Efficacy of an Individualized Adherence Support Program With Contingent Reinforcement Among Nonadherent HIV-Positive Patients

Results From a Randomized Trial

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Objective: **To evaluate the efficacy of a program designed to improve adherence to antiretroviral therapy among patients with poor adherence.** ***Methods:*** **A randomized intervention trial was conducted among 90 HIV-positive patients experiencing treatment failure as a result of noncompliance with their medication regimen. Eligible participants were randomly assigned to an adherence case management intervention with monetary reinforcement (CM) or to a standard of care group (SC). The CM participants met regularly with a treatment advocate for individualized adherence support. Efficacy was measured in terms of reductions in viral load and improvements in immune function at weeks 12, 24, and 48.** ***Results:*** **After 48 weeks, 55% (n = 26) of those in the CM achieved at least a 1-$\log_{10}$ drop in viral load as compared to 28% (n = 12) in the SC group ($P = .0089$). Furthermore, the mean CD4 count was 209 cells/mm^3 for the CM group as compared to 150 cells/mm^3 in the SC group ($P = .0333$). Based on logistic regression analysis, being in the CM was an independent predictor of reduction in viral load (odds ratio = 2.49; $P = .0514$).** ***Conclusion:*** **The individualized adherence intervention is feasible and effective in reducing viral load and improving immune function.**

Keywords: ***adherence; compliance; antiretroviral therapy; HIV/AIDS; intervention; contingency management***

Although the advent of highly active antiretroviral therapy (HAART) has dramatically reduced the morbidity and mortality associated with HIV infection,[1,2] clinicians continue to struggle with strategies that maximize the benefits of treatments for patients living with HIV. Evidence suggests that almost-perfect levels of adherence are necessary to maintain viral suppression and achieve treatment success.[3] However, patients face an especially difficult challenge remaining adherent given the considerable number of barriers to adherence. Some of the barriers relate to the medication regimen itself, including dosing schedules and food restrictions, as well as side effects and drug toxicities.[4-6] Other adherence determinants are linked to the patient. Specifically, poor compliance has been shown to be associated with psychosocial factors such as psychological distress, substance abuse, and lack of social or family support.[5,7-10] Finally, patients' knowledge of therapy and lower patient self-efficacy as well as the clinical care setting also play a role in adherence with antiretroviral regimen.[4,11-14] Indeed, it is not surprising that in clinical practice the therapeutic goal of effective viral suppression is only achieved in 40% to 50% of patients.[15-18]

Clearly, strategies to optimize adherence to HAART are needed to help patients overcome obstacles in maintaining consistent medication-taking behavior. Although the efficacy of a number of adherence support programs in which patients receive behavior modification or educational interventions has been tested,[19-24] data are limited. In fact, few studies have used a randomized control design with an intervention strategy that is based on a comprehensive assessment of each subject's adherence needs. In addition, few programs have targeted patients with evidence of repeated poor compliance and have allowed enough time to repeat and reinforce information and skills required to produce a lasting impact on adherence. Finally, few programs have included contingency

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management strategies along with behavior modification programs to provide reinforcers that shape consistent medication-taking behavior.

Given these challenges, we developed an intensive adherence case management program aimed at patients experiencing treatment failure as a result of nonadherence. Furthermore, contingency management strategies were used to encourage and reinforce consistent medication-taking behavior. In this article, we present the results of a randomized control trial designed to evaluate the efficacy of an adherence case management program plus monetary reinforcement as compared to the standard of care model. The adherence program, which was based on an evaluation of each patient's adherence needs, included an education program, individualized planning of regimen, the use of adherence aids and devices, as well as referrals to psychosocial services as necessary. In addition, participants received monetary incentives at visits that corresponded to decreases in HIV viral load. The primary objective of this study was to assess the impact of the case management program on biological correlates of adherence, namely, plasma levels of HIV-1 RNA and CD4 counts.

Methods

Patients and Study Design

To meet the objectives of the study, a prospective, randomized controlled study was conducted among 90 adult HIV-1 infected patients experiencing treatment failure as a result of repeated noncompliance with their medication regimen. The sample size was determined to allow for at least 80% power to detect meaningful differences in terms of viral replication and immune function between the 2 study groups. Participants were recruited from November 2002 to October 2004. Specifically, patients on stable antiretroviral therapy who had HIV-1 RNA levels >5000 copies/mL and CD4 counts <200/mm^3, with no evidence of genotypic drug resistance, were eligible to participate. All study participants were recruited from patients receiving care at AIDS Healthcare Foundation in Los Angeles, California. Written informed consent was obtained from all study participants, and the study was approved by the Western Institutional Review Board.

Eligible patients were randomized to 1 of 2 groups: (1) case management plus contingency management (CM) intervention group, conducted by a trained treatment advocate, or (2) standard of care (SC) group, which consisted of ongoing adherence support activities provided at the clinic. Details of the intervention groups are provided later in this article. The randomization was conducted and retained by an investigator not involved in the selection of patients or the ongoing follow-up and care of patients. The randomization sequence was concealed until interventions were assigned. Furthermore, those assessing the outcome measures were not aware of the participant's group assignment. Both groups were seen for data collection at baseline and at weeks 4, 8, 12, 16, 20, 24, and 48.

Study End Points and Assessment of Variables

The primary outcome measure of this study was the proportion of patients who achieved a 10-fold (1-$\log_{10}$) decrease in HIV-1 RNA levels at weeks 12, 24, and 48 in both study groups. Secondary outcome measures included the percentage of patients achieving plasma HIV-1 RNA levels of <400 copies/mL at weeks 12, 24, and 48 in both study groups and improvements in immune function as measured by mean increase in CD4 counts at weeks 12, 24, and 48.

In addition to virologic and immunologic measurements, patients completed a self-administered survey to assess the following factors:

1. Sociodemographic characteristics: age, gender, race/ethnicity, education, employment status, and education
2. Alcohol and drug use: Patients were explicitly questioned about their drug and alcohol use in the past 30 days prior to the study visit. In terms of alcohol use, patients were asked about any drink containing alcohol and the average daily quantities of each that was consumed, using a Likert scale. In addition, patients were questioned about both injection and noninjection drug use in the past month using a yes-or-no nominal type of measure.
3. Mental health status: Patients were questioned about current diagnosis and specific type of mental health illness and whether medication and/or therapy was prescribed for those diagnosed.
4. Medication adherence issues: A number of factors associated with medication-taking behavior was also assessed, including dosing instructions and medication details, as well as an assessment of perceived self-efficacy, level of support, and reasons for missed medications. Specifically, perceived self-efficacy,[25] or the perceived ability to follow treatment was assessed using a 4-point Likert-type scale ranging from *not sure at all* to *extremely sure*. In addition, patients were asked to rate the overall support they receive from family and friends as well as specific reasons for missed medications.

Case Management Plus Contingency Management Intervention Program

The objective of the case management intervention was to identify barriers, develop solutions to these

barriers, and increase the patients' self-efficacy. Specifically, patients randomized to the case management program met with a trained treatment advocate who conducted a comprehensive review of each patient's adherence needs. The assessment included an evaluation of the patient's medical as well as psychosocial and environmental needs. Adherence barriers identified by the assessment included problems with medication dosing and side effects, as well as insufficient knowledge on the importance of strict adherence to medication regimen. In addition, mental health issues, substance abuse, and communication of the identified barriers with the patient's provider were also assessed. After the initial assessment, an individualized adherence plan was developed based on the adherence barriers identified by the assessment. Depending on the issues identified, components of the intervention may have included, but were not limited to, educational materials and guidance on the importance of adherence, medication boxes, pagers and reminder calls, management of side effects, and referrals to social service organizations to deal with issues of substance abuse and mental health. Follow-up visits were scheduled such that the treatment advocate and patient met every week for the first 3 months, every 2 weeks for the next 3 months, and once a month for the remaining 6 months of the program. During these approximately 30-minute visits, success and progress were evaluated, and the information and skills necessary to produce a lasting impact on adherence were repeated and reinforced.

Finally, participants in the case management program received monetary incentives for improvements in viral load. Previous studies show that monetary incentives or contingency management has been successfully used in retaining substance-abusing clients in treatment and encouraging appropriate behaviors.[26-28] Specifically, contingency management is based on behavioral principles that involve frequent monitoring of a target behavior and provisions for tangible positive reinforcements when the target behavior is achieved. In this study, participants who had monthly follow-up visits that corresponded with at least a 3-fold (0.5-$\log_{10}$) decrease in HIV-1 RNA levels or undetectable levels (<400 copies/mL) were reimbursed $20 for each such visit. Conversely, those randomized to the SC group continued to receive the current adherence support activities available at the HIV clinic. This included counseling and educational sessions on the importance of adherence provided during patients' clinic visits. In addition, based on each patient's adherence issues, support such as medication boxes and pagers may have also been provided.

Statistical Analysis

All data analyses were conducted using an intent-to-treat approach. Consequently, all patients who were randomized into the study were included in the analysis and missing outcome data (HIV-1 RNA levels and/or CD4 counts) were set to the time of drop-out (last observation carried forward). HIV-1 RNA levels were dichotomized in several ways including having a 10-fold decrease (1-$\log_{10}$) from baseline levels and achieving levels <400 copies/mL. In addition, improvements in immune function were analyzed by comparing mean CD4 counts across the 2 study groups. Differences between the study groups were evaluated using χ^2 methods and Fisher exact test for categorical variables and *t* test for continuous variables. In addition, to control for factors associated with adherence and thus virologic response, factors such as gender, race/ethnicity, and current substance abuse were controlled for by using logistic regression analysis. The unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) are presented. All analyses were conducted using SAS software, version 9.1 (SAS Inc, Cary, NC).

Results

A total of 90 HIV-positive patients were enrolled in the study. Baseline characteristics of the study population are shown in Table 1. There were no statistically meaningful differences between the 2 study groups. The majority of participants were male (n = 81; 90%), with Hispanics comprising the single largest racial/ethnic group (n = 35; 39%). In addition, although 79% (n = 71) reported having at least a high school education, only 13% (n = 12) reported being employed. Overall, the median baseline HIV-1 RNA level was 4.74 $\log_{10}$ copies/mL and the mean baseline CD4 count was 115 cells/mm^3.

Regarding drug and alcohol use, no differences were found between the intervention and control groups. Furthermore, although 16% (n = 7) of the control group reported low perceived self-efficacy to follow treatment as compared to 6% (n = 3) of the intervention group, these differences were not statistically significant (P = .1810). Belief in the positive effects of medications as well as satisfaction with overall support also did not differ significantly between the 2 groups.

In terms of study follow-up, 4 participants (4%) discontinued their medication regimen (n = 3 intervention groups, n = 1 control group), 2 participants (2%) moved out of the area (1 in each study group), and 3 (3%) discontinued the study at the request of their primary care provider to participate in an intensive inpatient adherence support program. There

Table 1. Baseline Sociodemographic and Clinical Characteristics of Study Participants*

	Total (n = 90)	*Intervention Group (n = 47)*	*Control Group (n = 43)*	P†
Age, mean ± SD, y	42 ± 7	41 ± 6	43 ± 7	.1602
Gender, n (%)				.3012
Male	81 (90)	44 (94)	37 (86)	
Female‡	9 (10)	3 (6)	6 (14)	
Race/Ethnicity, n (%)				.5054
African American	32 (36)	14 (30)	18 (42)	
Hispanic	35 (39)	21 (45)	14 (33)	
White	21 (23)	11 (23)	10 (23)	
Other§	2 (2)	1 (2)	1 (2)	
Education, n (%)				.3560
<High school graduate	19 (21)	7 (14)	12 (28)	
High school graduate	35 (39)	20 (43)	15 (35)	
Some college/college graduate	36 (40)	20 (43)	16 (37)	
Employed,‖ n (%)	12 (13)	8 (17)	4 (9)	.3595
Active drug use, n (%)	36 (40)	20 (43)	16 (37)	.7630
Heavy alcohol use, n (%)				
>14 drinks per week	7 (8)	4 (8)	3 (7)	.7872
Ability to take medications as directed, n (%)				
Not at all sure	10 (11)	3 (6)	7 (16)	.1810
Belief in positive effects of medications, n (%)				
Not at all sure	14 (16)	8 (17)	6 (14)	.7249
Satisfaction with overall support, n (%)				
Very or somewhat dissatisfied	20 (23)	12 (26)	8 (19)	.5856
Median baseline viral load, $\log_{10}$ copies/mL (IQR)	4.74 (0.73)	4.83 (0.67)	4.69 (0.77)	.3620
Baseline CD4 counts, mean ±SD, cells/mm^3	115 ± 74	116 ± 76	113 ± 73	.8895

*IQR, interquartile range; SD, standard deviation.
†*P*-value based on *t* test for continuous variables, χ^2 test for categorical variables and Fisher exact test as necessary.
‡Includes 1 male-to-female transgender.
§Includes participants identified as Asian and "other."
‖Includes part-time and full-time employment.

were no differences between the study groups when comparing those who did not complete the study.

HIV-1 RNA Levels

Based on intent-to-treat analysis, there were both clinically and statistically meaningful differences in HIV-1 RNA levels between the 2 study arms (Figure 1). Furthermore, these differences remained at weeks 12, 24, and 48. Specifically, after 24 weeks of follow-up, 26% (n = 11) of the SC group achieved at least a 10-fold (1-$\log_{10}$) decrease in viral load as compared to 45% (n = 21) of the CM group (*P* = .0601). Similar changes were seen at week 48 with 28% (n = 12) of the SC group achieving at least a 1-$\log_{10}$ decrease in viral load as compared to 55% (n = 26) of the CM group (*P* = .0130). However, an examination of those who were able to achieve HIV-1 RNA levels of <400 copies/mL revealed that regardless of study group or follow-up period, fewer than 30% were able to achieve this goal. Furthermore, the differences between the 2 study groups were not statistically significant (data not shown). In fact, at week 48, only 25% (n = 10) of those in the SC group had plasma viremia of <400 copies/mL as compared to 30% (n = 14) of those in the CM group (*P* = .6581). This may partly reflect the fact that "undetectable" HIV-1 RNA levels may not be a realistic or achievable goal among repeatedly non-adherent patients experiencing treatment failure.

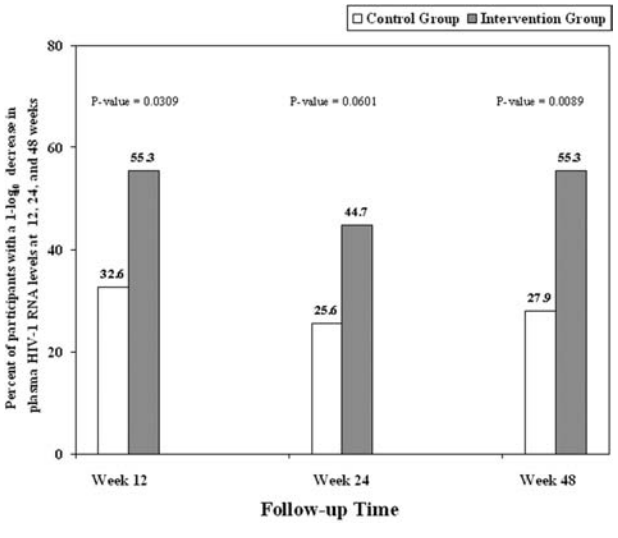

Figure 1 Proportion of participants with 1-log10 reductions in plasma HIV-1 RNA levels at follow-up weeks 12, 24, and 48, by intervention group.

Table 2. Factors Associated With Decrease in Plasma HIV-1 RNA Levels at Weeks 12, 24, and 48*

	Univariate Analysis			*Multivariate Analysis*		
	Week 12			*Week 12*		
Variable	*Unadjusted OR*	*95% CI*	P	*Adjusted OR*	*95% CI*	P
Intervention group	2.96	1.26-6.99	.0132	2.27	0.91-5.69	.0703
Age <45 years	3.60	1.31-9.94	.0133	3.48	1.20-10.07	.0216
Able to take medications†	5.58	1.11-27.97	.0368	4.95	0.93-26.36	.0612
	Week 24			*Week 24*		
Intervention group	3.61	1.50-8.64	.0040	2.84	1.12-7.17	.0422
Age <45 years	3.15	1.17-8.48	.0232	2.98	1.04-8.56	.0275
Able to take medications†	6.19	1.23-31.11	.0268	5.36	1.00-28.74	.0501
	Week 48			*Week 48*		
Intervention group	2.98	1.25-7.09	.0137	2.49	1.00-6.23	.0514
Age <45 years	2.79	1.05-7.39	.0394	2.33	0.82-6.60	.1124
Able to take medications†	3.61	0.87-15.03	.0775	2.21	0.71-12.26	.1706
≥High school education	2.97	1.04-8.48	.0423	2.72	0.60-12.26	.1925

*OR, odds ratio; CI, confidence interval.
†Ability to take medications, based on self-report comparing those who are sure to those who are "not at all sure" about ability to take HIV medications as directed.

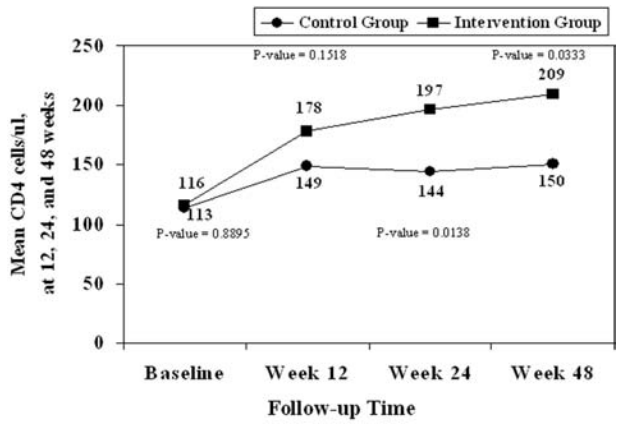

Figure 2 Mean CD4 count at baseline and follow-up weeks 12, 24, and 48, by intervention group.

CD4 Counts

Differences in improvements in immune function were also seen across the 2 study groups. Mean baseline CD4 count was 115 cells/mm^3 and did not differ significantly across the 2 study groups (Table 1). However, after 24 weeks of follow-up, mean CD4 counts increased to 144 cells/mm^3 among the SC group as compared to 197 cells/mm^3 among the CM group (P = .0138) (Figure 2). Furthermore, these improvements were still greater among the intervention group after 48 weeks of follow-up, with mean CD4 counts increasing to 209 cells/mm^3 among the intervention group as compared to 150 cells/mm^3 among the SC group (P = .0333).

Factors Associated With Reductions in HIV-1 RNA Levels

Based on univariate analysis, factors associated with a decrease in HIV-1 RNA levels at weeks 12 and 24 included being in the CM group, age, and perceived self-efficacy to take medications (Table 2). In fact, by week 48, those in the intervention group were nearly 3 times as likely to have reductions in viral load as compared to those in the SC group (OR = 2.98; P = .0137). Interestingly, by week 48, education level was also associated with reductions in plasma virus levels, such that those with at least a high school education were almost 3 times more likely to have a 1-log$_{10}$ decrease in viral load as compared to those with less than a high school education (OR = 2.97; P = .0423). In multivariate analysis, although the intervention case management program, age, and perceived self-efficacy were associated with reductions in plasma HIV-1 RNA levels at week 24, the only independent predictor of reductions in viral load at week 48 was receiving the intervention (OR = 2.49; P = .0514; Table 2).

Discussion

This study examined the effects of a comprehensive, individualized, adherence case management program among patients experiencing treatment failure as a

result of repeated low adherence with their HIV medications. Participants randomized to the intervention, which consisted of individualized medication counseling and skill building, psychosocial support, as well as monetary rewards for reductions in viral load, had clinically and statistically meaningful reductions in HIV-1 RNA levels and improvements in CD4 counts as compared to controls receiving the standard of care. Furthermore, these effects were apparent by 3 months after the initiation of the program and were maintained after completion of the intensive phase of the program at months 6 and 12.

Overall, data on randomized studies designed to evaluate strategies to improve adherence to HIV/AIDS medication regimen are limited.[19-24,29] Furthermore, even fewer studies have focused on patients identified as repeatedly nonadherent or have reported on biological correlates of adherence, namely viral load and immune function.[21-23,29] Tuldra et al evaluated the efficacy of a psychoeducative intervention and found that after 48 weeks, 58% of patients in the experimental group versus 45% of patients in the control group had HIV-1 RNA levels <400 copies/mL.[21] Unlike the study conducted by Tuldra et al, the study conducted by Knobel and colleagues was similar to our study in terms of its inclusion criteria.[29] Although there were improvements in adherence after 24 weeks, there was no significant association between the intervention and achieving undetectable viremia. In this study, we report that after 48 weeks of follow-up among repeatedly nonadherent patients experiencing treatment failure, 55% of participants in the experimental group had at least a 1-$\log_{10}$ drop in HIV-1 RNA levels as compared to 28% of those in the SC group. The differences between the study populations and the reported outcome could explain the various effects of the interventions on the response seen in the different studies. However, a strength of this study was the long-term duration of the intervention and follow-up, which allowed for continued reinforcement of consistent medication-taking behavior and thus demonstrated a sustained effect among some of the most noncompliant patients.

Evidence suggests that interventions designed to enhance medication adherence, including antiretroviral therapy are most likely to be successful if they are comprehensive and address more than one dimension of this complex behavior. In this study, the monetary incentives may have served as a motivational factor as well as positive reinforcement of skill building and adherence success. Although data on contingency management with respect to adherence to antiretroviral medications are limited, incentives have been used in a number of health care settings, including treatment of drug and alcohol dependence as well as tuberculosis treatment.[26-28,30] Furthermore, in one of the few studies to use cash incentives for improvements in adherence to antiretroviral medications, Rigsby and colleagues were able to demonstrate a significant short-term benefit.[20] Although widespread use of such an intervention may not be feasible, it can serve as a strategy among repeatedly noncompliant patients, such as those in this study.

Interestingly, we also observed a number of other factors associated with reductions in viral load, independent of the intervention. Specifically, perceived self-efficacy and reported ability to take medications as directed was significantly associated with a decrease in viral load at 3- and 6-month follow-up. In fact, while controlling for group assignment, those who reported high self-efficacy were more than 5 times more likely to show reductions in viral load as compared to those who reported low self-efficacy. Although self-efficacy has been identified as a predictor of adherence,[31,32] findings from this study suggest that identifying these patients in advance would allow us the opportunity to intensify out interventions among this group to improve adherence and achieve optimal clinical outcomes. Another interesting finding is that although education level was not a significant predictor of reduction in viral load at 12 and 24 weeks of follow-up, at week 48, those with at least a high school education were nearly 3 times more likely to have reductions in viral load. Although the findings on education and medication adherence are mixed,[5,31] the results here suggest that education level may have an influence in terms of sustainability of the impact of the intervention. These findings imply that assessment of education level and more intensive ongoing support for those with lower education levels, particularly those with less than high school education, may be necessary to ensure continued improvements in adherence.

The results of this study should be interpreted in light of its limitations. First, the sample size limited the interpretation of findings to moderate to large effects and did not allow for a more complex exploration of other factors involved in adherence. Second, reductions in viral load, as opposed to undetectable viremia, were used as an outcome measure, as few participants were able to achieve a viral load below 400 copies/mL. However, a 1-$\log_{10}$ decrease in viral load is notable in this patient group, who were included in the study because they demonstrated substantial and persistent difficulty with adherence. Finally, threats to external validity included the interaction between participation and the intervention as well the use of a multicomponent intervention. Given that participation in the study was voluntary, findings

may be applicable to those who volunteer to participate and not to all patients nonadherent to their medication regimen. In addition, although the beneficial impact of the intervention seem clear, the comprehensive and individualized nature of the program make it difficult to identify the specific aspect of the program, which may help explain why the intervention works. In fact, examination of one potential explanation of the intervention effect, namely, treatment changes, revealed that there were no significant differences between groups in terms of the percentage who had a change in medication regimen (SC, 23% vs CM, 17%; $P = .4627$), had a decrease in daily dosing (SC, 9% vs CM, 13%; $P = .6035$), or switched to more potent regimen (SC, 7% vs CM, 4%; $P = .5756$). Nonetheless, medication adherence is a complex behavior, which may not only involve education and skill but also motivation and reinforcement. Therefore, multidimensional interventions, which attempt to address more than one aspect of adherence behavior, are more likely to be successful than those that target a single aspect.

In conclusion, this study demonstrates that the adherence support program appears to be acceptable, feasible, and effective in reducing viral load and improving immune function, particularly among patients who have experienced treatment failure as a result of poor adherence. In addition, this study demonstrates that because of the complexity of the factors behind adherence, it is important that patients are supported with individualized medication management programs. Finally, assessment of certain factors including self-efficacy and education level may help identify patients who require more intensive clinical management.

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