removed one study.

A more recent meta-analysis scrutinized 19 randomized controlled trials published through March 2013 involving 6312 adults.\(^12\) In both once- and twice-daily groups, taking more pills daily predicted lower adherence (\( P = 0.0014 \)) and worse virologic suppression (\( P < 0.0001 \)). Adherence measured by pill count or MEMS again proved slightly but significantly higher with once-a-day dosing (weighted mean difference +2.55%, 95% CI 1.23% to 3.87%, \( P = 0.002 \)). Adherence decreased less over time with once-daily regimens than twice-daily regimens.

continued...
Meta-analysis of 21 studies presented up to March 2013 and involving 27,230 people compared regimens containing fixed-dose agents combining two or three antiretrovirals with regimens containing no fixed-dose agents. In six randomized trials, random effects meta-analysis determined that fixed-dose agents conferred a 10% higher chance of adherence as defined in the original study (nonsignificant at relative risk [RR] 1.10, 95% CI 0.98 to 1.22). In observational studies, chances of adherence were significantly higher with fixed-dose antiretrovirals (RR 1.17, 95% CI 1.07 to 1.28). Virologic suppression tended to be better with fixed-dose drugs in randomized trials (RR 1.04, 95% CI 0.99 to 1.10) and observational studies (RR 1.07, 95% CI 0.97 to 1.18).

Analysis of 7381 US Medicaid patients from 11 states in care between 2005 and 2009 compared adherence measured by medication possession ratio in people taking a once-daily single-tablet regimen versus those taking two or more antiretroviral pills daily. Almost half of study participants (46%) in this low-income group were women. One quarter of participants taking a single-tablet regimen (25.3%) compared with 17.4% taking multiple pills had at least 95% adherence ($P < 0.0001$). The hospital admission rate proved significantly lower in the single-tablet group than in the multitablet group (21% versus 24.4%, $P = 0.003$). Multivariate Poisson regression analysis linked single-tablet regimens to a 15% lower chance of hospital admission (incidence rate ratio 0.8457, $P < 0.001$). Total monthly healthcare costs averaged $2959 in the single-tablet group versus $3544 in the multitablet group ($P < 0.001$). A more recent study of 2174 South Carolina Medicaid recipients used multivariate regression models to confirm greater adherence and a lower hospital admission risk (hazard ratio 0.71, 95% CI 0.59 to 0.86) with single-tablet antiretroviral regimens than with multiple-tablet combinations.

A study of 327 women in the US WIHS cohort determined that self-reported 95% adherence to a single-tablet regimen did not differ between the luteal phase of menstruation and the follicular phase—a finding allaying concern that changing cognition, mood, and premenstrual symptoms in the luteal phase imperil adherence. But adjusted analyses showed that suboptimal adherence was more likely in women with 12 or fewer years of education (aOR 3.55, 95% CI 1.04 to 12.2, $P = 0.04$) and in those with more CES-D-determined depressive symptoms (aOR 2.60, 95% CI 1.15 to 5.90, $P = 0.02$).

Despite this strong evidence of better adherence and fewer hospital admissions with single-tablet regimens, some people taking a suppressive two-pill once-daily regimen may prefer to stick with that treatment rather than switching to a single-tablet combination. That conclusion emerged from a Swiss study of 84 people taking fixed-dose TDF/emtricitabine plus efavirenz who switched to the 3-in-1 combination of these antiretrovirals. Six of the 88 people (7%) opted to return to their two-pill regimen, while efavirenz blood levels rose and a score estimating perception of treatment necessity fell significantly after the switch. Although self-reported adherence did not change after patients traded two pills daily for one, the researchers suggest that the waning treatment-necessity score and higher risk of efavirenz side effects could eventually dim adherence with the one-tablet regimen.
Swiss investigators found a higher risk of virologic failure with once- versus twice-daily regimens among cohort members who reported missing one or two doses in the past 4 days. The analysis involved 3150 people starting their first antiretrovirals between 2003 and 2012. Through a median follow-up of 4.7 years, 480 people (15%) had virologic failure (a viral load above 500 copies/mL after being below 50 copies/mL or on treatment for more than 24 weeks). Compared with people who missed no doses, those missing one or two doses of a once-daily combination had a two-thirds higher risk of virologic failure (HR 1.67, 95% CI 1.11 to 2.50). But people starting a twice-daily regimen did not risk failure with one or two missed doses more than those with no misses (HR 0.99, 95% CI 0.64 to 1.54).

**Clinical consequences of unsteady adherence**

As the just-discussed Swiss HIV Cohort Study found, missing even one or two doses of a once-daily antiretroviral medley can boost chances of virologic failure. And failure poses a risk of emergent resistance and narrowed antiretroviral options. But worse adherence may have graver and more immediate consequences—including hospital admission and death (Figure 1). As US AIDS care guidelines warn, “adherence is second only to the CD4 cell count as a predictor of progression to AIDS and death.”

*continued...*
US researchers used a validated model of HIV disease progression and death to weigh the impact of starting ART at 200, 350, or 500 cells/mm$^3$ with adherence ranging from 50% to 100% of prescribed doses taken.\textsuperscript{20} The model projected that starting ART at 500 rather than 350 cells/mm$^3$ added 3.7 life-years and 3.3 quality-adjusted life-years (QALYs) in people with 100% adherence. Improving adherence from 50% to 80% added up to 2.0 life-years and 1.9 QALYs, while improving adherence from 80% to 100% tacked on up to 4.8 life-years and 4.5 QALYs.

Gauging the impact of adherence on mortality in an epidemiologic study can be difficult, but the Swiss HIV Cohort Study described in the preceding section managed to do so.\textsuperscript{18} In this analysis of 3150 people who started their first ART between 2003 and 2012 and had almost 5 years of follow-up, multivariate analysis determined that missing more than two antiretroviral doses in the previous 4 weeks (compared with missing no doses) almost tripled the risk of death (HR 2.89, 95% CI 1.13 to 7.41). In an analysis limited to MSM, missing two doses in the past 4 weeks almost quintupled the risk of death (HR 4.87, 95% CI 2.21 to 10.73). Among MSM 90% to 95% adherence (versus better than 95%) did not significantly affect mortality. But less than 90% adherence more than quadrupled the risk of death (HR 4.45, 95% CI 1.99 to 9.93).

AIDS Clinical Trials Group (ACTG) investigators explored the mortality impact of adherence to first-generation ART in ACTG protocol 362, a study of \textit{Mycobacterium avium} prophylaxis in 643 people enrolled between October 1997 and April 1999.\textsuperscript{21} A generalized estimating equation (GEE) model determined that hard drug use (cocaine, amphetamines, or heroin) doubled the odds of antiretroviral nonadherence (self-reported missed dose in the past 48 hours) (OR 2.14, 95% CI 1.36 to 3.38, $P < 0.001$). A Cox regression model figured that time-updated nonadherence almost doubled the risk of AIDS progression or death (adjusted HR 1.84, 95% CI 1.15 to 2.94, $P = 0.01$).

A study of 5177 HIV-positive people using Medicaid in 2008-2009 in 29 states linked poor self-reported adherence to more emergency department visits and longer hospital stays.\textsuperscript{22} In a cohort of 50- to 64-year-olds, the researchers used multivariable regression adjusted for race, sex, age, urban residence, and comorbidity to determine the impact of three adherence levels (below 80%, 80% to 89%, and 90% to 94%) compared with optimal adherence (95% or greater). Cohort members with adherence below 80% had a longer hospital stay (regression coefficient 1.24, 95% CI 0.53 to 1.96, $P = 0.0007$) and 34% higher odds of an emergency department visit (aOR 1.34, 95% CI 1.08 to 1.48, $P < 0.0001$). But people with adherence of 80% to 89% or 90% to 94% did not differ significantly from the optimal adherence group in emergency visits or hospital duration.

One does not need advanced degrees in pathophysiology and statistics to understand why poor antiretroviral adherence leads to worsening health and sometimes death: Skipping enough doses engenders resistant HIV, which propels rebounds in viral replication and consequent clinical risks. Many studies trace the tie between faulty adherence and detectable or climbing viral load. A 2016 meta-analysis of 43 studies involving
27,905 people in more than 26 countries conflates many of these findings into pooled odds ratios linking suboptimal adherence to virologic failure. While 15 studies took place in North America, 14 occurred in sub-Saharan Africa, 6 in Europe or Australia, 5 in Asia, and 3 in several countries. Most studies (70%) defined optimal adherence at 95% or greater, while the others used cutoffs ranging from 80% to 100%. A random-effects model determined that optimal adherence compared with suboptimal adherence lowered chances of virologic failure 66% (OR 0.34, 95% CI 0.26 to 0.44). Risk of failure did not differ among three clusters of optimal adherence thresholds (98% to 100%, 95% or greater, 80% to 90%).

Spuriously high adherence levels indicated by pill counts—called “overadherence” by University of Pennsylvania researchers—correlated with virologic failure in adolescents taking ART. The study involved 300 adolescents who apparently dumped pills before pill counts to mask poor adherence, a practice resulting in the calculation that they took more than 100% of prescribed doses. Defining “overadherence” as greater than 100% adherence on more than one third of pill counts during a year, the researchers identified “overadherence” in 33% of adolescents with virologic failure versus 13% with suppressed viral loads (P = 0.001).

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1. ClinicalTrials.gov. Study to evaluate the efficacy, safety, and tolerability of long-acting intramuscular cabotegravir and rilpivirine for maintenance of virologic suppression following switch from an integrase inhibitor in HIV-1 infected therapy naive participants. ClinicalTrials.gov identifier NCT02938520. [https://clinicaltrials.gov/ct2/show/NCT02938520](https://clinicaltrials.gov/ct2/show/NCT02938520)

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Correcting mistakes and misperceptions in managing antiretroviral adherence

An interview with Seth Kalichman, PhD

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Dr. Kalichman ranks among the leading experts on antiretroviral adherence and psychological aspects of HIV infection. Besides being Principal Investigator in Psychological Sciences at the University of Connecticut, he directs the Southeast HIV and AIDS Research and Evaluation (SHARE) Project in Atlanta and pursues HIV research in South Africa in collaboration with the Medical Research Council. The author of more than 300 peer-reviewed articles, Dr. Kalichman has also written and edited five books on HIV infection, most recently Denying AIDS: Conspiracy Theories, Pseudoscience, and Human Tragedy. He is current editor of the monthly journal AIDS and Behavior. Dr. Kalichman received the 2005 Distinguished Scientist Award from the Society of Behavioral Medicine.

Mascolini: With widening use of tolerable once-daily regimens, has antiretroviral adherence become less of a problem?

Kalichman: Yes, for most people adherence is certainly much easier than it used to be, primarily because of the simplicity of the drug regimens—most people are taking only one or two pills a day—and because toxicity is much less frequent. So certainly adherence is easier for most people.

Adherence used to be very difficult for almost everyone being treated with antiretrovirals. Then, as the medications improved, grew simpler, and became less toxic, more-resourced patients who have the capacity to adhere certainly began having an easier time. But there’s a substantial patient population that continues to struggle with adherence, and we have to target this select group for added support.

Key indicators in assessing need for adherence support

Mascolini: How should clinicians determine whether a person otherwise ready for antiretroviral therapy will be adherent?

Kalichman: That’s a real challenge for many clinicians. Our view is that patients shouldn’t be denied...
antiretroviral therapy because they may have adherence challenges. We believe the burden lies on the clinician to provide adherence support to all patients, depending on how much support they need.

To estimate how much support a patient needs, clinicians should look for key indicators of potential nonadherence. For example, depression is a very good indicator that a patient may have difficulty adhering and will require support. Any kind of substance use—including and maybe especially alcohol use—is another good indicator of adherence problems down the road. And indicators of poverty are a potential warning of poor adherence. So patients who have mental health or substance use problems or are living in poverty are people who are going to be facing the most adherence challenges and will often require adherence support.

Clinicians can try to assess patients’ organizational skills or their ability to store and maintain their medications in an organized way and have a daily routine. Another indicator may be how well connected into care a patient is in the first place. But those factors may be less important than issues of mental health, substance use, and poverty. Those are the things clinicians should be looking for to see what kind of adherence support the patient is going to need.

\textbf{Mascolini:} When antiretroviral-naive patients run a high risk of poor adherence because of problems like substance use, should clinicians defer antiretroviral therapy until they take steps to remedy the obstacles?

\textbf{Kalichman:} That’s a philosophy of clinical practice question that may not have a right or wrong answer. I believe there’s a consensus emerging—and it’s certainly the view of our research team—that antiretroviral therapy should \textit{not} be deferred because of challenges to adherence until those challenges are resolved. There are interventions that can be done to support patients. And often patients with nonadherence risk factors turn out to be quite adherent. An awful lot of our study participants who actively use alcohol or drugs, or who are significantly depressed, nonetheless have good antiretroviral adherence.

It’s not a one-to-one relationship. Those adherence predictors are just that—they’re just predictors, not determinants. Researchers often use those words interchangeably and that’s a big mistake. Something that’s a determinant is definite to happen. Something that’s a predictor or a correlate raises the odds of it happening, but it isn’t a perfect relationship.

\textit{Mental health, substance use, and poverty . . . are the things clinicians should be looking for to see what kind of adherence support the patient is going to need.}
Alcohol and drug use do not determine nonadherence, but they’re pretty good predictors. They tell you that patients with substance use problems, for example, may require some adherence support. Of course we always want to move patients toward stopping substance use, but the predictor and the outcome are absolutely not a one-to-one relationship: patients with substance use problems can adhere and do adhere quite well. So we do not advocate deferring antiretroviral therapy for anyone unless they refuse therapy.

**Gauging adherence after treatment begins**

**Mascolini:** Once a person starts antiretroviral therapy, how should clinicians assess adherence?

**Kalichman:** This is a significant issue. Clinicians I work with will often determine adherence based on viral load. When people have a suppressed viral load, you can pretty much assume that they’re adhering to their medications. But when their viral load starts to creep up, that may indicate the patient is not adhering well and risks developing resistance. But by relying on viral load as the indicator of adherence, clinicians will intervene when it’s too late. What you want to do is monitor adherence and make adjustments in adherence before the viral load begins rebounding and resistant virus emerges. So this is the challenge to clinicians—detecting nonadherence early, before viral load starts creeping up.

Clinicians in tune with this thinking usually rely on patient self-report, and there are good, evidence-based self-report questions that clinicians can ask (Table 1). But clinicians often aren’t aware of validated self-report measures. And these validated self-report measures are good, but they’re not great. Patients may not provide a valid self-report for a variety of reasons, such as saying what they think their clinicians want to hear. And often patients are simply unaware of their own nonadherence. What we’re asking patients to do in self-reporting adherence is to remember something that they forgot or to report something that they’re intentionally not doing.

So evaluating adherence in the treated patient remains a real challenge for clinicians. We’ve been working on trying to use pill counts done over the telephone with patients. The goal is to have patients count their pills and monitor their pill taking over the course of time. In our research we use that technique routinely. We’ve been trying to make that a clinical tool, but it isn’t something clinicians are doing right now.
We also have to remember that patients face structural challenges to adherence. Specifically, AIDS Drug Assistance Program (ADAP) reauthorization is a huge challenge for some patients, simply because the case management system may not do those reauthorizations early enough. So some patients bump up against reauthorization deadlines and face a lapse in their antiretroviral therapy, which is a very bad thing.

**Which antiretroviral adherence interventions work?**

**Mascolini:** Is there an antiretroviral adherence strategy that has proved both simple and effective and that clinicians can put into use with most patients?

**Kalichman:** Sometimes a simple thing can make a huge difference. In our behavioral interventions, we routinely use pill organizers for patients. It’s remarkable how few patients are trained in organizing their pills and maintaining their medications. Very carefully statistically controlled retrospective analyses show that just providing a patient with a cheap weekly pill box can improve adherence dramatically.2,3

Sometimes clinicians will just give patients pill boxes, but very brief instructions on how the pill box can assist the patient can make a big difference. For example, patients who have adherence challenges may not only forget to take their medications, they may forget they did take them. They can double-dose on a day because they forgot they took the medication once. When that happens, their pills will run out before the end of their prescription. And of course double-dosing can increase toxicity. A pill box really remedies that problem because if you forget you took your medications, you can go back and look at the pill box and see that you actually did take them today. Pill box organizers are a very powerful tool that is actually quite simple.

In our interventions we don’t just hand people pill boxes. We embed pill-box skills building in relatively

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**Table 1.** How to assess antiretroviral adherence with three questions

1. In the last 30 days, on how many days did you miss at least one dose of any of your HIV medicines? (Write in number of days: ____ 0-30)

2. In the last 30 days, how good a job did you do at taking your HIV medicines in the way you were supposed to? (Very poor, Poor, Fair, Good, Very good, excellent)

3. In the last 30 days, how often did you take your HIV medicines in the way you were supposed to? (Never, Rarely, Sometimes, Usually, Almost Always, Always)

brief phone calls that a case manager or adherence nurse can handle. Doing that provides a broader conversation about challenges that patients may be experiencing and then addresses those challenges one by one in a problem-solving way. We think our adherence counseling, delivered over the phone, is quite easy and simple. Counseling by phone reduces cost and gives adherence nurses, case managers, counselors, and sometimes peer advocates a tool that is easy to administer.

In the clinic itself, a clinician can assess adherence challenges and try to address them in a problem-solving way. To ask the right questions, clinicians can use validated tools to gauge adherence. Maybe the best set of questions out there is one developed by Ira Wilson at Brown University (Table 1). Dr. Wilson's three questions are validated and get you the best self-report, which I think is still limited because of factors we already discussed. After a validated assessment, clinicians can provide patients with simple tools like pill boxes and pocket dose-carriers. For many patients, that's going to be enough. However, some patients are going to require a lot more assistance, and there are demonstrated effective and validated brief interventions that can be delivered over the phone to those select patients (see Tables 3A, 3B, and 3C on pages 48 to 50).*

**Mascolini:** If a patient shows evidence of poor adherence, how does a clinician decide whether to implement one of these supportive strategies or to switch to another regimen that might be easier for the patient?

**Kalichman:** When clinicians see viral load start creeping up, they genotype the virus to see if it is still sensitive to the regimen; if not, they switch regimens. That's standard of care. What I don't think is standard of care in a lot of settings is assessing adherence and heading off the viral load rebound. In this case you wouldn't have to genotype the virus because it is still suppressed, but you would look for adherence indicators by self-report or assess predictors like depression or substance use. Reviewing these indicators of potential or actual nonadherence would suggest intervening with an adherence strategy before viral load goes up.

Patients who have adherence challenges may not only forget to take their medications, they may forget they did take them.

*The CDC plans to post the phone-delivered adherence intervention that Dr. Kalichman discusses around the time this issue of RITA becomes available.
Unless a patient is not tolerating a regimen well—which is also a good predictor of nonadherence—I don't think clinicians switch regimens based on adherence. They try to improve adherence. Regimens are typically switched when there's an indicator of resistance.

**Adherence mistakes and misperceptions**

**Mascolini:** What are the biggest mistakes HIV clinicians make regarding adherence?

**Kalichman:** As we've already discussed, relying on viral load to predict adherence is a mistake because by the time viral load is going up, resistance can be developing and it's too late. I do think that's something that needs to be remedied in clinical practice.

Another example of faulty thinking about adherence in the clinic is that an adherence intervention is going to be labor-intensive, difficult to implement, and expensive. And that's just not true. Every patient does not require an adherence intervention. In the developing world the World Health Organization has established a standard for differential adherence care: On the one hand there are patients who are doing well, taking a regimen that's working for them, with HIV suppressed for 6 months and with no indicators of nonadherence. Those patients can continue routine care.

On the other hand, there are patients who have indicators of nonadherence or who are late picking up their antiretrovirals or who report specific indicators of nonadherence in response to validated questions ([Table 1](#)). Those patients require adherence intervention. But that assistance is not necessarily burdensome or expensive—and it can be delivered by adherence intervention professionals.

**Mascolini:** Can busy HIV clinics make time to conduct adherence interventions?

**Kalichman:** HIV care clinics can develop the capacity to implement adherence interventions. We work in a very high-quality clinic in the middle of Georgia, which is a very under-resourced part of the country. You don't think of the middle of Georgia as a place that would have a state-of-the-science multifaceted infectious disease clinic like those in Atlanta, for example, where you have world-class comprehensive HIV care. But Macon, Georgia does too. In this poor setting the clinic has an adherence nurse, a community nurse, case managers, and peer advocates. Any one or all of those providers can deliver a brief, weekly or biweekly 15- to 30-minute adherence counseling session by phone to those patients who need it.

It's a mistake to wait until the 3-month routine viral load check and prescription refill to assess adherence. That's insufficient for patients who need assistance. It probably is sufficient for 65% of the patients at that clinic. But one third of those patients really need some support. And that support doesn't require an office visit. I think the billing for telemedicine is being worked out so that Ryan White can reimburse for those services. And if those services are not being reimbursed, certainly that needs to be addressed.

At the Macon clinic we're working with an infectious disease doctor, Harold Katner, at Mercer University, and our collaboration focuses on telemedicine-based
It’s a mistake for clinicians to think that early adherence detection and intervention are infeasible and expensive. That’s just not true.

adherence interventions. A 15- to 30-minute phone call every 2 weeks has demonstrated efficacy. These interventions are not hypothetical; they’re not just ideas. The National Institutes of Health has funded multiple studies demonstrating the effectiveness of relatively brief phone counseling for medication adherence. And the CDC has deemed this an effective intervention and lists it among their medication adherence evidence-based behavioral interventions.*4

These brief adherence interventions exist, they’re available, people can be trained in them. Even under-resourced clinics in the middle of Georgia and similar settings have providers who can do these interventions. I think it’s a mistake for clinicians to think that early adherence detection and intervention are infeasible and expensive. That’s just not true.

Mascolini: Are there any adherence issues we haven’t addressed that you’d like to emphasize for HIV clinicians?

Kalichman: I should mention one thing that’s come up an awful lot in our work, and that’s intentional nonadherence. This is a significant problem. We usually think of nonadherence as people forgetting to take their pills. That’s often true, but missing an occasional dose is not going to cause major problems with today’s antiretroviral regimens. It’s the longer gaps in adherence that we should worry about. These gaps can be caused by structural challenges—things that a person can’t readily change—poverty and transportation issues, for example. Adherence support can really assist people in solving those problems and getting the structural barriers out of the way so they can adhere.

But the problem we don’t think about very often is when the patient says, “I’m not going to take these drugs.” And they don’t necessarily tell their clinician. This can result from mistrust of the medications, but we’re finding as many as half of patients who drink alcohol will skip taking their antiretrovirals when they’re drinking—and that may be for days—because they believe it’s toxic to do that.5-7 Sometimes patients who believe it’s toxic to mix their medications with alcohol stop drinking, and that’s not a bad thing. But people who continue to drink may stop taking their antiretrovirals, and that is a bad thing.

Unless a person has a compromised liver, there’s no significant risk to taking antiretrovirals when they’re going to be drinking. But some people believe mixing antiretrovirals with alcohol has serious health repercussions because there can be with other

*The CDC plans to post this phone-delivered adherence intervention around the time this issue of RITA becomes available.
medications. We can’t mix sleeping pills with drinking; that’s pretty hazardous. But not antiretroviral therapy.

We’re trying to address the intentional nonadherence frequently seen in people who use alcohol and other drugs. I think intentional nonadherence is like the third spoke in the nonadherence wheel that’s often ignored. Instead we pay too much attention to forgetting. I think we can forget about forgetting. Occasionally forgetting an antiretroviral dose is not going to create a huge clinical problem. We should focus more attention on structural problems like ADAP reauthorization, and we also have to deal with intentional nonadherence, especially nonadherence related to substance use.

References

**Abstract:** Review of recent studies—from meta-analyses to cross-sectional cohorts—indicates more than 30 potential reasons for poor antiretroviral adherence. Many of these risk factors overlap with others, and multivariate analysis cannot always disentwine these overlaps. In addition, some studies disagree on whether certain variables impair or promote adherence. Although people taking antiretrovirals often cite “simply forgetting” as the prime reason for poor adherence, several analyses indicate that forgetting does not explain erratic pill taking for most HIV patients and that memory aids will not improve adherence. Adherence factors amenable to change include alcohol and other substance use, smoking, depression, and antiretroviral side effects. Some well-planned studies indicate that treating depression improves antiretroviral adherence. One study offers persuasive evidence that “nonspecific” side effects and seemingly minor side effects like cough, fatigue, and taste disturbances can imperil adherence. Plentiful research shows that adherence often slips measurably in the early postpartum period.

Potential reasons for poor antiretroviral adherence—and for good adherence—seem limited only by the imagination of adherence researchers. A review of meta-analyses, prospective and cross-sectional cohort studies, and randomized controlled trials turned up 32 reasons for good or bad adherence (Table 1). Even grouping these reasons into broad categories still leaves seven: demographic, habitual, behavioral, economic, HIV-related, non-HIV clinical, and psychological. And this breakdown relies on studies published mostly in the past 10 years that typically used statistical analysis beyond descriptive comparisons—such as multivariate analysis or data pooling.

Certain studies disagree on whether a particular factor promotes or impairs adherence. Most studies, for example, find better adherence with older age and worse adherence with younger age. But secondary analysis of data from 326 participants in a US randomized smoking cessation trial linked older age to worse adherence in these smokers.12 In a 28-study meta-analysis, employment promoted adherence in high-income countries and low-income countries.29 But an older analysis of US patients at 10 AIDS Clinical Trials Group (ACTG) sites found worse adherence among people employed outside the home.15 Analysis of the international SMART trial9 and the Swiss HIV Cohort Study13 confirmed better adherence in people taking comediations for non-HIV conditions, while a prospective cohort study in Spain linked more comediations to worse adherence.41 People with a higher current CD4 count had worse adherence in a cross-sectional Dutch study,40 but a lower enrollment CD4 count predicted worse adherence in a small study of US patients,25 while an 18-study meta-analysis yielded mixed results on the impact of CD4 tallies.39
Reasons for such contradictions—and for the vast array of potential adherence variables—reflect wide differences in study populations, methods, and antiretroviral era. Adherence is easier today than when most regimens hinged on a ritonavir-boosted protease inhibitor or efavirenz (see "How much has adherence changed" on page 5 of this issue). But difficulties in pinpointing discrete adherence promoters and barriers also reflect the confounding overlap of both individual variables and whole categories of variables. As just one example, the demographic variable race may easily overlap behavioral, economic, HIV-related, non-HIV clinical, and psychological barriers (Table 1).

Multivariate analysis can help sort out individual impacts of isolated factors, but no multivariate analysis can control for the dozens of confounders that may cloud results. One resonant example is female gender. HIV-positive women throughout the world endure disadvantages that also imperil adherence (Table 1) including (to name but a few) unemployment, financial constraints, food and housing insecurity, lack of social support, trauma and violence, less education, and HIV stigma. A 29-state 5177-person analysis of adherence in Medicaid recipients 50 to 64 years old found that men were 11% more likely to be adherent than women (adjusted prevalence ratio 1.11, 95% confidence interval [CI] 1.02 to 1.21, \( P = 0.0127 \)). But that analysis adjusted for only age and state, not for the just-listed socioeconomic variables.

### Table 1. Identified adherence promoters (+) and barriers (-)

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Behavioral</th>
<th>HIV-related</th>
<th>Non-HIV clinical</th>
<th>Psychological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender (-)(^{1-4})</td>
<td>Alcohol use (-)(^{12,16-18})</td>
<td>Concerns about ART (-)(^{23,24})</td>
<td>Comorbidities (-)(^{2,41})</td>
<td>Depressive/psychological symptoms (-)(^{8,17,21,22,26,42-44})</td>
</tr>
<tr>
<td>Postpartum vs pregnancy (-)(^{5-8})</td>
<td>Other substance use (-)(^{12,14,19-24})</td>
<td>Negative beliefs about necessity/utility of ART (-)(^{21,24})</td>
<td>Comedications (+/-)(^{9,13,41})</td>
<td>Antidepressant therapy (+)(^{10})</td>
</tr>
<tr>
<td>Black race (-)(^{9,10})</td>
<td>Smoking (-)(^{9,12,25})</td>
<td>Antiretroviral side effects (-)(^{4,37,38})</td>
<td>Feeling sick/feeling well (+/-)(^{14})</td>
<td>Stress/trama/violence (-)(^{34-36})</td>
</tr>
<tr>
<td>Older age (+/-)(^{9,11,12})</td>
<td>Conduct disorder/disruptive behavior in youth (-)(^{26,27})</td>
<td>CD4 count (+/-)(^{9,25,39,40})</td>
<td></td>
<td>Poor understanding of HIV (-)(^{15})</td>
</tr>
<tr>
<td>Younger age (-)(^{13})</td>
<td>Caregiver factors* (-)(^{28})</td>
<td>Trust/satisfaction with provider (+)(^{31})</td>
<td></td>
<td>More education (+)(^{9,25})</td>
</tr>
<tr>
<td>Habitual</td>
<td>Employment (+/-)(^{15,29})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forgetting (-)(^{14,15})</td>
<td>Financial constraints (-)(^{21})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Being away from home (-)(^{14,15})</td>
<td>Food insecurity (-)(^{30,31})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in daily routine (-)(^{14,15})</td>
<td>Housing instability (-)(^{32,33})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Being busy (-)(^{15})</td>
<td>Social support (+)(^{31,28})</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Caregiver not fully responsible for medications, low caregiver well-being, adolescent perceptions of poor caregiver-youth relations, caregiver perceptions of low social support.\(^{28}\)
Should adherence motivators “forget about forgetting”? 

Some research rates “just forgetting” the primary reason for shaky antiretroviral adherence. A 125-study meta-analysis involving 17,061 adults, 856 adolescents, and 1099 children found forgetting the most frequent patient-reported adherence barrier in adults (41.4%) and adolescents (63.1%), far ahead of the second-place barrier, being away from home (30.4% in adults and 40.7% in adolescents). A survey of 75 adult ACTG study participants at 10 trial sites found “simply forgot” the reason for missing doses in 66%, ahead of being away from home (57%) or being busy (53%). And multivariate analysis in an 80-person US CHARTER cohort substudy linked worse pharmacy refill adherence to worse working memory on standard tests.

Despite the frequency of forgetting to take antiretrovirals and the intuitively compelling tie between faulty memory and poor adherence, other research in the United States argues that “just forgetting” does not fundamentally explain erratic pill taking for most people with HIV. This work is important because, if correct, it means clinicians should spend less time promoting adherence memory aids and more time drilling down to underlying causes of poor adherence that need to be addressed. Here are the key findings:

A University of Connecticut group analyzed 556 people with less than 95% antiretroviral adherence according to phone-based unannounced pill count, dividing them into severely nonadherent patients (75% or fewer medications taken) and moderately nonadherent patients (more than 75% to less than 95% taken). As in other studies, forgetting topped the list of reasons for missing doses in severely nonadherent people (54%) and in moderately nonadherent people as well (41%). Reasons related to mental health, structural barriers, and substance use proved much less frequent. High and similar proportions of the severely and moderately nonadherent groups relied on multiple dosing-reminder strategies, such as using bedtime as a cue (67% and 65%), using mealtimes as a cue (61% and 61%), storing medicines where they can be easily seen (58% and 56%), and using pill box organizers (42% and 39%).

Multivariate logistic regression to distinguish severe nonadherence from moderate nonadherence controlled for the four sets of adherence barriers analyzed: cognitive/organizational (which includes forgetting), mental health (such as depression), structural barriers (such as running out of pills or being unable to pay for them), and substance use. Neither cognitive/organizational nor mental health barrier composites distinguished severe from moderate nonadherence. But structural barriers boosted odds of severe nonadherence almost 50% (adjusted odds ratio [aOR] 1.49, 95% CI 1.17 to 1.89, \( P < 0.05 \)), and substance use raised odds of severe nonadherence by one third (aOR 1.32, 95% CI 1.02 to 1.73, \( P < 0.01 \)). The researchers suggest that colleagues “forget about forgetting” as a way to improve antiretroviral adherence. Rather, they propose, efforts should “concentrate on substance use treatment and providing case management to resolve structural barriers to adherence.”

In a study of 223 US adults with adherence measured by electronic MEMS pill bottle caps, the more adherence reminders people used, the worse their adherence got. The largely male (83%), white (66%) study group completed the Prospective Memory for Medications Questionnaire to assess use of 28 adherence strategies. Participants reported using an average 8.7 strategies at least sometimes. The most frequent memory aids were
leaving pill bottles in a prominent place (69% at least sometimes), linking dose times to something done routinely (68%), and thinking about dosing times at the beginning of the day (61%). But statistical analysis linked use of more adherence strategies to worse antiretroviral adherence (–0.15, P = 0.02). The study also found that using more reminder strategies did not reflect patient belief that they would work. Perhaps the researchers discovered a dismal feedback loop in which people use more and more reminders, yet adhere less and less, leading to less belief that strategies work, prompting use of even more reminders (Figure 1, outside arrows). Or maybe the loop runs the other way: people use more and more reminders, yet believe less and less that the strategies work, fulfill their own forecast by taking fewer antiretrovirals, and thus prompt use of even more reminders (Figure 1, inside arrows).

Analysis of 1496 adults in 11 ACTG studies that ended from 2002 through 2012 also found memory-related pitfalls the most common self-reported reasons for poor adherence at treatment week 12.48 But forgetting ranked far behind other barriers (too many pills, side effects, depression) in explaining a detectable viral load at 24 weeks. The most frequently cited adherence barriers were being away from home (21.9%), simply forgetting (19.6%), a change in daily routine (19.5%), and falling asleep (18.9%). Multivariate analysis adjusted for all 14 potential adherence barriers found one independent predictor of failure to have an undetectable viral load at 24 weeks, “felt sick” (aOR 0.53, 95% CI 0.37 to 0.76, P < 0.001). Two variables marginally predicted virologic failure, “too many pills” (aOR 0.61, 95% CI 0.37 to 1.01, P = 0.06) and “felt drug was harmful” (aOR 0.62, 95% CI 0.37 to 1.04, P = 0.07). “Simply forgot” had no impact on virologic response in bivariate analysis (OR 0.99, 95% CI 0.76 to 1.30, P = 0.95).

Figure 1. Research linking more adherence reminders to worse adherence—with no link between using more reminders and believing they work—suggests one of two negative feedback loops in which people use more adherence reminders to no avail.
Dominance analysis to assess the relative importance of each adherence barrier at 12 weeks in promoting virologic detectability at 24 weeks rated “simply forgot” ninth in importance. (Dominance analysis is a regression-based approach calculating effect size.) The top five barriers were (1) felt sick, (2) too many pills, (3) felt drug was harmful, (4) wanted to avoid side effects, and (5) felt depressed/overwhelmed. The 1-through-14 dominance ranking did not even remotely reflect the 1-through-14 self-reporting frequency (Table 2). The ACTG researchers propose that “interventions should focus on barriers that have been associated with poor virologic outcomes rather than focusing on the most commonly reported barriers.”

Another study used dominance analysis to rank the importance of nine barriers to self-reported non-adherence (a 4-day interruption) in 1217 US adults (95% men, 76% white, 87% with an undetectable viral load). The analysis relied on an online survey to rate self-reported frequency of the nine barriers in this order:

1. Simply forgot
2. Day-to-day life
3. Alcohol or illicit drug use
4. Felt depressed/overwhelmed
5. Ran out of pills
6. Fell asleep
7. Pharmacy/insurance problems
8. Wanted to avoid side effects
9. Felt sick

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**Table 2.** Adherence barriers in 11 ACTG trials ranked for impact on virologic response vs self-reported frequency

<table>
<thead>
<tr>
<th>Resistance barrier</th>
<th>Ranked impact on undetectable viral load (24 wk)</th>
<th>Patient self-reported frequency (12 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felt sick</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Too many pills</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Felt drug was harmful</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Wanted to avoid side effects</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Felt depressed/overwhelmed</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Ran out of pills</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Busy with other things</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Taking pills at specified time</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Simply forgot</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Need to hide pill taking</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Felt good</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Change in daily routine</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Fell asleep</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Away from home</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

*Source: Saberi et al.*
In the dominance analysis “simply forgot” fell to sixth place while “fell asleep” jumped to first:

1. Fell asleep
2. Felt depressed/overwhelmed
3. Day-to-day life
4. Wanted to avoid side effects
5. Alcohol or illicit drug use
6. Simply forgot
7. Ran out of pills
8. Felt sick
9. Pharmacy/insurance problems

The ACTG researchers suggest that forgetting to take pills “may be . . . multi-faceted and may include other barriers such as stigma, depression, drug and alcohol use, and lack of social support.”48 They propose that basing adherence strategies solely on patient report frequency “may potentially lead investigators in the wrong direction and may result in ineffective interventions.”

**Turning adherence research into clinical action**

Most findings on factors tied to good or bad adherence bear out a priori intuition. Social support,21,28 more education,9,25 and provider satisfaction21 favor good adherence. Alcohol and other substance use,12,14,16-24 food insecurity,30,31 and concerns about ART foster poor adherence. But research on adherence correlates comes laden with nuance and sprinkled with surprise. The second paragraph of this article sampled contradictory findings related to adherence and age, employment, comedications, and CD4 count. The rest of this article spotlights some fine points clinicians can use to shape clinical adherence strategies.

**Adherence drops after delivery.**

Studies of pregnant women in the United States5,8,19 and an international meta-analysis52 agree that antiretroviral adherence during pregnancy drops 10% to 25% after delivery. In the bustle of perinatal and postnatal concerns, even clinicians well aware of this adherence threat may miss the opportunity to prevent a clinically meaningful slip in pill taking. With 14 of 51 studies in the meta-analysis coming from the United States, this study found that a 75.7% pooled prevalence of better than 80% adherence before delivery dropped to 53% postpartum (P = 0.005).52 Barriers to adherence included depression; physical, economic, and emotional stress; alcohol or drug use; and antiretroviral dosing frequency.

A US Pediatric ACTG study involved 519 women, 75% of whom reported perfect adherence (no missed doses in preceding 4 day) during pregnancy.5 Six, 24, and 48 weeks after delivery, the perfect adherence rate dipped to 65%, 64%, and 66% (P < 0.01). Among 149 women in ACTG protocol A5084, 57% reported adherence during pregnancy (no missed doses in past 3 months), and that rate dropped to 45% in the first 12 postpartum weeks (P = 0.03).19 Multivariate analysis determined that women who ever used illicit drugs had almost 6-fold higher odds of nonadherence (P = 0.002), and those who missed prenatal vitamins had almost 5-fold higher odds (P = 0.001). The latter finding suggests vitamin taking during pregnancy may offer a signal of antiretroviral adherence after delivery. In a US Women and Infants Transmission Study of 309 women, the self-reported complete adherence rate fell from 61% during pregnancy to 44% postpartum.8 More health-related symptoms and alcohol use emerged as independent predictors of nonadherence before and after delivery.
Table 3. Reasons for better adherence during pregnancy than postpartum

- More frequent monitoring/adherence reinforcement during pregnancy
- Mother’s desire to protect fetus/neonate from HIV
- Refraining from drug/alcohol use during pregnancy
- Postpartum challenges in caring for infant
- Postpartum physiologic changes/health challenges
- Postpartum depression

Adherence may be better during pregnancy because women want to protect their infant from HIV and because frequent monitoring during pregnancy can promote adherence (Table 3). After delivery, the HIV transmission motivation declines for nonbreastfeeding women, while they confront new demands in caring for an infant and often face postpartum depression. US Department of Health and Human Services (DHHS) guidelines for pregnant women with HIV caution, however, that adherence may also falter during the first trimester because of the nausea and vomiting common during that phase of pregnancy.53 These guidelines recommend more frequent viral load monitoring during pregnancy if adherence is a concern, and they endorse a protease inhibitor over an integrase inhibitor for women at risk of stopping therapy after delivery. For the same reason, switching from twice- to once-daily dosing could make sense.

“Because the immediate postpartum period poses unique challenges to antiretroviral adherence,” the DHHS experts counsel, “arrangements for new or continued supportive services should be made before hospital discharge.”53

Depression undermines adherence.

The well-appreciated link between depression and wavering adherence in people with HIV rests on data from three meta-analyses14,21,44 and countless smaller studies. Meta-analysis of 207 studies presented from 1996 through 2014 determined that depression trailed only current substance use and concerns about ART in predicting poor adherence (Figure 2), but depression had a much greater negative impact than HIV stigma, protease inhibitor therapy, dosing frequency, financial constraints, or pill burden.21

Figure 2. Meta-analysis of 207 studies involving 103,836 people with HIV ranked depressive symptoms as the third strongest independent predictor of poor adherence, with effect size calculated as standard mean difference (SMD).21 (PI, protease inhibitor.)
A 111-study meta-analysis involving 43,366 HIV-positive people found no difference in depression prevalence by country income group. Overall chances of attaining at least 80% adherence was 42% lower in people with depressive symptoms (pooled OR 0.58, 95% CI 0.55 to 0.62), and that association did not differ by country income group, study design, or adherence rate.

**Depression and adherence in youth.**

Adherence poses a sterner challenge to HIV-positive youth than to older or younger age groups. And depression may play a big part youth's inconsistent pill taking. A 125-study meta-analysis of 17,061 adults, 856 adolescents, and 1099 children found that similar proportions of adults (15.5%) and children (15.1%) self-reported depression as an adherence barrier, rates well below the 25.7% of adolescents attributing poor adherence to depression.

A US Adolescent Trials Network analysis of 956 minority HIV-positive 16- to 24-year-olds found that 39% of them reported taking fewer than 90% of antiretrovirals in the past 7 days. Path analysis determined that higher self-efficacy (belief in one's ability to do something) predicted good adherence, while psychological symptoms (measured on the Brief Symptom Inventory) predicted lower self-efficacy, more substance use, and lower adherence. A longitudinal study of 294 US youngsters 6 to 17 years old found that 38% had at least one psychiatric condition at the baseline visit. Multivariable logistic regression determined that youngsters with depression had 4-fold higher odds of missing more than 5% of doses in the past 3 days at follow-up week 96 (aOR 4.14, 95% CI 1.11 to 15.42).

**Treating depression improves adherence.**

If depression promotes poor adherence, one would expect that treating depression improves adherence. That doesn't always happen, learned US researchers who randomized 304 HIV-positive people with major depressive disorder to antidepressant therapy or usual care. After 12 months, lack of improvement in pill count-based adherence with versus without therapy, the authors suggest, could reflect high baseline adherence rates in both study groups (about 86%).

But a clutch of other recent studies, including one meta-analysis and one systematic review, did find that treating depression improves adherence in people with HIV. The meta-analysis considered 29 studies published between 2001 and 2012 involving antidepressant therapy, cognitive behavioral therapy, and mixed approaches. Meta-analysis indicated that odds of antiretroviral adherence were 83% better (standardized OR 1.83, 95% CI 1.27 to 2.55) in people treated for depression or psychological distress than in untreated people. In 17 intervention studies, people randomized to the intervention arm versus the control arm had twice high odds of improvement in depressive symptoms (standardized OR 2.07, 95% CI 1.38 to 3.30). Longer treatment yielded greater adherence rates than shorter treatments (random effects r = 0.43, P = 0.02). The systematic review found that 7 of 9 studies produced evidence that antidepressant treatment improved antiretroviral adherence.

In a study of 7034 antiretroviral-treated Medicaid recipients, 66% were black, 47% experienced depression during the study period, and 32% had optimal adherence,
defined as at least 90% adherence by prescription refill. Multivariate logistic regression determined that black participants had 30% lower odds of optimal adherence (aOR 0.70, 95% CI 0.63 to 0.78), while antidepressant therapy nearly doubled chances of optimal adherence (aOR 1.92, 95% CI 1.12 to 3.29).

Retrospective analysis of 3359 HIV-positive people in the Kaiser Permanente healthcare system in 8 states used medical records to determine that 1398 (42%) had a depression diagnosis, yet only 508 of these 1398 (36%) had a prescription for a selective serotonin reuptake inhibitor (SSRI). Chances of at least 90% antiretroviral adherence (determined by pharmacy refills) were almost 20% lower in people with depression not treated by SSRIs than in people without depression (aOR 0.81, 95% CI 0.70 to 0.98, P = 0.03). But chances of at least 90% antiretroviral adherence did not differ significantly between people without depression and (1) people with depression and prescribed an SSRI (aOR 0.91, 95% CI 0.72 to 1.15) or (2) people with depression and greater than 80% adherence to an SSRI (aOR 1.13, 95% CI 0.86 to 1.49).

US depression researchers calculated that only 48% of HIV-positive people with major depressive disorder get recognized clinically, only 18% get treated, only 7% get treated adequately, and only 5% achieve remission through treatment. See the Summer 2016 issue of RITA for a detailed review of depression in people with HIV (http://centerforaids.org/pdfs/rita0616.pdf).

**Alcohol, hard drugs, and toxicity beliefs.**

Alcohol use and drug use are well-studied predictors of poor antiretroviral adherence. Systematic review of 7 prospective observational cohorts, 11 cross-sectional analyses, and 2 randomized controlled trials found links between alcohol use disorder and poor adherence in most of these studies. The researchers site evidence that alcohol abuse and faulty adherence have a synergistic impact on morbidity and mortality, calling the literature on this interface “staggering.” In the United States, alcohol use affects adherence in women as well as men with HIV. Analysis of 1304 HIV-positive women in the Women’s Interagency HIV Study (WIHS), 82% of them black or Hispanic, recorded low alcohol drinking in 28%, moderate to heavy drinking in 8%, and binge drinking in 4%. More than one third of women (37%) had symptoms of depression. The researchers defined decreasing adherence as 100% self-reported adherence at one visit followed by less adherence at a subsequent visit. Multivariate logistic regression determined that all three drinking levels (compared with no drinking) independently predicted decreasing adherence in women (Figure 3).

A prospective study of 559 men and 84 women enrolled in an ACTG trial linked hard drug use (cocaine, amphetamines, or heroin) to poor adherence and AIDS progression or death. The researchers defined nonadherence as missed antiretroviral doses in the 48 hours before study visits. The ACTG team collected data from October 1997 through April 2007, and median follow-up measured 6 years. High proportions of participants reported ever using cocaine (39%), amphetamines (24%), or heroin (10%), while 8% called themselves heavy drinkers and 32% binge drinkers. Generalized estimating equation models determined that hard drug use doubled the odds of nonadherence (aOR 2.14, 95% CI 1.36 to 3.38, P < 0.001), while binge drinking upped the odds about 50% (aOR 1.53, 95% CI 1.21 to 1.92, P < 0.01). Time-updated nonadherence
almost doubled the odds of a new AIDS condition or death in a Cox proportional hazards model (adjusted hazard ratio 1.84, 95% CI 1.15 to 2.94, \( P = 0.01 \)).

People who drink alcohol\(^{59,60}\) or use drugs\(^{61}\) may interrupt their antiretrovirals because they incorrectly fear interactive toxicity between the alcohol or drugs and their antiretrovirals. In one study 57 men and women reported alcohol use over 45 days by text messaging, while researchers recorded antiretroviral adherence by the Wisepill device, a wireless pill container.\(^{59}\) Participants who believed alcohol interacts with antiretrovirals missed doses on significantly more days. Multivariate regression determined that interactive toxicity beliefs predicted daily missed doses regardless of depression, general medication concerns, or the amount of alcohol consumed. In an interview in this issue, Seth Kalichman stresses that mixing alcohol and antiretrovirals poses risks only in people with a compromised liver (see page 19).

> **When good adherence goes up in smoke.**

Studies disagree on whether smoking cigarettes independently predicts poor adherence in people with HIV. Sorting out the independent impact of smoking is complicated because so many people with HIV smoke and so many smokers have other addictive habits—and socioeconomic traits—that also promote poor adherence. Even robust multivariate analyses cannot hope to adjust for all adherence-related risks, some of which may remain unknown to the investigators.

Two recent studies could not confirm an independent link between cigarette smoking and poor antiretroviral adherence\(^{62,63}\) and four studies could.\(^{9,12,25,64}\) The two studies that could not link smoking to poor adherence have their limits. One study focused only on men who have sex with men who report heavy drinking—itself a notable adherence risk factor.\(^{62}\) Almost half of the 185 study participants smoked. A significantly higher
fraction of current smokers had imperfect adherence (37% versus 22%, \( P < 0.05 \)). But multivariate regression singled out only lower education as an independent predictor of faulty adherence.

The second inconclusive study focused on 203 HIV-positive people enrolled in a US trial to test adherence interventions, which did not improve adherence. So these 87 daily smokers, 48 occasional smokers, and 68 nonsmokers had tough adherence problems. One third had a monthly household income below $500, 43% recently used drugs, and 56% drank alcohol. Proportions of antiretroviral doses taken at five intervals up to 48 weeks (measured by MEMS caps) did not differ significantly between daily smokers, occasional smokers, and nonsmokers. Longitudinal generalized estimating equation analysis found no association between smoking status and adherence over time.

Four recent studies that did pinpoint smoking as an independent predictor of flawed adherence are (1) a 5295-person analysis of the international randomized SMART trial (current smoking aOR 1.54, 95% CI 1.41 to 1.68, \( P < 0.0001 \)), (2) a 326-person US randomized smoking-cessation trial (nicotine dependence aOR 1.13, 95% CI 1.02 to 1.25, \( P = 0.023 \)), (3) a 64-person prospective US study using MEMS monitoring (current smoking \( P = 0.001 \)), and (4) a 218-person Belgian study in which smoking, neurocognitive complaints, and female sex independently predicted nonadherence.

“Mild” side effects can thwart adherence.

Clinical trials of new antiretrovirals typically find most side effects are “mild or moderate,” but research shows that even side effects managed by pat-on-the-back counseling can have a big impact on antiretroviral adherence. Teaming with a British research firm, Merck investigators conducted a meta-analysis of studies weighing the impact of specific and nonspecific treatment-related adverse events on adult adherence to antiretroviral therapy (Figure 4). Focusing on 18

![Figure 4. Even antiretroviral side effects typically considered “mild” or “minor” can impair adherence, according to results of a 19-study meta-analysis. (Source: Al-Dakkak I, et al. See text for pooled odds ratios. Clinical images from Servier PowerPoint Image Bank http://servier.com/Powerpoint-image-bank.]
antiretroviral side effects in 19 studies, the researchers found significantly lower pooled odds of adherence in people who endured “nonspecific” adverse events than in those with no adverse events (pooled OR 0.62, 95% CI 0.46 to 0.83, \( P = 0.001 \)). Patients reporting certain specific but seemingly second-tier side effects proved significantly less likely to adhere to ART: cough (pooled OR 0.65, 95% CI 0.53 to 0.79, \( P < 0.001 \)), fatigue (OR 0.63, 95% CI 0.43 to 0.92, \( P = 0.016 \)), anxiety (OR 0.63, 95% CI 0.41 to 0.95, \( P = 0.028 \)), confusion (OR 0.35, 95% CI 0.18 to 0.66, \( P = 0.001 \)), taste disturbance (OR 0.49, 95% CI 0.30 to 0.77, \( P = 0.003 \)), nausea (OR 0.57, 95% CI 0.43 to 0.77, \( P < 0.001 \)), vomiting (OR 0.49, 95% CI 0.24 to 1.02, \( P = 0.056 \)), and tingling in mouth or tongue (OR 0.67, 95% CI 0.42 to 1.05, \( P = 0.079 \)).

Dermatologic side effects and lipodystrophy did not dim adherence in the 19-study meta-analysis. But a 39-article systematic review identified 16 studies (41%) that found visually noticeable antiretroviral side effects contributed to poor adherence (weight gain/loss, excess sweating, darkening skin color, body odor, hair loss, rash). Seven studies (18%) produced evidence that psychological adverse reactions impaired antiretroviral adherence. Six studies (15%) found that neuropsychological side effects in people taking efavirenz weakened adherence. Overall 33 of 39 articles (85%) reported that adverse antiretroviral drug reactions impair adherence, while 6 did not.

A cross-sectional study of the national Swedish HIV cohort also linked side effects to adherence. The analysis involved 2846 HIV-positive people who completed a 9-item health questionnaire from 2012 through 2014. Two thirds of participants were men, and heterosexual HIV transmission was more common than male-to-male transmission (49% versus 40%). Logistic regression modeling determined that chances of adherence (missing no doses in the past week) were almost twice higher in people reporting no side effects (aOR 1.79, 95% CI 1.38 to 2.31).

**Low perception of side effects as adherence barrier, but high impact.**

AIDS Clinical Trials Group (ACTG) investigators studying 1496 people enrolled in 11 clinical trials found that side effects ranked low as a patient-reported barrier to adherence. But dominance analysis (a regression-based approach calculating effect size) determined that side effects have a big impact on viral load. Study participants reported adherence barriers after the first 12 weeks of therapy, and researchers measured viral load at week 24. On a list of 14 potential self-reported barriers to resistance, wanting to avoid side effects ranked eighth in patient-reported frequency and feeling an antiretroviral was harmful ranked twelfth (Table 2). But the dominance analysis rated wanting to avoid side effects the fourth most important factor in affecting week-24 viral load, while feeling an antiretroviral was harmful came in third in that analysis (Table 2).

**Keys to counseling on side effects.**

People starting antiretrovirals cope with manageable side effects better if they know what to expect, and as a result they have a better shot at good adherence. That guidance emerged from the systematic review of 39 studies exploring how antiretroviral side effects shape adherence. “When people receiving ART had prior...
knowledge of antiretroviral adverse drug reactions, or had been informed in advance of potential adverse reactions and how to manage them,” four studies showed, “they felt these reactions were expected, normal and manageable, and therefore reported less non-adherence.”

Patients had better adherence when armed with coping strategies for antiretroviral side effects—like drinking fluids and resting to reduce dizziness or taking pills with a snack or meal to avoid nausea.

References


Clinician’s checklist for checking on good antiretroviral adherence

By Mark Mascolini

Abstract: HIV care guidelines and national studies offer plentiful detailed suggestions on how clinicians should work with patients to assess antiretroviral adherence readiness and ongoing pill taking. This article organizes these recommendations by addressing three questions: (1) Will a person who needs antiretroviral therapy (ART) be adherent? (2) Is a person who just started ART adherent? (3) Will a person adhering to ongoing ART stay on track? Work by US, Swiss, and Swedish investigators suggests that just three, two, or even one question can elicit a reasonable indication of adherence to ongoing therapy.

Current HIV care guidelines come loaded with advice on how to check for good (or bad) antiretroviral adherence. The challenge is sifting out a manageable amount of useful guidance that clinicians can apply in practice. That’s what this article aims to do by addressing three questions: (1) Will a person who needs antiretroviral therapy (ART) be adherent? (2) Is a person who just started ART adherent? (3) Will a person adhering to ongoing ART stay on track?

Will a person who needs ART be adherent?

Three sets of HIV care guidelines offer advice on evaluating potential adherence in people who need to start ART: the European AIDS Clinical Society (EACS),1 the US Health Resources and Services Administration (HRSA),2 and the Infectious Diseases Society of America/HIV Medicine Association (IDSA/HIVMA).3 (All of these guidelines and others cited in this article are freely accessible at the links provided after the corresponding reference. The highly detailed AIDS Clinical Trials Group (ACTG) baseline adherence questionnaire, designed for research purposes, is also available online.)

EACS experts define three stages of readiness to start ART and the appropriate clinician response to each: (1) precontemplation (patients doesn’t want to think about ART), (2) contemplation (patient has mixed feelings about ART), and (3) preparation (patient wants to start ART).1 Suggested provider responses to precontemplation and contemplation involve respecting the patient’s opinion and providing concise and individualized information, but not pushing the patient to start therapy. Patients in the preparation stage should be asked how confident they are in their ability to take antiretrovirals as scheduled. For some individuals, the EACS suggests, skills training may be appropriate, including:

- Medicine-taking training (possibly with MEMS caps, the electronic pill bottles)
- Directly observed therapy with educational support
- Devices such as mobile phone alarms or pill organizers
- Supportive tools or persons
To help providers plan antiretroviral dosing and adherence support, HRSA HIV care guidelines suggest 8 questions clinicians might ask patients considering ART:\(^2\)

- Do you believe ART is effective?
- What are your biggest concerns about ART?
- Are you ready to take the medications every day, around the same time each day?
- What other medications are you taking: prescription, over-the-counter, herbals?
- Are you a morning or an afternoon person?
- What’s your daily routine, including waking and bed times?
- How many meals and snacks do you eat per day, and at what times?
- Do you use alcohol, marijuana, cocaine, or injectable drugs? If so, how much do you use and how long have you used them?

HRSA also offers a 5-item checklist for clinicians with a patient starting ART (Table 1).\(^2\)

IDSA/HIVMA experts underline the importance of evaluating patients for depression and substance use before starting ART because both are cardinal risk factors for poor adherence (see pages 27 and 29 of this issue).\(^3\) For patients with depression or substance use, a management plan involving appropriate providers should be implemented.

**Is a person who just started ART adherent?**

As just noted in Table 1, HRSA HIV care guidelines urge clinicians to follow up in the first few days after a patient starts a new regimen to (1) check for early side effects, (2) make sure the patient understands how to take the regimen, and (3) address early concerns before they evolve into adherence barriers.\(^2\) HRSA says this quick check can be done by phone or in person.

US Department of Health and Human Services (DHHS) antiretroviral guidelines stress that viral load monitoring offers a clear guide to adherence.\(^5\) HIV RNA should

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**Table 1.** Clinician’s to-do checklist for patients starting ART

- Identify potential barriers to adherence before starting.
- Provide mental health and substance abuse resources for the patient if needed.
- Provide resources to obtain prescription drug coverage.
- Use educational aids including pictures, pillboxes, and calendars.
- Plan close follow-up (in phone or in person) in the first few days of ART to identify early side effects, assess understanding of regimen, and address concerns before they become significant barriers.

*Source: US Health Resources and Services Administration.*\(^2\)
be measured within 2 to 4 weeks—and no later than 8 weeks—after starting ART. After that, viral load should be assessed every 4 to 8 weeks until it becomes undetectable. Failure to suppress viremia within 24 weeks of starting a new regimen raises a red flag signaling a strong possibility of poor adherence. (But see page 15 of the interview with Seth Kalichman for discussion of the limits of viral load monitoring in gauging adherence.) When a patient switches to a different regimen, viral load should be measured 4 to 8 weeks after the change. **Table 4** of the DHHS guidelines provides clear advice on when to check viral load throughout a course of treatment.5

The International Association of Providers in AIDS Care (IAPAC) convened a blue-ribbon panel to formulate evidence-based guidelines for promoting entry to care, retention in care, and antiretroviral adherence.6 (These comprehensive guidelines are freely available at the link provided after reference 6.) Both the DHHS and IAPAC endorse patient self-reporting to gauge adherence. Unlike other measures of adherence, DHHS notes, self-reporting “allows for immediate patient-provider discussion to identify reasons for missed doses and to explore corrective strategies.” Although self-reports tend to overestimate adherence, a report of *nonadherence* by the Swiss HIV Cohort Study (SHCS) two-question formula (described in the next section) reliably predicts virologic failure.

IAPAC guidelines recommend routine patient self-reports of adherence, adding that pharmacy refill records can also be checked for clinical monitoring of patients without automatic refills.7 IAPAC does not recommend drug concentrations, pill counts, or electronic bottle caps for clinical monitoring.

**Will a person adhering to ongoing ART stay on track?**

DHHS antiretroviral guidelines emphasize the value of routine viral load monitoring as an ongoing adherence check. “Viral load suppression is one of the most reliable indicators of adherence,” DHHS experts write, “and can be used as positive reinforcement to encourage continuous adherence.” A detectable viral load “during chronic care is most likely the result of non-adherence.” During the first 2 years of ART, the DHHS recommends viral load monitoring every 3 or 4 months. After that the interval can stretch to 6 months in people with consistent virologic suppression.

Current guidelines endorse asking antiretroviral-treated patients about adherence at every office visit. Advice varies on exactly how to do that. The DHHS recommends “a simple, nonjudgmental, routine, and structured format that normalizes less-than-perfect adherence and minimizes socially desirable or ‘white coat adherence’ responses.” Guidelines typically suggest avoiding open-ended questions like “Are you taking your medicines?” Rather they recommend asking how many doses a person has missed in a fixed period of time.

US researchers tested and validated the utility of three simple adherence-recall questions in gauging adherence in almost 7000 people with HIV (see **Table 1** on page 16). Internal reliability of the three questions proved excellent (Cronbach’s alpha 0.89), and HIV-positive people from “diverse sociodemographic and educational backgrounds” consistently understood the questions.
Swiss HIV Cohort Study (SHCS) investigators narrowed the adherence interview to two questions asked to 2664 adults first seen before March 2007 and with a viral load at or below 50 copies/mL for at least 3 months *(Table 2).* They aimed to test the accuracy of answers to these questions in predicting viral rebound (above 500 copies/mL):

A Cox proportional hazards model controlling for a long list of confounding variables determined that time-updated self-report of two or more missed doses in the last 4 weeks (compared with no missed doses) independently predicted viral rebound:

- Two missed doses (versus none): adjusted hazard ratio (aHR) 2.17, 95% confidence interval (CI) 1.46 to 3.25
- More than two missed doses (versus none): aHR 3.66, 95% CI 2.50 to 5.34

Notably, further analysis determined that missing just one dose of a once-daily regimen nearly tripled the rebound risk (aHR 2.82, 95% CI 1.32 to 6.01), while missing one dose of a twice-daily regimen did not affect rebound risk (aHR 0.91, 95% CI 0.60 to 1.36).

The SHCS team advises that “self-report provides the most practical approach” to adherence monitoring and “our instrument, with only two questions, provides a sensitive indicator of future virological failure.” *(EACS)* guidelines endorse asking patients these two questions every 3 to 6 months. In addition, the EACS recommends asking patients whether they expect to maintain good adherence by rating their resolve on a 0 to 10 scale in answering one question:

- In the next 3 to 6 months, how confident are you that you can take your medicines?

Researchers working with the national Swedish HIV Cohort limited the patient-provider adherence quiz to a single question:*9

- How many doses have you missed in the past 7 days?

The study involved 2846 adults seen from 2012 through 2014 and representing 44% of all active patients in the national HIV cohort. The proportion of participants with a viral load below 50 copies/mL rose from 81% to 88% over the study period *(P = 0.001).* A simple comparative analysis determined that 94% of people who missed no doses in the past week had a sub-50-copy viral load, compared with 86% who missed 1 to 2 doses and 69% who missed 3 or more doses *(P < 0.001).*

HRSA HIV care guidelines suggest additional questions that may yield more information on why people forget to take their antiretrovirals:

1. How do you remember to take your medications?
2. When are you most likely to miss doses?
3. Do you have any adverse effects from your HIV medications? If so, what are they?
4. What’s most difficult about taking your medications?

*continued...*


Which simple adherence interventions work best for people with HIV?

By Mark Mascolini

Abstract: Industrious behavioral and clinical researchers have devised and tested a daunting array of strategies to improve antiretroviral adherence. Busy clinicians cannot hope to wade through the literature assessing these interventions to find simple strategies that work for their patients, but expert teams have narrowed the field by dint of careful collaborative analysis. Routine viral load monitoring and questions designed to elicit accurate self-reports rank as the most basic adherence-gauging tools—though viral load testing has its limits. Starting or switching to convenient and safer contemporary regimens has become a standard of adherence-promoting care. Diagnosing and treating depression and guiding substance users into drug treatment programs have proved their value in bolstering adherence. The CDC offers a list of carefully scrutinized evidence-based interventions that boost antiretroviral adherence, including brief and ongoing provider-patient exchanges and an interactive computer program. Pretreatment pill-taking practice and text-message reminders could have an adherence-enhancing role for some patients.

Prodigious amounts of research time and money have gone toward finding strategies that improve antiretroviral adherence. PubMed lists 644 articles reporting clinical trials involving antiretroviral adherence, and 472 of these articles get indexed as randomized controlled trials. Even limiting the randomized trials to those published in the last 10 years still leaves 354.

This RITA review makes no attempt to distill the findings of these adherence intervention trials because other, worthier analysts have already done much to pinpoint simple strategies that work. The International Association of Providers in AIDS Care (IAPAC) empaneled 20 experts to sift the data and propose recommendations not only for antiretroviral adherence, but also for entry into care and retention in care. The Centers for Disease Control and Prevention (CDC) reviews adherence strategy trials, selects those strategies that meet their standards of effectiveness, and organizes the findings into an easy-to-use online source. Researchers versed in the intricacies of meta-analysis pour over published findings and pool data to give readers an overall view of what works and what doesn’t. And certain other publications demand attention because they fill evidentiary crannies left by the three just-noted sources.

The basics: viral load monitoring and self-report

US antiretroviral guidelines from the Department of Health and Human Services (DHHS) recommend routine viral load monitoring as a reliable way to see whether a regimen is working and thus to confirm good adherence or detect a pill-taking lapse. “Viral load suppression is one of the most reliable indicators of adherence,” DHHS experts note, “and can be used as positive reinforcement to encourage continuous

continued...
adherence.” But in the interview starting on page 13, adherence expert Seth Kalichman cautions against monitoring viral load as the sole adherence gauge. By the time viral load starts to rebound, he explains, resistant HIV could be emerging and it’s too late to correct the poor adherence to that regimen.

DHHS advice to make viral load monitoring part of the adherence plan rests on a meta-analysis assessing viral load testing as a tool to reinforce adherence. Researchers identified six retrospective and two prospective observational studies that used viral load monitoring as a means to spot patients who need adherence support. Five studies analyzed how an adherence intervention cued by viral load monitoring affected viremic resuppression, defined as achieving a viral load below a certain threshold after an elevated viral load despite antiretroviral therapy (ART). In those five studies random-effects meta-analysis determined a pooled resuppression rate of 70.5% with viral load monitoring (range 54.2% to 89.1%). The other three studies all reported declining viral load with HIV RNA monitoring.

Both the DHHS and IAPAC encourage clinicians to question patients routinely about antiretroviral adherence. Even though both groups acknowledge that self-report may overestimate adherence, a simple two-question adherence review devised by the Swiss HIV Cohort Study accurately predicted viral rebound in multivariate analysis (see page 39).

The two questions are:

1. How often did you miss a dose of your medication in the last 4 weeks? (Daily, more than once a week, once a week, once every two weeks, once a month, never)

2. Did you miss more than one dose in a row? (Yes, no)

**Use simpler regimens to hike adherence**

Clinicians are well aware of the two primary antiretroviral treatment strategies IAPAC endorses for improving adherence, once-daily dosing and fixed-dose combinations (Table 1). The first article in this issue of RITA cites abundant research linking steady improvements in antiretroviral adherence to the arrival of once-daily dosing and single-tablet regimens as standards of care.

A 2014 meta-analysis of 19 randomized controlled trials comparing once- with twice-daily regimens confirmed significantly greater average adherence with once-a-day
Table 1. IAPAC panel—recommended interventions to improve ART adherence\(^1\)

**ART strategies**
- Once-daily regimens for patients beginning ART
- For patients taking complex or poorly tolerated regimens, switch to once-daily regimen
- Fixed-dose combinations to decrease pill burden

**Adherence tools for patients**
- Try reminder devices and communication technologies with an interactive component
- Consider education and counseling using specific adherence-related tools

**Education and counseling interventions**
- Individual one-on-one ART education
- One-on-one adherence support with one or more adherence counseling approaches
- Group education and group counseling recommended, but need more data on format
- Multidisciplinary education and counseling interventions
- Consider peer support

**Health system and service delivery interventions**
- Nurse or community counselor adherence care recommended in underresourced settings
- Case management and resources to address food insecurity, housing, and transportation
- Consider integrating medication management services into pharmacy systems
- Directly administered ART not recommended for routine clinical care settings

*Source: IAPAC panel.\(^1\)*
Table 2. IAPAC panel—recommended adherence strategies for special populations

- **Pregnant women**
  - Targeted PMTCT treatment (including HIV testing and serostatus awareness) in high HIV prevalence settings
  - Labor ward-based PMTCT adherence services for women not on ART before labor

- **Substance use disorders**
  - Buprenorphine or methadone for opioid-dependent patients
  - DAART for individuals with substance use disorders
  - Integration of DAART into methadone maintenance treatment

- **Mental health**
  - Screening, management, and treatment for depression and other mental illnesses

- **Incarceration**
  - DAART during incarceration and possibly after release

- **Homeless and marginally housed individuals**
  - Case management to mitigate multiple adherence barriers
  - Pillbox organizers for homeless persons

- **Children and adolescents**
  - Intensive youth-focused case management to improve entry into and retention in care
  - Pediatric- and adolescent-focused therapeutic support with problem-solving approaches addressing psychosocial context
  - Pill-swallowing training particularly for younger patients
  - Consider DAART for pediatric and adolescent patients

*Source: IAPAC panel.*  

DAART, directly observed antiretroviral therapy; PMTCT, prevention of mother-to-child transmission.
dosing (weighted mean difference 2.55%, 95% confidence interval [CI] 1.23 to 3.87, \( P = 0.0002 \)). Adherence waned over time in the 6312 study participants, but less so with once-daily dosing. Another 2014 meta-analysis involving 27,230 adults and adolescents in 21 studies confirmed better adherence in people using fixed-dose combinations (relative risk [RR] 1.10, 95% CI 0.98 to 1.22 in randomized trials; RR 1.17, 95% CI 1.07 to 1.28 in observational cohorts). Several other studies summarized in the first article in this issue lend weight to these meta-analyses.

**Treat depression to improve adherence**

In its advice for special populations, the IAPAC panel underlines the importance of screening for, managing, and treating depression (Table 2). The preceding article in this issue reviews three meta-analyses that confirm an association between depression and poor adherence. Depression poses an especially tough adherence barrier for young people in the United States and worldwide.

A recent meta-analysis determined that treating depression or psychological distress in people with HIV nearly doubles the odds of antiretroviral adherence (standardized odds ratio [OR] 1.83, 95% CI 1.27 to 2.55). Other large studies add to the evidence that treating depression improves antiretroviral adherence. Depression experts calculate that nearly half of all major depressive disorder cases go unrecognized in HIV-positive US residents, that only 18% get treated, only 7% get treated adequately, and only 5% of patients control their depression through treatment.

**Use drug abuse programs to bolster adherence**

IAPAC adherence guidelines urge clinicians to address opioid dependence with opioid substitution therapy and possibly with directly observed ART (Table 2). Recent studies demonstrate that drug abuse treatment improves antiretroviral adherence in men and women with HIV. Meta-analysis of 32 studies in North America, Europe, and Asia used random-effects modeling to determine that opioid-substitution therapy (compared with none) more than doubled the odds of adherence (OR, 2.14, 95% CI 1.41 to 3.26) and boosted odds of viral suppression 45% (OR 1.45, 95% CI 1.21 to 1.73). Opioid substitution also independently inflated odds of starting ART (OR 1.69, 95% CI 1.32 to 2.15) while cutting chances of dropping out of care (OR 0.77, 95% CI 0.63 to 0.95).

In British Columbia, where antiretroviral therapy is free, researchers estimated the impact of opioid substitution therapy on medication-refill adherence in 1852 drug users, 34% of them women. Similar to the meta-analysis, a baseline covariate-adjusted analysis determined that opioid substitution doubled the odds of adherence (aOR 1.96, 95% CI 1.72 to 2.24). In a marginal structural model, the impact of opioid substitution was smaller though still significant (aOR 1.68, 95% CI 1.48 to 1.92). Prospective analysis of data from the US Women’s Interagency HIV Study (WIHS) indicated that participating in any drug abuse treatment program inflated odds of 95% or better adherence (aOR 1.39, 95% CI 1.01 to 1.92). Results were similar whether the program relied on opioid substitution or not.

**CDC-reviewed evidence-based adherence interventions**

Research soundly supports adherence strategies discussed so far—monitoring viral load, simplifying regimens, and managing depression and drug dependence. And all those straightforward plans invoke a basic understanding of adherence barriers shared by all HIV providers. But what

*continued...*
about the dozens of behavioral interventions designed by adherence mavens to encourage adherence in habitually wayward patients? Clinicians don’t have the time even to scan the vast literature on these interventions, much less to pinpoint a few effective strategies that stand a fair chance of success in practice.

But the CDC’s HIV/AIDS Prevention Research Synthesis (PRS) project does have the time for this task and in fact routinely analyzes and evaluates newly identified evidence-based interventions that improve antiretroviral adherence or viral suppression. The PRS team regularly updates lists on interventions for medication adherence; linkage to, retention in, and reengagement in care; and HIV risk reduction. The adherence list includes 12 strategies outlined and linked to resources in Tables 3A, 3B, and 3C. For convenience in reviewing these strategies, RITA has numbered the interventions 1 through 12. These numbers do not suggest ranking; they merely follow the order in which the CDC lists them. The CDC is adding a 13th intervention described in the interview with Seth Kalichman.

All 12 adherence interventions receive a “good evidence” rating, a step below the highest “best evidence” rating. Good evidence interventions “have shown significant effects in reducing HIV viral load or improving medication adherence behaviors” but they “do not meet the same level of rigor as the best-evidence interventions.” One intervention (11. SMART Couples) focuses on HIV-discordant straight or gay couples; all the other interventions focus on individual patients in one-on-one and/or group settings. One intervention (3. Directly Administered Antiretroviral Therapy, DAART) is designed for drug users in opioid substitution programs, not for routine clinic use. For six interventions (2, 4, 5, 9, 10, 11) program materials can be accessed online; for the other six (1, 3, 6, 7, 8, 12), clinicians must contact researchers or administrators for program materials. (Availability status may change; check links in Tables 3A, 3B, and 3C.)

Individual interventions last from 5 weeks (6, 11) to 12 months. One intervention (9. Partnership for Health) takes 3 to 5 minutes of each clinic visit over 10 to 11 months. Of the 5-week and each-clinic-visit interventions, two (9 and 11) have program materials online. SMART Couples (11) addresses both adherence and safer sex in HIV-discordant gay or straight couples at four 45- to 60-minute sessions over the course of 5 weeks. A trained nurse practitioner conducts the sessions. Partnership for Health (9) involves a 3- to 5-minute provider-patient interaction at each clinic visit for 10 to 11 months. This intervention may be the most convenient and direct strategy clinicians can adopt for individual patients with adherence challenges, but it has a notable limitation:

→ Brief provider-patient interaction at each visit.

Links in Table 3C detail the rationale and procedures for the Partnership in Health adherence strategy (9). Briefly, the intervention relies on office posters, patient handouts, and a 3- to 5-minute exchange between provider and patient at each office visit “to establish and solidify the partnership, present adherence messages, and discuss pill scheduling and adherence goals” (9). (All these materials are online at the link provided in Table 3C). The US study involved 288 adults (88% continued from page 45
male, 40% white, 39% Hispanic, 15% black) randomized to the intervention or to safer-sex counseling. In the primary analysis, a significantly higher proportion in the intervention group had self-reported adherence at or above 95% at the end of follow-up (85.9% versus 69.8%, \( P < 0.01 \)). But in subgroup analysis the difference was significant only among people who had at least 95% adherence at baseline (91.1% versus 75.2%, \( P < 0.01 \)), not among those with worse baseline adherence (61.5% versus 56.1%, \( P = 0.63 \)). Logistic regression analysis determined that the intervention more than doubled odds of at least 95% adherence even after adjustment for covariates.

In other words, Partnership for Health helped people with good baseline adherence maintain that good adherence through 11 to 18 months of follow-up but did not help significantly more people with worse baseline adherence improve their pill taking. The researchers suggest that “nonadherent patients may need referral for more in-depth counseling or interventions that provide more monitoring, check-ins, and strategies for overcoming barriers to adherence.” Notably, this study took place in 1999–2000, when antiretroviral regimens were more toxic and less convenient than today. With the high initial adherence expected in patients taking today’s regimens, Partnership for Health may be a simple way to maintain that good adherence over the long term. But it may not help people with tough adherence challenges.

**Interactive computer program in clinic.**

Another easy-to-implement intervention, CARE (2, Table 3A) involves an interactive computer program that patients can access in a clinic or AIDS service organization (ASO). During every clinic or ASO visit, people use a tablet computer to detail their current patterns of adherence, sex behavior, substance use, and mental health. The computer program then gives tailored feedback and loads relevant videos. After participants view the videos, they develop plans for medication adherence and safer sex. A personalized printout summarizes this feedback. In a trial that randomized 239 adults (89% men, 55% white) to CARE or standard counseling, those using CARE had significantly greater medication adherence at 3, 6, and 9 months. Viral load fell in the intervention arm and rose in the control arm (mean -0.17 log10 versus +0.13 log10, \( P = 0.053 \)). Clinicians who want to learn more about integrating CARE into their practice can click on the CARE intervention program link on Table 3A and submit a request.

**Try texting adherence support.**

On the CDC list of evidence-based adherence interventions, the newest is TXTXT, a text messaging protocol to improve adherence in HIV-positive adolescents and young adults (12, Table 3C). TXTXT relies on daily text reminders delivered by cell phone
### Table 3A. CDC Antiretroviral Adherence-Based Behavioral Interventions (links and references below)

<table>
<thead>
<tr>
<th>Intervention; study years</th>
<th>Type of intervention</th>
<th>Duration; setting; deliverer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adherence Through Home Education and Nursing Assessment (ATHENA); 1999-2002</td>
<td>Individual-level intervention</td>
<td>24 visits over 12 months; patient residence or community setting; nurse and community/peer worker pair</td>
</tr>
<tr>
<td>2. CARE; 2006-2008*</td>
<td>Individual-level, interactive, computer-based counseling</td>
<td>4 sessions in 3-month intervals over 9 months; HIV clinic and AIDS service organization; computer program</td>
</tr>
<tr>
<td>3. Directly Administered Antiretroviral Therapy (DAART) for Drug Users; 2001-2006</td>
<td>Individual-level directly observed therapy</td>
<td>Every morning of methadone clinic visit over at least 1 year; methadone clinic; nurse or medical assistant</td>
</tr>
<tr>
<td>4. Healthy Living Project (HLP); 2000-2004*</td>
<td>One-on-one intervention addressing physical, mental, and sexual health</td>
<td>3 modules of 5 sessions each over 12 months; clinic or community-based organization; gender-matched facilitators with social work experience</td>
</tr>
</tbody>
</table>

*Program materials available online. See links below.

**LINKS AND REFERENCES:**

**ATHENA**
CDC list link: [https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-athena_ma_good.pdf](https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-athena_ma_good.pdf)
[http://journals.lww.com/jaids/Fulltext/2006/07000/Home_Visits_to_Improve_Adherence_to_Highly_Active.8.aspx](http://journals.lww.com/jaids/Fulltext/2006/07000/Home_Visits_to_Improve_Adherence_to_Highly_Active.8.aspx)
For program materials, email contact: karina.danvers@yale.edu

**CARE**
CDC list link: [https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-care_ma_good.pdf](https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-care_ma_good.pdf)
[http://journals.lww.com/jaids/Fulltext/2014/04150/Computerized_Counseling_Reduces_HIV_1_Viral_Load.15.aspx](http://journals.lww.com/jaids/Fulltext/2014/04150/Computerized_Counseling_Reduces_HIV_1_Viral_Load.15.aspx)
Intervention program at: [http://care.ronline.com/try-the-care-solution/](http://care.ronline.com/try-the-care-solution/) • Contact: akurth@nyu.edu

**DAART for Drug Users**
CDC list link: [https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-daart_methadoneclinic_ma_good.pdf](https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-daart_methadoneclinic_ma_good.pdf)
For program materials, email frederick.altice@yale.edu • Contact: glucas@jhmi.edu

**HLP**
CDC list link: [https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-hlp_ma_good.pdf](https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-hlp_ma_good.pdf)
Intervention program at: [http://caps.ucsf.edu/resources/intervention-curricula/](http://caps.ucsf.edu/resources/intervention-curricula/) • Contact: mallory.johnson@ucsf.edu

Source: Centers for Disease Control and Prevention (CDC).
[https://www.cdc.gov/hiv/research/interventionresearch/compendium/ma/complete.html](https://www.cdc.gov/hiv/research/interventionresearch/compendium/ma/complete.html)
### Table 3B. CDC Antiretroviral Adherence-Based Behavioral Interventions (links and references below)

<table>
<thead>
<tr>
<th>Intervention/ study years</th>
<th>Type of intervention</th>
<th>Duration; setting; deliverer</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Helping Enhance Adherence to antiRetroviral Therapy (Project HEART); 1999-2002*</td>
<td>One-on-one social-support and problem-solving intervention</td>
<td>5 sessions, 2 before ART begins, 3 during ART, plus 5 support phone calls; HIV clinic; nurse interventionist, group discussion facilitator, support partner</td>
</tr>
<tr>
<td>6. In the Mix; 2005-2009</td>
<td>Individual or group intervention targeting adherence and sexual transmission</td>
<td>7 sessions over 5 weeks; AIDS service organization; trained male/female facilitator pair</td>
</tr>
<tr>
<td>7. Management Problem Solving (MAPS); 2005-2010</td>
<td>Individual-level 5-step problem-solving intervention in person and via phone</td>
<td>Four in-person sessions and 12 weekly phone calls delivered over 9 months; HIV clinic; trained interventionist</td>
</tr>
<tr>
<td>8. Pager Messaging; 2003-2007</td>
<td>Individual-level pager intervention with or without peer support</td>
<td>Daily customized pager messages over 3 months; anywhere with pager access; two-way pager</td>
</tr>
</tbody>
</table>

*Program materials available online. See links below.

**LINKS AND REFERENCES:**

**Project HEART**
- CDC list link: [https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-projectheart_ma_good.pdf](https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-projectheart_ma_good.pdf)
- Intervention program at: [https://effectiveinterventions.cdc.gov/en/HighImpactPrevention/BiomedicalInterventions/MedicationAdherence/WhatsIsHeart.aspx](https://effectiveinterventions.cdc.gov/en/HighImpactPrevention/BiomedicalInterventions/MedicationAdherence/WhatsIsHeart.aspx)
- Contact: lkoenig@cdc.gov

**In the Mix**
- CDC list link: [https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-inthemix_ma_good.pdf](https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-inthemix_ma_good.pdf)
- [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3036694/pdf/531.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3036694/pdf/531.pdf)
- For program materials, email: seth.k@uconn.edu

**MAPS**
- CDC list link: [https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-maps_ma_good.pdf](https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-maps_ma_good.pdf)
- [http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1566609](http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1566609)
- For program materials, email: grossr@mail.med.upenn.edu

**Pager Messaging**
- CDC list link: [https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-pagermessaging_ma_good.pdf](https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-pagermessaging_ma_good.pdf)
- For program materials, email: jsimoni@uw.edu

Source: Centers for Disease Control and Prevention (CDC).
[https://www.cdc.gov/hiv/research/interventionresearch/compendium/ma/complete.html](https://www.cdc.gov/hiv/research/interventionresearch/compendium/ma/complete.html)
Table 3C. CDC Antiretroviral Adherence-Based Behavioral Interventions (links and references below)

<table>
<thead>
<tr>
<th>Intervention; study years</th>
<th>Type of intervention</th>
<th>Duration; setting; deliverer</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Partnership for Health; 1999-2000*</td>
<td>Brief provider-patient intervention promoting healthful behavior</td>
<td>3- to 5-minute session at each clinic visit for 10 to 11 months; HIV clinic; primary care provider</td>
</tr>
<tr>
<td>10. Peer Support; 2003-2007*</td>
<td>Peer support with or without pager messaging</td>
<td>6 twice-monthly group meetings and weekly phone calls for 3 months; HIV clinic; peer and research staff</td>
</tr>
<tr>
<td>11. Sharing Medical Adherence Responsibilities Together (SMART Couples); 2000-2004*</td>
<td>Couple-level intervention addressing adherence and safer sex</td>
<td>Four 45- to 60-minute sessions over 5 weeks; HIV clinic; nurse practitioner</td>
</tr>
<tr>
<td>12. Text Messaging Intervention to Improve Antiretroviral Adherence among HIV-Positive Youth (TXTXT); 2010-2014</td>
<td>Individual-level two-way text messaging aimed at youth</td>
<td>Daily text reminders over 6 months; anywhere with cell access; messages delivered by Remedy Health Media</td>
</tr>
</tbody>
</table>

*Program materials available online. See links below.

LINKS AND REFERENCES:

**Partnership for Health**


Intervention program at: [https://effectiveinterventions.cdc.gov/en/HighImpactPrevention/BiomedicalInterventions/MedicationAdherence/PartnershipforHealthforMA.aspx](https://effectiveinterventions.cdc.gov/en/HighImpactPrevention/BiomedicalInterventions/MedicationAdherence/PartnershipforHealthforMA.aspx) • Contact: milam@usc.edu

**Peer Support**

CDC list link: [https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-peersupport_ma_good.pdf](https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-peersupport_ma_good.pdf)


Intervention program at: [https://effectiveinterventions.cdc.gov/en/HighImpactPrevention/BiomedicalInterventions/MedicationAdherence/WhatsPeerSupport.aspx](https://effectiveinterventions.cdc.gov/en/HighImpactPrevention/BiomedicalInterventions/MedicationAdherence/WhatsPeerSupport.aspx) • Contact: jsimoni@uw.edu

**SMART Couples**

CDC list link: [https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-smartcouples_ma_good.pdf](https://www.cdc.gov/hiv/pdf/research/interventionresearch/compendium/ma/cdc-hiv-smartcouples_ma_good.pdf)


Intervention program at: [https://effectiveinterventions.cdc.gov/en/HighImpactPrevention/BiomedicalInterventions/MedicationAdherence/WhatsSMARTCouples.aspx](https://effectiveinterventions.cdc.gov/en/HighImpactPrevention/BiomedicalInterventions/MedicationAdherence/WhatsSMARTCouples.aspx) • Contact: rhr1@columbia.edu

**TXTXT**


Source: Centers for Disease Control and Prevention (CDC).

[https://www.cdc.gov/hiv/research/interventionresearch/compendium/ma/complete.html](https://www.cdc.gov/hiv/research/interventionresearch/compendium/ma/complete.html)
over 6 months. This study randomized 105 poorly adherent people 16 to 29 years old (74% black) to two-way personalized daily text messaging to support adherence or to standard care. After 6 months of texting, chances of self-reported 90% or greater adherence were twice higher in the intervention group (OR 2.12, 95% CI 1.01 to 4.45, \( P < 0.05 \)). The impact of texting remained significant at month 12, a half-year after texting stopped.

Three recent meta-analyses confirm that texting can improve adherence. Meta-analysis of 85 trials involving 16,271 people determined that text messaging improved adherence in the overall analysis (OR 1.48, 95% CI 1.00 to 2.16) and in a subanalysis of 21 trials in low- and middle-income countries (OR 1.49, 95% CI 1.04 to 2.09). The other meta-analyses involved 8 studies (4 in North America, 3 in Africa, 1 in South America) and 3 studies in Cameroon and Kenya. Odds of better adherence with text messaging than standard care were similar in the 8-study meta-analysis (OR 1.39, 95% CI 1.18 to 1.64) and the 3-study meta-analysis (OR 1.46, 95% CI 1.13 to 1.88, \( P = 0.004 \)) and about the same as in the 85-study analysis. The two smaller meta-analyses agreed that text messaging worked better if interactive and if delivered less often than daily (perhaps because of habituation or fatigue with daily or more frequent texting). The 8-study survey also found better results with personalized message content and text timing to match the dosing schedule.

Texting to enhance adherence has the advantage of fitting the lifestyle of growing numbers of people of all incomes worldwide, especially adherence-challenged younger people. It can be personalized, interactive, timed precisely to dosing schedules, and continued for extended periods. Disadvantages include the time and expense involved in setting up and maintaining a texting schedule with individual patients, especially if messages are personalized, two-way, and timed to dosing.

**Consider pre-ART pill-taking practice.**

European AIDS Clinical Society (EACS) guidelines suggest some patients planning to start antiretroviral therapy may benefit from skills training, including pill-taking practice. Such practice with dummy pills and ART-like dosing instructions has seen use in evaluating patient readiness to start ART, but a US pilot trial appears to be the first to assess the impact of pre-ART pill-taking training—plus on-ART counseling—on adherence and virologic response.

Researchers randomized 60 adults starting or restarting ART to the pill-taking practice arm or to usual care. People in the intervention arm completed up to four 1-week placebo-practice trials plus counseling until they achieved electronically measured adherence of at least 85%. The intervention also included (1) counseling sessions 2 and 4 weeks after ART began to help patients meet early adherence challenges, and (2) two training modules at treatment weeks 8 and 16 to help patients maintain optimal adherence.

At week 24 optimal dose timing (at least 85% of doses taken on time) was substantially better in the intervention arm than the usual-care arm (50.0% versus 16.7%). Optimal dose taking (85% or more doses taken) was marginally better in the intervention group (54.2% versus 43.3%), while the impact of the intervention on undetectable viral load was moderate (62.5% versus 43.3%).

continued...
Some of the same investigators are now testing pill-taking training in the larger Supporting Treatment Adherence Readiness through Training (START) trial (ClinicalTrials.gov identifier NCT02329782). START is randomizing 240 people to a pill-taking practice intervention plus counseling or to usual care (as in the pilot trial) and will assess optimal dose-taking and virologic response at treatment month 6 and 24. The investigators aim to complete the trial in November 2019.

In an interview in this issue of RITA, adherence maven Seth Kalichman notes underuse of perhaps the simplest adherence-booster—the pill box organizer. These day-by-day bins not only tell people when a dose is due, they also clear up any doubt about whether a dose has been taken. Kalichman urges clinicians to give patients pill organizers and to instruct them in their use.

References

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