ABSTRACT

The available follow-up measurements of the efficacy of antiretroviral therapy (ART), tell us a great deal about the potency of various treatment regimens. Of particular importance is that the regimen be salvageable, i.e., the necessary drugs are available for sequencing, to preserve further options. Of primary importance is whether the patient accepts and adheres to the therapy, since virologic success has been directly correlated to adherence. However, potency should not be compromised in the quest for simplified therapy.

Several factors have been related to loss of adherence: younger age and unstable housing, increased alcohol consumption, and adverse events related to therapy (especially lipodystrophy syndrome and worsening of depression between month 4 and month 20).

With regard to factors that might have the strongest influence on compliance and to what degree, AIDS patients and physicians have indicated that their perceptions differ. In a national survey of 1599 patients and 138 physicians, participants gave varying responses when asked about number of pills required daily, number of daily intakes, side effects, and the need for lifelong treatment. The number of pills, specifically, has been shown to be an important issue for predicting treatment outcome.

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while Paterson et al and others have demonstrated that high levels of adherence are required for success, the actual degree of adherence required has not been uniformly quantified. In fact, the rate of adherence needed might vary according to the potency and pharmacokinetics of the specific regimens as well as a variety of host factors.

Adherence is a complex phenomenon and a dynamic process. In a cohort of patients (N = 277) who began PI therapy in 1997 APROCO Cohort, France, we provided self-administered questionnaires, which were completed at 4 months, 12 months, and 20 months after the commencement of the regimen, to determine the extent of adherence. At each time point, approximately 60% of patients were totally adherent to their regimen, however, only 30% of patients were adherent at every time point.

While we know that adherence is important, it is also important for physicians to know what factors affect adherence. In patients in the APROCO cohort who were fully adherent 4 months after starting PI therapy, 30% lost adherence after 20 months of follow-up. Using a multivariate model, we identified several factors related to loss of adherence: younger age and unstable housing were most significant, followed by increased alcohol consumption, adverse events related to therapy (especially, lipodystrophy syndrome and worsening of depression between month 4 and month 20). Physicians should remain proactive in discussing treatment options for alterable events, e.g., depression, with patients.

With regard to which factors might have the strongest influence on compliance and to what degree, AIDS patients and physicians have indicated that their perceptions differ. In a national survey of 1599 patients and 138 physicians, participants gave varying responses when asked about number of pills required daily, number of daily intakes, side effects, and

Figure 1. Meta-Analysis Data Illustrate that Pill Burden Is a Factor in Predicting Treatment Outcome

![Virologic response by pill burden](image)

Figure 2. CNA30017 Study Design


ART = antiretroviral therapy; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ABC = abacavir.

the need for lifelong treatment. The number of pills, specifically, has shown to be an important issue for predicting treatment outcome. A meta-analysis by Bartlett et al showed a clear correlation between the number of pills in different trials and virologic control after 48 weeks of treatment (Figure 1). A daily regimen of 15 to 20 pills was associated with a suboptimal response, compared with a daily regimen of only 5 to 10 pills, which yielded improved results. Two separate, randomized trials using ART-naïve patients compared a regimen of Combivir-abacavir with one of Combivir-indinavir (CNA3005, a double-blind, double-classical study, and CNA3014, an open-label study, respectively). [Please Note: CNA3014 will be discussed in greater detail in the section on Poster Presentations of this publication.] The rate of discontinuation varied widely between the studies, with a higher rate of discontinuation in CNA3005. Although the rate of virologic success with indinavir was similar in both studies, the rate of virologic success was higher with abacavir in the open-label study. The main factors leading to discontinuations in CNA3005 were shown to be side effects, complexity of regimen, constraints of the protocol, and having to take too many pills. Since the combination of Combivir and abacavir is known to be potent, there must be another variable to explain the differences in outcomes, despite similar efficacy in the 2 studies. We believe that the simpler regimen available with abacavir led to better adherence and may therefore hold the key.

A switch study (CNA30017) was conducted on 213 patients taking 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus a PI. Two strategies were designed: in the first, the regimen remained unchanged; in the second, patients were switched from the PI to abacavir (Figure 2). The NRTIs were not modified in either arm. Switching to the abacavir regimen, however, led to a better
outcome compared with continuing the same PI. This was explained by a better adherence rate with abacavir (adherence improved in the PI arm, as well, but not as significantly) (Figure 3). Quality of life and general satisfaction of the patient were also greater in the abacavir arm than in the PI arm (Figure 4).

The first feature of a drug that should be considered in treatment selection, therefore, is the simplicity of the regimen, which leads to a greater likelihood of adherence. However, potency should not be compromised in the quest for simplified therapy. In addition, salvageability should be considered to preserve future therapy options.

Treatment simplification should not modify the goal of therapy but should be part of a global strategy of care that includes decisions on when to start therapy (or when the patient is able to start), individualization of therapy, support for long-term adherence, and daily management of side effects. The ultimate goal in treating patients with a chronic disease, as always, is to preserve their quality of life.

REFERENCES