

Update Report #34



Medication Adherence and Patient Outcomes

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Medication Adherence and Patient Outcomes

Background

The association between the sharp decline in mortality during the latter half of the 1990s and the widespread introduction of combination antiretroviral therapies (ART) has been documented for the CHAIN cohort (Update Report #26) and for other HIV+ populations. Two important conclusions are routinely drawn from these findings. First, people taking these medications are not only living longer with the virus, but they are in better health. Consequently, planning for HIV services is increasingly focusing its attention on services such as job training, career counseling and rehabilitation services that assist in returning to productive lives. A second implication is that infected individuals are experiencing fewer acute illnesses, and there should be a corresponding decline in inpatient care and visits to emergency rooms. Neither of these conclusions should be taken at face value. To begin with, debilitating side effects are a common occurrence when taking ART. While individuals taking ART may show improvements on clinical markers of health status (e.g. CD4 counts), they may not necessarily feel better. In addition, as HIV+ individuals live longer they may increasingly be subject to health conditions such as liver, kidney and coronary heart diseases unrelated to their HIV conditions that result in new and emerging needs for intensive medical care.

There is further concern that difficulties adhering to these complex medical regimens may reduce long-term benefits of these medications. Previous CHAIN Update Reports (#20 and #23) have documented that many CHAIN participants do in fact report both difficulties in maintaining pill taking schedules and side effects that interfere with maintaining the high levels of adherence believed to be necessary for the continuing therapeutic efficacy of these medications.

This report extends the previous analysis of the life prolonging benefits of ART to assess the association of ART with improved health related quality of life and reduction in use of acute medical care services in addition to its effect on reducing mortality. We further test the extent to which adherence to ART, as measured in the CHAIN interviews, is associated with further improvements in patient outcomes.

Key Findings

- Although over 80 percent of CHAIN participants report use of combination antiretroviral therapies at either the 5th or 6th round of interviews, only a small fraction of this cohort, approximately 1 in 5, report consistent and adherent use of combination therapies.
- Individuals who report adherent medication use at both the 5th and 6th rounds of interviews report a 100 point rise in the mean CD4 count between the 4th and 6th interviews. This increase is substantially larger than the changes in CD4 count for less

adherent users of combination therapy and for those who have either *stopped* or were *not using* combination therapy at these two rounds of interviews.

- We found no association between adherent use of combination therapies and either improvement in various self-reported measures of health function or reduction in use of inpatient care.
- The lack of an improvement in perceived health status associated with adherent use of combination therapies suggests that while people are doing better on these medications many do not necessarily feel better. The lack of positive experiential response to taking these medications may be a factor that reduces motivation either for long-term maintenance of complex medications or re-engagement in a productive life style.
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Methodology

The Community Health Advisory and Information Network (CHAIN) Study is a longitudinal study of persons living with HIV, conducted as part of the evaluation activities of New York City's Title I Health and Human Services Planning Council. Its purpose is to provide systematic data from the perspective of HIV+ adults about their needs for health and human services, their encounters with the full continuum of HIV services, and their physical, mental, and social well being.

The CHAIN sample design and participant recruitment

At its inception in 1994, the CHAIN Project pursued a recruitment procedure designed to yield a broadly representative sample of people known to be living with HIV in New York City. Study recruitment was conducted collaboratively with 43 randomly selected agencies, stratified to represent roughly equal numbers of medical care and social service sites as well as sites that were and were not recipients of Ryan White Title I grants. A total of 648 individuals recruited from participating agencies completed baseline interviews. The agency-based sample was supplemented with 52 interviews conducted with HIV+ individuals with little or no connection to medical and social services.

Since their original interview in 1994-1995, individuals in the study have been re-interviewed six times, at six to twelve month intervals. In 1998, the HIV Planning Council asked the Columbia research team to recruit additional participants into the CHAIN study. In consultation with MHRA, the NYC Department of Health, and the HIV Planning Council, the researchers returned to the original 43 agencies for assistance in recruiting individuals more newly diagnosed with HIV, since 1994. Twenty-two agencies participated in the refresher effort. A total of 267 refresher respondents (including 14 individuals unconnected to medical care) were added to the CHAIN cohort, resulting in a total sample of 652 participants at the fifth round of interviews. Information on sampling strategy is described in more detail in earlier Update reports. A comprehensive discussion of sampling and recruitment for the original cohort, may be obtained upon request from MHRA (CHAIN Technical Report #1). For further information about the sampling strategy, recruitment, and comparability of the refreshed cohort refer to the

Cohort Comparison Report (Update Report #18) and the Unconnected Revisited (Briefing Paper #1).

Very few individuals have refused to participate in follow-up interviews (fewer than 4% since the 2nd round of interviews); the majority of individuals lost to follow up have been due to death from AIDS-related causes.

For this study our analysis is restricted to the 305 CHAIN participants from the original 1994 cohort who were interviewed through the first six rounds of CHAIN interviews. Patient outcome data were obtained for all six rounds of interviews. As described below, use of combination therapy and adherence to these medical regimens were examined for the 5th and 6th round of interviews. As illustrated in Table 1, the composition of the full complement of CHAIN participants interviewed for round 6 and those forming the sample for this study are generally similar to the composition of living adult AIDS cases in 1998. However, blacks comprise a greater percentage of the CHAIN cohort than are represented by living AIDS cases in 1998, and Hispanic and whites are under represented. More refined analyses of the CHAIN cohort can be found in The Cohort Comparison Report (Update Report #18, May 1999).

Table 1. Comparison of Epidemiological Data with CHAIN Wave 6, and Study Sample (original cohort interviewed at Round 6)

	Surviving AIDS Cases, NYC†	CHAIN: Round 6	Study Sample
	1998	1999	1999
n	40,014	495	305
MALE	29,900	286	191
<i>Non-Hispanic White</i>	28%	21%	23%
<i>Non-Hispanic Black</i>	38%	54%	50%
<i>Hispanic</i>	33%	24%	26%
<i>Other</i>	1%	1%	1%
FEMALE	10,114	209	116
<i>Non-Hispanic White</i>	12%	6%	7%
<i>Non-Hispanic Black</i>	53%	67%	65%
<i>Hispanic</i>	34%	27%	27%
<i>Other</i>	1%	1%	1%

† Source: NYC DOH Office of AIDS Surveillance, "Estimates of Persons Living with AIDS in NYC." NYC data includes 221 adolescents, as compared to CHAIN adults, but those numbers are too few to change the proportions.

Interview schedule

In the two-hour long interview, participants are asked about: (1) their initial encounter with the health care delivery system, (2) their need for services, (3) their access, utilization and satisfaction with health and social services, (4) key sociodemographic characteristics, (5) informal care giving from friends, family and volunteers, and (6) their quality of life with respect to health status, psychological and social functioning. A number of items have been added over the years related to antiretroviral therapies, specific medical care services, viral load levels, adherence, managed care, and other topics of interest to policymakers, planners, providers, and consumers on the Planning Council

Medications and adherence

At each round of interviews, CHAIN participants are asked to list the medications they are currently taking. From this information we are able to determine whether an individual is taking two or more antiretroviral therapies at each round of interviews and specifically whether they constitute a HAART combination. To simplify our analysis and presentation, we concentrate on any combination of antiretroviral medications and ignore the distinction between HAART and non-HAART combinations. We have no data that would allow us to distinguish whether a non-HAART combination represents a clinician's decision about appropriate medication or evidence for non-adherence. Given this uncertainty, we have to be broadly inclusive regarding the possible efficacy of different medications.

Self-reported data on adherence to medications has only been collected since round 5 and the battery of adherence questions has expanded in subsequent rounds. Detailed information about adherence measures employed in this study are found in CHAIN Update reports #20 and #23. Here we point out the major difference in the way adherence was ascertained at the two rounds of interviews. For round 5 the question was worded as follows: "Next are some questions about your experiences in taking protease inhibitors. Over the last six months, which of the following best describes your general experience taking your medication...."

- 01 I take them exactly as prescribed, almost never missing a dose.
- 02 I sometimes skip a dose or forget to take my pills.
- 03 I often skip a dose or forget to take my pills.
- 04 I rarely take my pills as prescribed.

For round 6 the wording of the question was changed to refer to any "HIV medication." The response categories, however remained the same. The consequence of this shift in question wording was to expand the number of people asked this question. At round 5 individuals taking combination therapy without a protease inhibitor were not asked about difficulties in adhering to medications, whereas at round 6 we obtained adherence information for all individuals taking any combination of antiretroviral therapy. Based on prior analysis, we find that a majority of individuals self report the highest level of adherence. Consequently, we have collapsed the remaining three responses into a single non adherent category. Round 6 further specifies adherence based upon reports of missed pills for any reason over last two days.

Table 2 presents the distribution of the study sample with respect to current use of combination therapy and adherence at rounds 5 and 6, and a classification that combines use of medication and adherence at both rounds of interviews. For this study, presentation of findings concentrates on the categorization that combines rounds 5 and 6 status. In particular we wish to compare the trajectory of health outcomes for the individuals who report being adherent at both rounds with the trajectory for other groupings of individuals whose responses suggest less consistent use and adherence to these medications.

Table 2: Current Use of Combination Therapy and Medication Adherence at Rounds 5 and 6 (N=305)

Medication Adherence Categories	Round 5	Round 6	Combined Rounds 5 and 6 Status
No use of combination therapy	29%	25%	18%*
Stopped use between rounds 5 and 6			7%
Use of non PI combination therapy, unknown adherence status	10%		
Non-adherent use of combination Therapy	27%	32%	32%**
Adherent use	34%	43%	22%***
Adherent Use at rounds 5 and 6			21%

Source: CHAIN Interviews, Rounds 5 and 6

Notes:

Shaded cells indicate categories that are not relevant to division of sample at particular rounds.

*For combined round status, no use at both rounds 5 and 6.

**For combined round status, non-adherent use for round 6 only, not contingent on round 5 status.

***For combined round status, adherent use indicates adherent at round 6 only. Round 5 status could be from any category but adherent use.

Outcomes

We examined the impact of combination therapy and adherence to these medications for a large number of outcomes. We have chosen to organize these outcomes following a common schema that distinguishes disease from experiences of discomfort and ultimately disability. Markers of disease progression examined here are indicators of immune system functioning: self-reports of CD4 T-cell counts, and occurrence of opportunistic infection. It is hypothesized that adherent use of combination therapies will greatly reduce viral loads, increase CD4 counts among adherent individuals. Of course even when adherence is successful, drug resistance may develop and therefore reverse prior gains in immune system functioning achieved through ART.

A second cluster of outcomes include measures we refer to as “discomfort” and are often referred to as “health status” or “health functioning”. It is hypothesized that one experiences perceived improvements in quality of life because of the reduced occurrence of opportunistic infections and other acute health conditions that are associated with feelings of ill health and impairments in perceived physical and mental functioning. The experience of succeeding on ART may also engender a more positive mental outlook. Of course, ART is not without its side effects. These may well offset some of the expected improvements in quality of life. The quality of life measures examined here are constructed from a widely used, standardized instrument to measure health functioning, developed for the Medical Outcomes Study (MOS). CHAIN interviews include a 26-item version of the SF-36 specifically developed and validated in HIV+ populations. For this report we include both summary physical and mental well-being scales. These are respectively referred to as the Physical Components Summary (PCS) and Mental Components Summary (MCS) scales. We have also examined the multiple components that form these summary scales. These scales assess general health, physical functioning (mobility), bodily pain, and vitality. Each of these scales are computed following algorithms published by the creators of the MOS quality of life instruments. The PCS and MCS are standardized such that a score of 50.0 is equal to average health functioning for a general population of adults. Scores of 45 or lower are associated with work limitations due to physical health problems. The MOS sub-scales range in values from 0 to 100 with higher values indicating better health.

Our third cluster of outcomes measures disability. These measures relate how experiences of poor physical and mental health impair the ability to participate fully in normal social and economic roles. For this cluster we present employment rates and scales measuring impairment of role performance and social functioning and employment. The latter two scales come from the MOS-HIV instrument.

Use of emergency room and hospitalization form a final outcome cluster. These outcomes may be interpreted as measures of expensive health care services or indirect markers of treatment for acute and life threatening diseases. Table 3 lists brief descriptions for the patient outcomes examined in this report. We compare the mean values of these outcomes for the full 1994 cohort and the sample examined for this study. Generally the health status of the study sample does not differ greatly from individuals who died or were lost to follow-up by round 6. Not surprisingly, what differences emerge indicate that those remaining in the study were in somewhat better health. At baseline they had higher CD4 T-cell counts, were in slightly better physical health and were less likely to have a hospital stay within six months of the interview than those not included in this study. However, there is no reason to suspect that this slight bias has consequences for the way in which use and adherence to combination therapy affects health outcomes within the study sample.

Table 3: Patient Outcomes and Baseline Mean Values for Study Sample and Full 1994 Cohort

Outcome Measure	Baseline Mean/% for Study Sample (N=305)	Baseline Mean/% for Full Cohort (N=700)
<i>Markers of Disease Progression</i>		
CD4 T-Cell Count (Range <50 to 600+)	342*	285
Experience opportunistic infection in last 6 months	53%	55%
One or more inpatient visits in last 6 months	18%*	25%
One or more visits to the emergency room	41%	40%
<i>Perceived Health Status Measures (Discomfort)</i>		
Physical Component Summary Scale (PCS) range: 14-63, national norm for general population=50	44*	42
Mental Component Summary Scale(MCS) range: 10-66, national norm for general population=50	41	41
General Health (How healthy do you feel?)†	59*	54
Physical Functioning (Carry out every day tasks)†	68	66
Mental Health (Mood Disorder)†	59	59
Vitality†	51	50
Bodily Pain†	61	61
<i>Impaired Social Role Performance (Disability)</i>		
Role-Emotional functioning (emotional impairs ability to perform normal roles)†	39	36
Role-physical functioning (physical health impairs ability to perform normal roles)†	39	38
Social Functioning (ability to interact with family and friends)†	70	69
Employment	11%	9%

†Scale values range from 0 to 100 with higher values indicating better health status.* Difference in means between CHAIN cohort continuing and not continuing through interview 6 is statistically significant at the p<.05 level

Method of analysis

The preferred statistical procedures for measuring the likely outcomes of medical interventions for “natural population” studies such as the CHAIN cohort are relatively complex and are not easily summarized in nontechnical terms. Here we briefly review the major methodological complications this analysis needs to address, how we conducted the analysis, and the format we have chosen for presentation of findings.

The fundamental methodological problem when conducting outcomes analysis with non-experimental data is that the decision to initiate and continue using medications is invariably partly influenced by the patient outcomes that medications are intended to ameliorate. For example, disease progression is central to clinical guidelines when deciding whether to start individuals on ART. Good clinical practice will be associated with an increased likelihood of prescribing ART as CD4 counts drop. Other things being equal, individuals on ART may feel in poorer health than those not on ART because they typically are further along in HIV-disease progression. If some attempt is not made to adjust for stage of disease, the observed differences between treated and untreated individuals may understate medication benefits or even erroneously appear to show negative effects on outcomes.

Potential influences on decisions about use of ART may bias comparisons in the opposite direction. Certain conditions such as unstable housing and current drug use that may restrain use of and adherence to ART may also operate independently to adversely impact health-related outcomes. Adverse side effects and failure of medications may result in people in poorer health withdrawing from medications. Such factors that associate poorer health with non use may exaggerate the perceived positive impact of adherence to treatment on patient outcomes

There is no a priori basis for assuming whether, on balance, the factors influencing medication use and adherence have a net positive, negative or even neutral effect on observed differences between treated and untreated groups. What one attempts to do is measure the plausible sources of confounding effects or apply other statistical techniques that adjust for possible “non-equivalences” between different study groups

There are other methodological complications more specific to the design of the CHAIN study. While information on current use of antiretroviral medications has been collected since the start of the study, adherence measures have been collected only since the 5th round of interviews and these measures were augmented for the sixth round of interviews. Finally, the CHAIN data rely on self reported data that may be prone to error. The direction of these errors and their relative impact with regard to treatment outcome are not easy to assess. Nevertheless, past CHAIN reports demonstrate the reliability and strong validity of many study variables. Prior experience suggests current use of antiretroviral medications and retrospective accounts of recent episodes of emergency room use, hospitalization and CD4 counts are reported with high levels of accuracy. Prior analysis of the quality of life measures show them to be highly reliable and valid indicators of clinical markers of disease progression both in the CHAIN cohort other populations with similar demographic characteristics. We are less confident about the degree of reliability that can be attributed to our measures of adherence. We concur with the prevailing belief that patients overestimate their compliance, but higher levels of reported adherence are

probably correlated with true levels of compliance. One reason for combining adherence information from rounds 5 and 6 is to obtain greater discrimination between those who are and are not truly adherent.

Although the methodological challenges in attempting to estimate the outcomes associated with medication and adherence are formidable, the situation is not hopeless. We have applied relatively sophisticated statistical techniques that are intended to adjust or remove the non-equivalences between the different medication adherence groupings. We take full advantage of the longitudinal nature of the CHAIN study. Use of repeated measures on the same individuals is a powerful technique for correcting potential biases. Twelve analyses were run for each patient outcome. Three different statistical techniques were applied for removing intergroup differences and the operational measures of medication use and adherence were varied. Unfortunately the results of these analyses do not reduce to a simple pattern of findings that can be easily summarized. After reviewing the results we believe that a comparison of mean change in health outcomes between the groups is as good a methodology as any for exploring possible associations between adherence and improved health functioning.

Presentation of change in patient outcomes are best visualized through graphic displays that plot the mean values of outcomes for the five medication adherence categories at each of the six rounds of interviews. The rounds of interviews divide into three periods. The first two interviews correspond to the pre-ART era. Rounds 3 and 4 mark the initiation of widespread combination therapy. Close to 70 percent of the sample at each round are on combination therapy beginning with the 3rd round of interviews. Rounds 5 and 6 are the period when information first becomes available on adherence. Our major interest is to compare the change in outcomes for the 5 medication adherence groups between rounds 4 and 6. Differential trends between the adherence groups are most readily interpretable when the average values of outcomes for each group closely cluster about the same value during early rounds of interviews. In this ideal situation we would expect to see that the mean values for each group become increasingly dispersed in rounds 5 and 6, exhibiting a fan like pattern. As we shall shortly see, this ideal pattern was not typically achieved and therefore complicates our interpretation of findings.

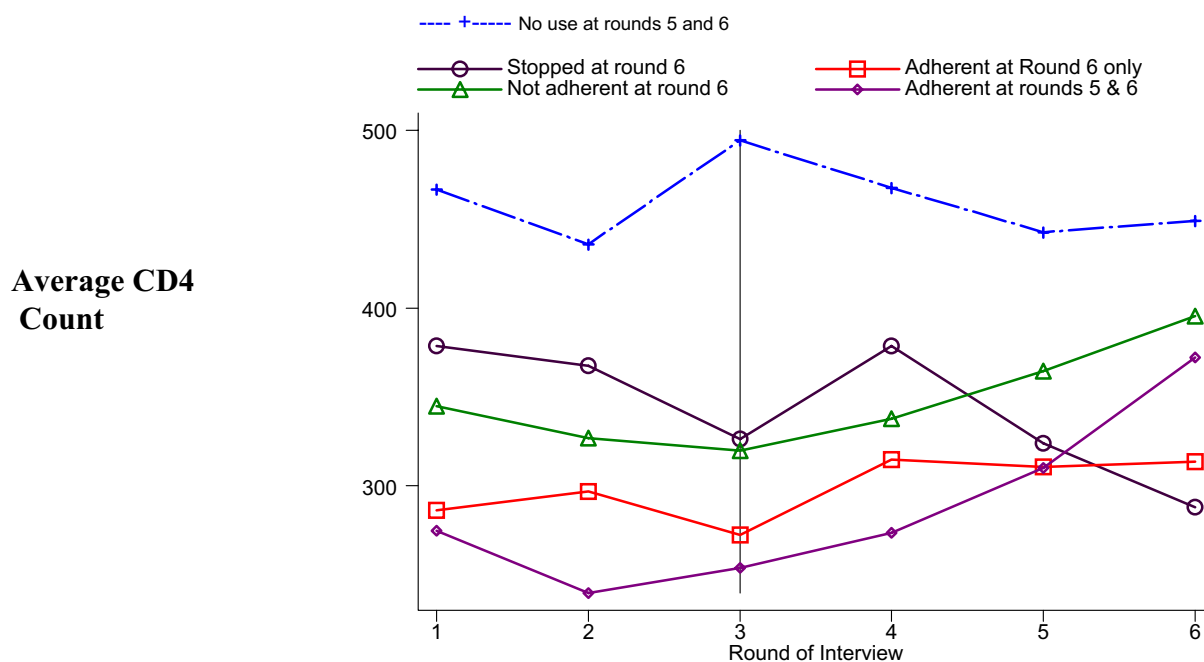
The statistical analysis conducted for this report informs our interpretation, but is not summarized here. The appendix to this report tabulates changes in group means between the 4th and 6th rounds of interviews and between the 2nd and 6th rounds for the patient outcomes selected for presentation.

Findings

Table 2 shows that the CHAIN cohort reported a high level of experience with combination therapies. Eighty-two percent of the sample reports current use of combination therapy at either or both the 5th and 6th rounds of interviews. It is also apparent that a large majority taking combination therapy report being adherent at each round of interview. However, when individuals are linked across interviews, we find that only 1 in 5 CHAIN participants (21%) report the adherent use at both rounds that we would associate with optimal therapeutic benefits. A much larger group, 54%, of the study sample show less consistent adherence to taking their medications over an extended period of time. Less consistent adherence may be either non-adherent use at round 6 (32%) or adherent use at round 6 but either no use or non-adherent use at round 5. Only a very small group report having stopped use between interviews (7%).

Examination of the statistical analysis and graphs of the trend lines suggests two basic findings. On the one hand, there is some evidence that taking medications as prescribed at both rounds of interviews is associated with an expected improvement in clinical measures of disease progression. This group exhibits increases in CD4 count that compare favorably to changes for less adherent and less consistent users of these medications. On the other hand, the data failed to find an association between consistent and adherent use of these medications and appreciable improvements in perceived health nor in increased engagement in employment or everyday social activities.

Below we present graphs of trends for selected outcomes to illustrate these basic results.

Figure 1 : CD4 T-Cell Count by Adherence to Combination Therapy

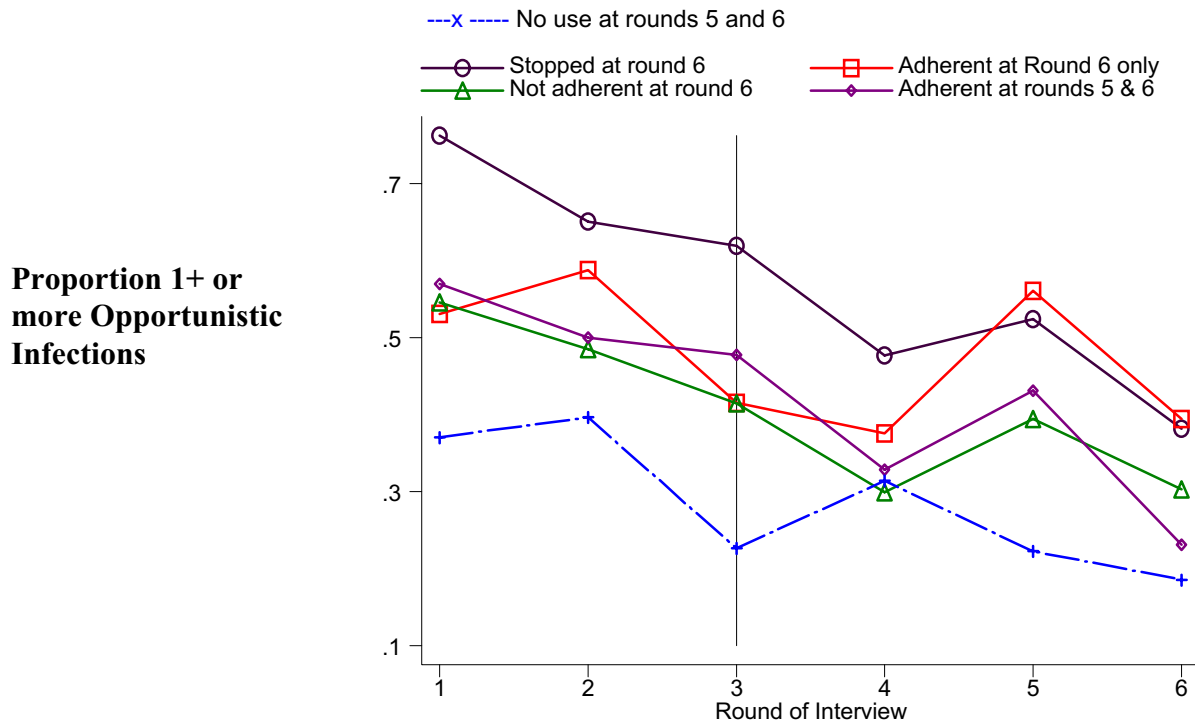
Source: CHAIN

Interviews, Rounds 1 through 6

Sample: Individuals interviewed at start of Study through wave 6 (N=305)

The association between consistent medication adherence and improvement in patient outcomes is most evident for CD4 T-Cell counts. Figure 1 shows a steady increase in CD4 T-Cell counts between the second and sixth interview for individuals who were adherent to combination therapy at both the 5th and 6th rounds of interviews. For this group CD4 T-Cell counts rise an average of 100 between the 4th and 6th interviews and 130 if we start from the second interview. We further observe that the consistency and magnitude of the increase in CD4 T-Cell counts is unmatched by any less adherent study participants. The statistical analysis confirms that the increase between the 4th and 6th round for the consistently adherent groups significantly greater than that of other study participants. It is also of interest to note that the small group of individuals who did not use combination therapy at both rounds of interviews exhibit consistently higher and relatively stable levels of CD4 T-cell counts. The sharp decline in CD4 T-Cell counts for people who stopped taking medications between the 5th and 6th rounds of interviews is consistent with the interpretation that this pattern isolates a group of individuals who experienced adverse side effects from the drugs or medication failure. In contrast, the nonusers of medication at both rounds of interviews appear to have a history of generally better health that can be traced back to the start of the study. It should be emphasized that a fair number of CHAIN participants who have maintained CD4 T-Cell counts above 500 since the start of the study have reported using combination therapies. Removing the people with sustained high CD4 T-Cell does not change the relative patterns observed for this and other outcomes. It is also of interest to observe that those in the “consistent adherence group” reported the lowest average CD4 T-Cell counts during the early interviews. Possibly this group, because of their low CD4 T-Cell count was put on combination therapy earlier, and perhaps they were the recipients of focused assistance to support long-term adherence.

Figure 2 : Opportunistic Infections by Adherence to Combination Therapy

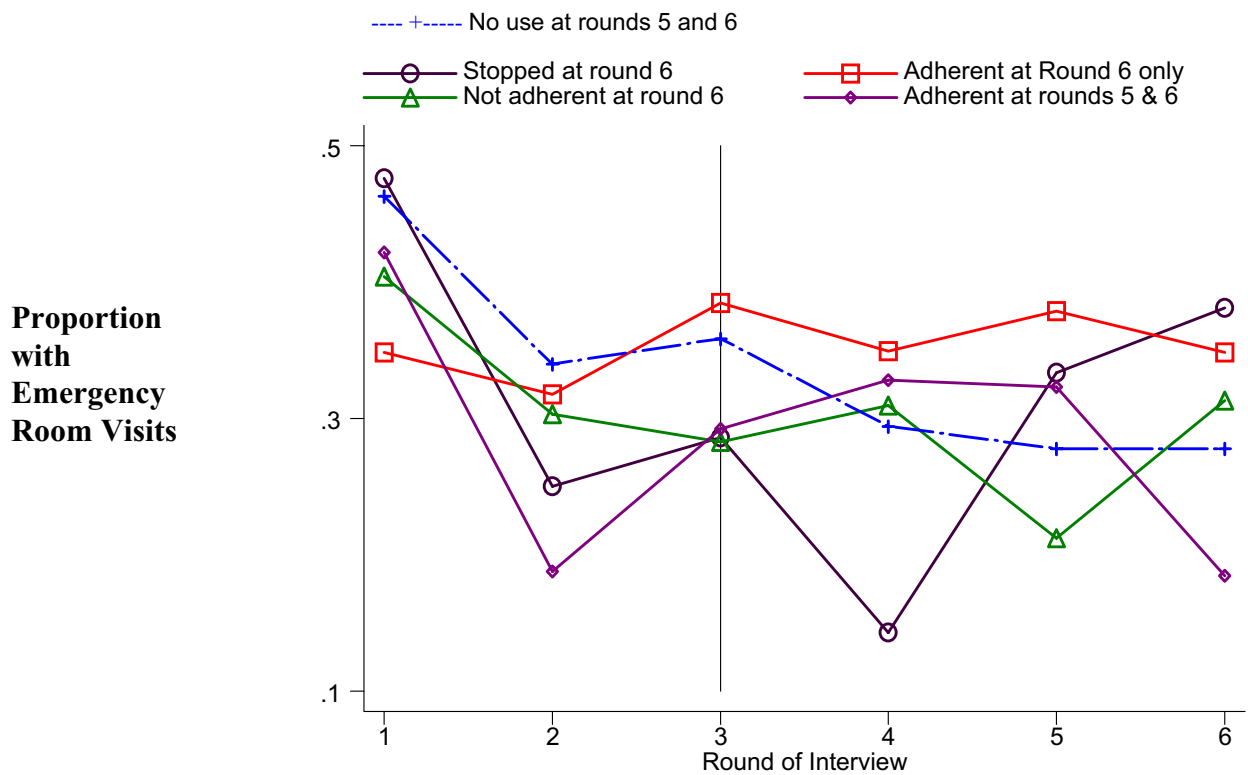


Source: CHAIN interviews, Rounds 1 through 6
 Sample: Individuals interviewed at start of Study through wave 6 (N=305)

In

The differential pattern of increased CD4 T-cell counts is not replicated for trends in opportunistic infections. (Figure 2). To be sure, adherent individuals show a sharp decline in opportunistic infections. The proportion of individuals reporting one or more opportunistic infections between interviews is cut in half between the 2nd and 6th interviews. However, a declining trend is evident for all groups back to the start of the study that pre-dates the widespread introduction of combination therapies. There is also no evidence for an accelerating decline in conjunction with consistent adherence. Moreover, the sharp decline in opportunistic infections is present for virtually the entire study sample regardless of their adherence status. Indeed among the largest declines in occurrence of opportunistic infections is found for individuals who initiated but had stopped combination therapy by round 6.

Figure 3 : Emergency Room Visits by Adherence to Combination Therapy



Source: CHAIN Interviews, Rounds 1 through 6
 Sample: Individuals interviewed at start of Study through wave 6 (N=305)

Emergency room visits (Figure 3) follow an erratic pattern that is generally difficult to interpret, but differences in change in group means between rounds 4 and 6 are statistically significant. The consistently adherent group experienced a drop of 15 percentage points in use of emergency rooms between the 4th and 6th round of interviews, while other groups showed either no trend in emergency room or in the case of one group (stopped use at round 6) a discernable rise in use.

Figure 4: Physical Health Components Summary Scale (PCS) by Adherence to Combination Therapy

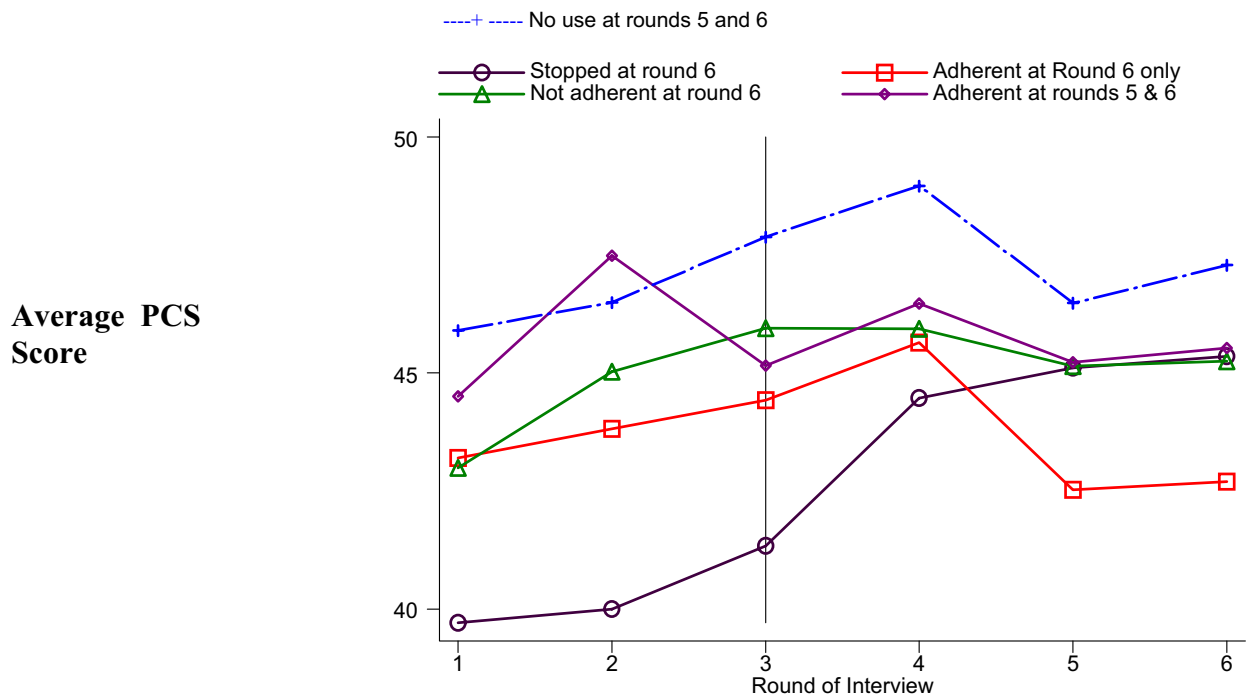
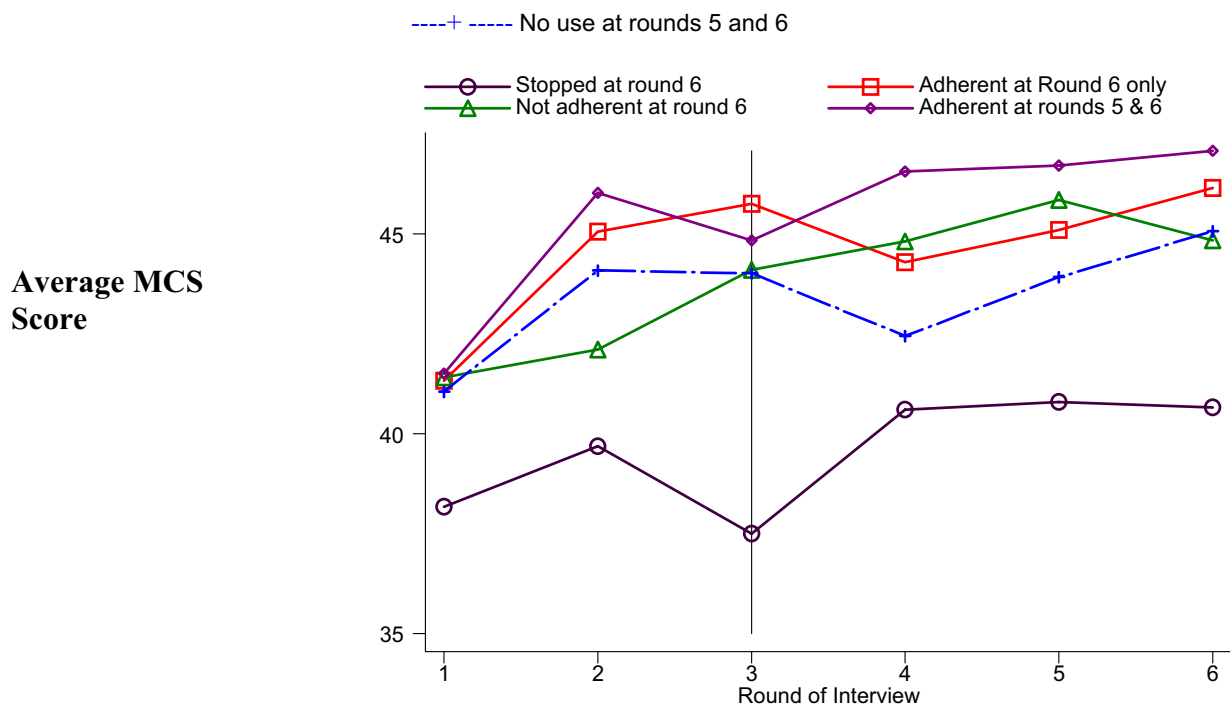


Figure 5: Mental Health Components Summary Scale (MCS) by adherence to Combination Therapy



As Figures 4 and 5 show, there is no relationship between adherence and either physical or mental health status. Nor does an examination of any of the component scales show any pattern of association. In short, CHAIN participants report that they don't experience or perceive any improvements in health status following use of combination therapy even when adherence is consistently reported across two rounds of interviews. Also observe that with the exception of the "never" user group, the mean values for physical functioning are below 45, the cut point for impaired ability to work.

Figure 6: Summary Social Functioning by Adherence to Combination Therapy

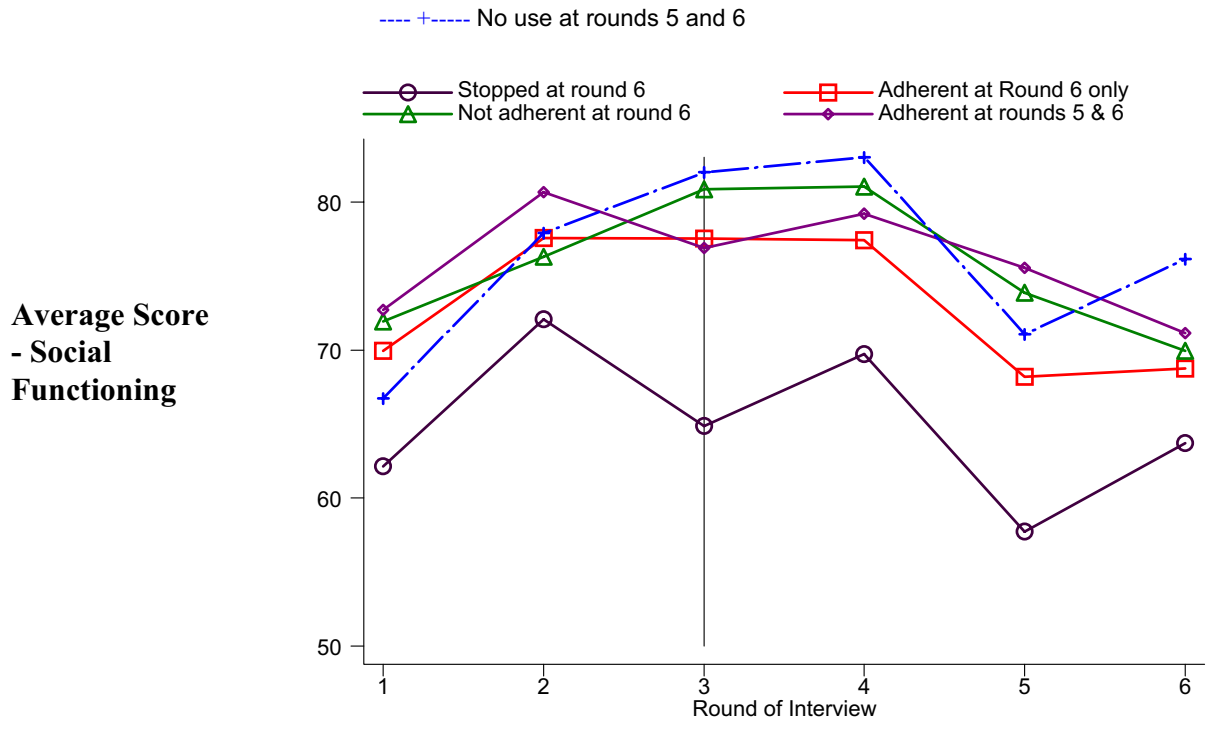
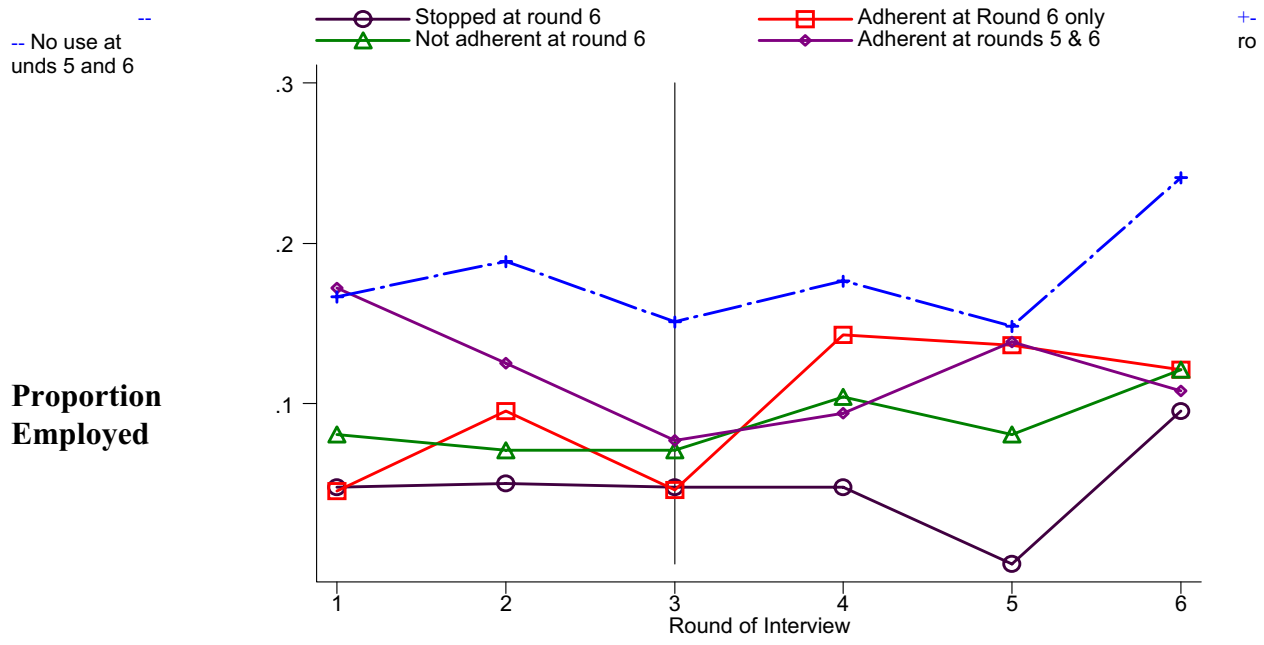


Figure 7 : Employment by Adherence to Combination Therapy



Figures 6 and 7 shift attention to the health status indicators of impaired social role performance and employment. Not only is adherence to medication not associated with greater social interaction with family and friends, but for reasons that are not obvious, the social functioning scale tracks a general decline across all groups. Similarly, employment stays at low levels throughout this period, with no clear differentiation in trend related to adherence or use of combination therapy.

Discussion and Conclusion

An extensive statistical analysis was undertaken to examine whether we could find a positive relationship between adherence to combination therapies and improvements in health status. This analysis included 15 patient outcomes that spanned measures of health from clinical markers for disease progression to various dimensions of perceived health status and through indicators of impaired social and economic role performance. In summary, we found that consistent adherence was associated with improvements in clinical markers for disease progression. This was most evident for higher CD4 counts with more tentative evidence for a decline in emergency room use that might indicate less frequent acute conditions. However, neither occurrence of opportunistic infections nor hospital stays was associated with medication use and adherence status. Despite evidence of the clinical benefits of consistent adherence to medication regimens, we found that such usage was not associated with improved health functioning compared to less adherent users and non users of ART. None of the health related quality of life and social role performance indicators showed any trends that could be associated with adherence.

Before we discuss some possible implications of study findings, let us briefly consider some of the methodological limitations of this study. To begin with, there may be concern that we may not have measured patient outcomes adequately. We believe that this is probably not the case. We have selected outcomes that are widely used in the research literature to indicate the various domains we associate with health and quality of life. Moreover, we have independent confirmation of the validity of several of these measures. In an earlier mortality study, we established that CD4 T-Cell counts, the PCS scale, opportunistic infections and inpatient hospitalization are all associated with increased risk of mortality (Update Report #26). In addition the PSC and MCS and their component sub scales have been validated in both the general population and in HIV+ populations. Furthermore, assessment of these scales for the CHAIN population indicates that they exhibit similar scaling properties and the high reliability reported for other populations. It is of course possible that we may have missed some salient dimension. For example, it is possible that use of combination therapy may be associated with a change in outlook even if other outcomes are not changed. It is also possible that the impact of medications on perceived health may vary by population. Perhaps feelings of better health are

restricted to middle class individuals, a group that composes only a small proportion of our sample.

Our adherence measures are open to more critical scrutiny. Nonetheless, for all their limitations, we do believe they offer a useful and pragmatic way to divide the sample in a way that corresponds to greater or lesser adherence. If anything of substantial import were happening we suspect that even this crude categorization would pick it up. Clearly, it would be desirable to administer more reliable measures of patient adherence.

The single most serious limitation to this study is that our “treatment groups” are subject to serious social and self selection that leave us far removed from simulating a randomized experiment, which would be the ideal research design for isolating the effects of adherence to medication on health outcomes. We have examined several ways to unconfound our findings, but none of the strategies proved entirely satisfactory. Consequently, we believe that these findings must be considered suggestive: they point out the need for more rigorous research to document the benefits of combination therapy administered in general practice on health outcomes.

For all these methodological weaknesses we do believe there is a lesson that can be drawn, if a cautionary one. One should refrain from automatically linking adherent use of combination therapy to improved health status, even where there is substantial improvement in clinical markers of health. Certainly combination therapy is associated with improved clinical markers of health, but our data illustrate that they do not necessarily translate into improvements in perceptions of physical and mental well being. Because of the side effects experienced while taking medications and the fact that people with HIV don’t always feel ill, it is in fact a plausible outcome for many people that taking these medications correctly may not ipso facto make them feel better.

Two important policy implications might follow from this reasoning. First, if people do not feel better by taking the drugs, then they may not experience an important positive feedback, or cue to action for maintaining long-term adherence. A second finding is that if people are not feeling better that might explain why we have yet to see a substantial increase in people wanting to or actually returning to work. This latter point builds on an earlier report (CHAIN Update #22) that summarized the many social and health factors that impede CHAIN cohort members’ ability to find and maintain full time employment even as many are living longer and from clinical measures appear to be in much better health. We should stress that even with general improvements in health status that no doubt are attributable to medications, many of our cohort, whether adherent or not, are still at diminished levels of physical functioning indicative of continued limitations for engaging in normal work-related activities. Also, many of our cohort members had minimal or no attachment to steady employment before they became infected. For them the problem is less how to re-enter the workforce, but the acquisition of skills necessary to enter the workforce for the first time. Consequently, services for job training and work re-entry

must be carefully planned for people with HIV as they must consider both pre-existing life course and the continued influence that less than normal health functioning has on the capacity of people living with HIV to fully engage in a socially active life and economically productive work.

Appendix: Change in Selected Patient Outcomes by Patient Adherence categories.

Change in mean CD4 T-cell count by medication adherence category

	Change between Round 4 and Round 6	Change between Round 2 and Round 6
Adherent at Rounds 5 and 6	99.00	132.00
Adherent at Round 6 only	-1.00	17.00
Used but not adherent at Round 6	58.00	68.00
Stopped using medications between Rounds 5 and 6	-90.00	-79.00
No current use at both rounds	-19.00	13.00

Change in proportion experiencing an opportunistic infection by medication adherence category

	Change between Round 4 and Round 6	Change between Round 2 and Round 6
Adherent at Rounds 5 and 6	-0.01	-0.30
Adherent at Round 6 only	0.02	-0.20
Used but not adherent at Round 6	0.00	-0.18
Stopped using medications between Rounds 5 and 6	-0.09	-0.30
No current use at both rounds	-0.10	-0.21

Change in proportion visiting an emergency room by medication adherence category

	Change between Round 4 and Round 6	Change between Round 2 and Round 6
Adherent at Rounds 5 and 6	-0.15	0.00
Adherent at Round 6 only	0.00	0.03
Used but not adherent at Round 6	-0.04	0.01
Stopped using medications between Rounds 5 and 6	0.24	0.13
No current use at both rounds	-0.02	-0.06

Change in mean physical functioning summary scale (PCS) by medication adherence category

	Change between Round 4 and Round 6	Change between Round 2 and Round 6
Adherent at Rounds 5 and 6	-1.00	-2.00
Adherent at Round 6 only	-3.00	-1.10
Used but not adherent at Round 6	-0.70	0.00
Stopped using medications between Rounds 5 and 6	0.90	5.30
No current use at both rounds	-1.70	0.80

Change in mean mental health functioning (MCS) by medication adherence category

	Change between Round 4 and Round 6	Change between Round 2 and Round 6
Adherent at Rounds 5 and 6	0.50	1.00
Adherent at Round 6 only	1.90	1.00
Used but not adherent at Round 6	0.00	2.70
Stopped using medications between Rounds 5 and 6	0.00	1.00
No current use at both rounds	2.60	1.00

Change in Mean Social Functioning by medication adherence category

	Change between Round 4 and Round 6	Change between Round 2 and Round 6
Adherent at Rounds 5 and 6	-8.10	-10.00
Adherent at Round 6 only	-8.70	-8.80
Used but not adherent at Round 6	-11.00	-6.40
Stopped using medications between Rounds 5 and 6	-6.20	-8.40
No current use at both rounds	-6.90	-1.70

Change in proportion employed by medication adherence category

	Change between Round 4 and Round 6	Change between Round 2 and Round 6
Adherent at Rounds 5 and 6	0.01	-0.02
Adherent at Round 6 only	-0.02	0.03
Used but not adherent at Round 6	0.02	0.05
Stopped using medications between Rounds 5 and 6	0.05	0.05
No current use at both rounds	0.06	0.05