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Adherence to Early Antiretroviral Therapy: Results from HPTN 052, A Phase III, Multinational Randomized Trial of ART to Prevent HIV-1 Sexual Transmission in Serodiscordant Couples

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Abstract

Background—Combination antiretroviral therapy (ART) for HIV-1 infected individuals prevents sexual transmission if viral load is suppressed.

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AUTHOR CONTRIBUTIONS

S.A.S. and D.C. lead the efforts to develop the measures and the behavioral science objectives of HPTN052 study, resulting in this publication. S.A.S. drafted the paper. KHM contributed to the design of the objectives. S.S.O. developed the study database and conducted statistical analyses. MM and IH contributed oversight to data collection, operations, and shaping of the objectives. BG, MH, NK were site investigators, contributed to the science. TG contributed to the logistical operations of data collection and adherence counseling. MC was the PI of HPTN052 and contributed to various aspects of the design of this substudy as well as drafting of various sections of the manuscript. Y.Q.C. oversaw statistical modeling, analysis and interpretation.

Methods—Participants were HIV-1 infected partners randomized to early ART (CD4 350-550) in HPTN052 (n=886, median follow-up = 2.1 years), a clinical trial of early ART to prevent sexual transmission of HIV-1 in serodiscordant couples at 13 sites in 9 countries. Adherence was assessed via pill-count (dichotomized at <95%) and via self-report items. Predictors of adherence were mental health and general health perceptions, substance use, binge drinking, social support, sexual behaviors, and demographics. Viral suppression was defined as HIV plasma viral load <400 copies/ml. Adherence counseling and couples counseling about safer sex was provided. Logistic and linear regression models using generalized estimating equation for repeated measurements were employed.

Findings—Via pill-count, 82% of participants were adherent at 1 month and 83.3% at 1 year. Mental health was the only psychosocial variable associated with adherence (pill-count OR=1.05: 95% CI: 1.00 – 1.11; self-report parameter estimate (b)=0.02, 95% CI: 0.01 –0.04), though regional differences emerged. Pill-count (OR=1.19, 95% CI: 1.10-1.30) and self-report (OR=1.42, 95% CI: 1.14-1.77) adherence were associated with viral suppression.

Interpretation—While adherence was high among individuals in stable relationships taking ART for prevention, mental health and adherence co-varied. Assessing and intervening on mental health in the context of promoting adherence to ART as prevention should be explored. Adherence and couples counseling, feedback about viral suppression, and/or altruism may also help explain the magnitude of adherence observed.

INTRODUCTION

HPTN 052 is a Phase III, randomized, multicenter study in 1763 HIV-1 serodiscordant couples in 9 countries where the HIV-1 infected partner was randomized to early or delayed ART. The trial demonstrated that ART prevented HIV-1 transmission.[1] These results were consistent with observational trials.[2–4]

However, the ability of ART to suppress viral replication is entirely dependent on adherence to the medications. Low social support, depression, substance use, side effects, lack of counseling, and socio-economic factors have been predictive of poor adherence to ART in diverse global settings.[5–8] Virtually all earlier studies have examined adherence to ART in individuals who were taking ART because it was indicated for more advanced HIV-1 disease, rather than to prevent transmission to a sexual partner. The present analysis from HPTN 052 among those who were randomized to early ART allowed us to evaluate predictors of adherence to medication in HIV-1 infected study subjects offered treatment directed toward HIV prevention.

METHODS

Details of the HPTN 052 study design can be found both on clinicaltrials.gov NCT00074581 and in the primary outcome papers.[1,9] Participants were enrolled from 13 sites in 9 countries (Botswana; Kenya; Malawi; South Africa; Zimbabwe; Brazil; India; Thailand; and United States). The study enrolled HIV-1 serodiscordant couples (one partner is infected with HIV-1 and the other is not), where the HIV-1 infected partner had a CD4 cell count of 350-550 cells/mm. Couples had to have been in a stable relationship for at least 3 months,

reported 3 or more episodes of vaginal or anal intercourse during the past 3 months, and willing to disclose their HIV-1 status to their partner. The study was unblinded. The partner infected with HIV-1 was randomized to early or delayed ART. Local Institutional Review Boards or Ethics Committees approved the study at each site.

For the present analysis, data were used only from participants randomized to the early treatment arm. Accordingly, all participants in the following analyses initiated ART upon study enrollment, and all data were from visits after the enrollment visit (following ART treatment initiation) through the time when the results of the primary outcome was publically released. The median follow up for the present analysis was 2.1 years.

When the study began in 2005, visits were monthly, and beginning in mid-2008 they transitioned to quarterly. Adherence and psychosocial data were recorded at each visit. Participants were provided regular adherence counseling using an adapted version of the Life-Steps intervention[10,11] as a base (see http://www.hptn.org/web%20documents/hptn052/hptn052adherencecounseling.pdf for the initial training material), and regular counseling on HIV risk reduction. The Life Steps adherence counseling included a medical provider portion, which provided education about ART medications and adherence, and a counselor portion, which provided assistance to participants in devising a plan and a back-up plan for potential impediments to adherence (e.g., creation of a daily medication schedule, developing reminder strategies, handling slips, discussion of involving social supports), following a cognitive-behavioral / problem-solving approach. See the on-line Appendix for the checklists used by counselors and medical providers. Study drugs included a combination of lamivudine and zidovudine (Combivir), efavirenz, atazanavir, nevirapine, tenofovir, lamivudine, zidovudine, didanosine, stavudine, a combination of lopinavir and ritonavir (Kaletra and Aluvia), ritonavir, and a combination of emtricitabine and tenofovir (Truvada). A pre-specified combination of these drugs was provided to participants at each visit. For participants with virologic failure, specified second-line treatment regimens were provided.

Measures

At every visit, participants completed an interviewer-administered adherence questionnaire in the local language (translated, back translated, discrepancies reviewed and corrected) and pill counts were conducted, which yielded a non-adherence self-report score and a non-adherent pill-count categorization respectively. The additional psychosocial variables were collected at every quarterly visit. At all sites, self-report measures were translated and back-translated to maximize accuracy. These measures are described below.

Adherence questionnaire—The adherence questionnaire began with a grid whereby each study drug was listed with the number of doses prescribed per day filled in by study staff. Participants would answer the number or prescribed doses missed for “yesterday”, “2 days ago”, “the past two weeks” and “the past 30 days”. We followed the methodology of Reynolds et al.[12] to calculate the adherence ratios for yesterday, 2 days ago, in the past two weeks and in the past 30 days as 1-(number of doses missed for the time period divided by the number of doses prescribed). They were then asked a series of questions including when

they last missed medications (within past week, 1-2 weeks ago, 2-4 weeks ago, or never, and skipped/not applicable), how many days they had missed taking all of their doses during the past four days (none, one day, two days, three days, four days), and whether they missed any medications over the past weekend (yes/no for Saturday or Sunday). The 7 self-report questions (4 adherence ratios and the 3 questions above) were subjected to a principal component analysis (PCA) to construct a non-adherence factor approximating a continuous latent variable. This PCA was conducted separately for each study visit. Inspection of the scree plot[13] and the result that only the first PC had an eigenvalue greater than 1[14] lead us to retain one principal component as the self-report PCA adherence score. This procedure of using the available self-report questions to create a self-report continuous PC, and maximize variability has been successfully employed in similar studies[12,15] and the resulting variable was relatively uni-modally distributed..

Additionally, participants were asked about potential reasons for non-adherence. This involved a checklist for “never,” “rarely,” “sometimes,” and “often,” and had 24 potential reasons for non-adherence such as “forgot,” “side effects,” “transportation problems getting to the clinic,” and “lost pills,” which were generated from the study sites and using items from prior AIDS Clinical Trials Group (ACTG) trials.[16] The most frequently reported reasons are described in the study results.

Pill Count—At each study visit, study nurses dispensed pills expected for the following quarter and participants were instructed to bring any remaining pills to the clinic at the next visit for a pill count. The adherence percentage was calculated for each participant as dividing the total number of pills taken by the total number of pills that should have been taken since ART initiation. A binary adherence variable (<95% vs. 95-100%) was then created.

Psychosocial Interview—The psychosocial interview included a modified version[17] of the ACTG SF-21[18] quality of life questionnaire. To simplify the analyses, and based on prior adherence research, only the general health perceptions and mental health subscales were included. We also included one question about general satisfaction with social support,[16,17,19] which asked about overall satisfaction with social support from friends and families, ranging from 0 (very dissatisfied) to 3 (Very satisfied). For substance use, there was a frequency question about binge drinking, asking how often participants drank 5 or more drinks of alcohol in the past month, ranging from never (0), to daily (6), a series of yes/no questions for various substances (e.g., cocaine, heroin, marijuana), followed by the frequency question for the substance used most. Lastly, there were questions about sexual behaviors in the past week, which yielded a variable indicating whether participants reported any condomless sex acts in the past week.

Viral Suppression—HIV-1 plasma viral load was collected quarterly, and viral suppression was defined as HIV-1 plasma viral load <400 copies/mL.

Data Analysis

Logistic (allowing for odds ratios) and linear regression (for continuous measures, with an unstandardized beta as the parameter estimate) models using generalized estimating equation (GEE) for repeated measurements were first fit to examine the associations between adherence measured by pill count and self-report with psychosocial and demographic predictors, respectively. In model building, all variables associated with the outcome with $p<0.1$ from the univariate regression model were included in later multivariable regression models. Similarly, logistic regression models were fit to examine the association between the two indicators of adherence (pill count and self-report) on viral suppression status (suppressed vs detectable) including the psychosocial and demographic predictors as covariates. All analyses were conducted using SAS version 9.2 (SAS Inc., Cary, NC).

RESULTS

Demographic variables for the sample are reported in the primary outcome paper for HPTN 052[1] and are included in the on-line Supplemental Appendix. Table 1 presents descriptive baseline data on the psychosocial and demographic data for the present sample. General health perception and mental health scores were in expected ranges, and most participants reported that they were either somewhat or very satisfied with social support. A small minority reported substance use, though almost 20% reported binge drinking. Only 4.2% of the sample reported less than 100% condom use during sex.

Levels of adherence and reasons for non-adherence

According to pill count, in the first month following ART initiation, 82.2% of participants were “adherent” (defined by 95% or greater levels), and 83.2% of participants were adherent one year after ART initiation. With respect to self-report items for how often they missed doses after ART initiation, 88.8% reported less than perfect adherence in the first month, and 84.2% at one year. In the first month the most frequent (more than 5%) reasons for non-adherence were: forgot (40.4%), traveling away from home (19.3%), wanted to avoid side effects (17.0%), busy doing other things (9.4%), other illness or health problems got in the way (8.2%), and ran out of pills (6.4%). At one year, the most frequent reasons given for non-adherence were: forgot (45.1%), busy doing other things (20.7), traveling away from home (22.6%), and ran out of pills (14%).

Longitudinal models of adherence

Pill count adherence—Tables 2 and 3 present univariate and multivariable logistic regression analyses of psychosocial and demographic predictors of pill count adherence, inclusive of corresponding odds ratios, confidence intervals, and significance levels. According to the estimates in both the univariate and multivariable analyses, having a higher mental health score was the only statistically significant psychosocial predictor associated with greater adherence as measured by pill count. Geographic region (specifically, Asia and Africa versus America) were also associated with adherence, with both groups having higher pill count adherence than America. In the univariate analyses, in addition to higher mental

health scores, higher general health perceptions and lower levels of unprotected sex were associated with greater adherence by pill count.

Self report (PCA) adherence score—Tables 2 and 3 also present univariate and multivariable linear regression analyses of psychosocial predictors of adherence measured by the self-report PCA scores,,with corresponding unstandardized beta regression coefficient estimates, confidence intervals, and significance levels. Similar to the adherence by pill-count, in both the univariate and the multivariable analyses, having a higher mental health score was statistically significantly associated with better adherence. However, in the analysis by geographic region, participants from Asia had lower self-reported adherence. Additionally, older age was associated with higher adherence in univariate analysis, but only marginally significant (p=.06) in multivariable analysis, Better social support (somewhat satisfied versus very dissatisfied) was associated with better adherence in univariate analysis only.

Predictors of viral suppression (Table 4)

Both univariate and multivariable analyses showed consistent significant associations between the self-report PCA medication adherence score and viral suppression. In the multivariable analysis of pill count adherence, those categorized as being 95-100% adherent were 1.42 times more likely to be virally suppressed; analysis of the self-report PCA adherence score showed each unit increase in the PCA resulting in a 1.20 fold increased likelihood of being virally suppressed.

DISCUSSION

ART that suppresses HIV-1 replication reduces transmission of HIV-1 to a sexual partner; however, this benefit requires strict adherence to treatment. Treatment for prevention purposes generally requires initiating ART when patients are healthier and therefore at higher CD4 counts. One study[20] compared 60 individuals in Uganda with CD4<250 cells to those >=250 cells and found greater number of treatment interruptions and more uncontrolled virus in those in the higher baseline CD4 category. No studies have examined adherence to ART when the stated purpose of the ART was specifically to test whether it would reduce transmission of HIV-1 to a sexual partner.

In the present analysis, we noted higher levels of adherence to ART than typically observed in the context of ART for treatment.[21] In addition, such adherence in the infected person is greater than reported in an observational study of couples in Zambia.[22] The high level of adherence in this report may have reflected the intense management in the conduct of the HPTN 052 study,[1,9] the benefit of couples counseling,[23] feedback about viral load suppression, or altruism related to prevention of transmission of HIV (a potential benefit communicated during the informed consent process). Additionally, counselors used an evidenced-based cognitive-behavioral counseling intervention (Life-Steps)[10,24] as the basis of their adherence counseling training, and utilized checklists and visit documentation to maximize the actual delivery of this counseling approach in these settings.

We found that the only psychosocial variable that predicted adherence in the multivariable models was the mental health score on the quality of life assessment. While the association of mental health to adherence is consistent with meta-analytic work in individuals with HIV-1 showing an association of depression to non-adherence,[25] the lack of associations of variables such as substance use[26–28] and social support,[29] differs from what has been reported in studies of adherence in patients prescribed ART for treatment.

Our HIV-1 serodiscordant couples were in relatively stable relationships, located in resource-limited countries where initiation of ART was recommended at lower CD4 cell counts than what was dictated by the study, and who were volunteering for a HIV prevention trial where provision of care might be greater than what would otherwise be received in the local setting. Accordingly, participants electing to take medications for prevention purposes, and/or for purposes of being in a prevention trial may have higher motivation for health behaviors in general. Hence, as seen in the present study, the strength of the association of some of the typical psychosocial variables to health behavior may be attenuated when the need for treatment is also not as strong.

Nevertheless, higher mental health scores remained independently associated with better adherence. A treatment study that complemented HPTN 052 and was conducted at the same sites, ACTG5175,[30] found that illicit drug use and general health perceptions but not mental health scores were variables associated with adherence in longitudinal multivariable models.[15] These results suggest that there may be different psychosocial variables predicting adherence when attempting to maximize ART for prevention rather than ART for treatment.

There are several limitations to this analysis. First, self-report and pill-count adherence are not as objective as other indicators such as medication event monitoring systems (MEMs), other electronically monitored adherence devices, unannounced pill counts, or blood ART levels. However, the association of viral load to both pill count and self-report PCA adherence scores shows that these can be useful indicators of adherence.[31] Second, this analysis mainly examined main effects, and not interactions because of the wide number of potential variables possible for interactions such as study site, HIV risk group, gender, and country. Third, although participants enrolled in the study as a prevention trial, it is possible that some participants' motivation to join was as a vehicle to gaining ART as treatment for themselves. Hence, although at the time the study began initiating ART was not considered necessarily beneficial to the patient, this could have affected the motivations to take ART and be adherent to ART.

The results of this analysis demonstrate a very high degree of adherence to ART, which correlates well with the durable suppression of viremia observed.[1,9] It seems likely that high adherence can be expected in many groups of couples given the fact that ART dramatically suppressed HIV transmission in 10/12 observational studies.[32] Adherence to treatment is likely optimized when evidence based counseling is an ongoing part of provision of ART,[33,34] when couples are counseled together, when the prevention benefit to the sexual partner is made clear, and when feedback about viral suppression is provided. These data suggest the potential utility of implementing these approaches in clinical settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline psychosocial characteristics of the participants in immediate arm.

	Immediate arm (N=886)
Psychosocial variables	
General health Perceptions	
Median	6.7
Min, Max	0.8, 10.0
Q1, Q3	5.8, 8.3
Mental health	
Median	9.3
Min, Max	0.0, 10.0
Q1, Q3	8.0, 10.0
Satisfied with support	
Missing	1 (0.1%)
Very dissatisfied	26 (2.9%)
Somewhat dissatisfied	15 (1.7%)
Somewhat satisfied	120 (13.5%)
Very satisfied	724 (81.7%)
Substance use	
Missing	4 (0.5%)
No	856 (96.6%)
Yes	26 (2.9%)
Binge drinking	
No	714 (80.6%)
Yes	172 (19.4%)
Unprotected sex	
Missing	5 (0.6%)
No sex or 100% condom use	844 (95.3%)
<100% condom use	37 (4.2%)

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Table 2

Longitudinal univariate predictors of adherence.

	Pill count adherence (95-100% vs. <95%)		PCA Self Report Adherence Score	
	OR (95% CI)	**p-value**	**Estimate (95% CI)**	**p-value**
Age (10 years increase)	1.11 (0.97, 1.27)	0.12	**0.04(0.004, 0.08)**	**0.03**
General health Perceptions	**1.06 (1.02, 1.10)**	**0.002**	0.01 (−0.01, 0.02)	0.29
Mental health	**1.09 (1.04, 1.14)**	**<0.001**	**0.03 (0.01, 0.05)**	**0.005**
Satisfied with support - Somewhat dissatisfied vs. very dissatisfied	1.30 (0.66, 2.59)	0.45	**0.25 (0.05, 0.45)**	**0.01**
Somewhat satisfied vs. very dissatisfied	1.42 (0.76, 2.64)	0.27	0.14 (−0.06, 0.33)	0.17
Very satisfied vs. very dissatisfied	1.54 (0.85, 2.78)	0.16	0.15 (−0.03, 0.34)	0.11
Substance use - Yes vs. No	1.64 (0.78, 3.45)	0.19	−0.08 (−0.24, 0.08)	0.33
Binge drinking - Yes vs. No	0.85 (0.67, 1.07)	0.17	−0.02 (−0.10, 0.05)	0.55
Unprotected sex - Yes vs. No	**0.67 (0.47, 0.94)**	**0.02**	−0.004 (−0.15, 0.14)	0.96
Gender - Female vs. male	0.88 (0.71, 1.09)	0.23	0.06 (−0.01, 0.13)	0.10
Region - Africa vs. America	**1.47 (1.15, 1.89)**	**0.002**	**−0.12 (−0.23, −0.01)**	**0.03**
Asia vs. America	**2.22 (1.63, 3.02)**	**<.0001**	**0.07(−0.02, 0.16)**	**0.14**

Table 3

Longitudinal multivariable predictors of adherence.

	Pill count adherence (95-100% vs. <95%)		PCA Self Report Adherence Score	
Predictors	**OR (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
Age (10 years increase)	--	--	0.03 (−0.001, 0.07)	0.06
General health Perceptions	1.04 (1.00, 1.08)	0.07	--	--
Mental health	**1.05 1.00, 1.11)**	**0.05**	**0.02 (0.01, 0.04)**	**0.01**
Satisfied with support - Somewhat dissatisfied vs. very dissatisfied	--	--	0.09 (−0.15, 0.33)	0.47
Somewhat satisfied vs. very dissatisfied	--	--	0.12 (−0.07, 0.31)	0.20
Very satisfied vs. very dissatisfied	--	--	0.12 (−0.06, 0.29)	0.20
Substance use - Yes vs. No	--	--	--	--
Binge drinking - Yes vs. No	--	--	--	--
Unprotected sex - Yes vs. No	0.76 (0.55, 1.05)	0.10	--	--
Gender - Female vs. male	--		--	--
Region - Africa vs. America	**1.43 (1.10, 1.87)**	**0.01**	**−0.17 (−0.28, −0.07)**	**0.001**
Asia vs. America	**2.13 (1.55, 2.91)**	**<.0001**	0.03 (−0.05, 0.10)	0.51

[1]The multivariate model includes only predictors with p<0.1 from the univariate results.

Table 4

Risk factors of viral suppression (un-detectable vs. detectable).

	Bivariate		Multivariable with pill count Predictor		Multivariable with PCA Self-Report Adherence Score Predictor	
Covariates	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Age (10 years increase)	1.17 (0.94, 1.45)	0.15	--	--	--	--
General health	**1.03 (1.00, 1.07)**	**0.07**	1.03 (1.00, 1.07)	0.06	1.03 (0.99, 1.07)	0.11
Mental health	1.02 (0.97, 1.06)	0.51	--	--	--	--
Satisfied with support– Somewhat dissatisfied vs. very dissatisfied	0.85 (0.42, 1.72)	0.66	--	--	--	--
Somewhat satisfied vs. very dissatisfied	1.11 (0.69, 1.79)	0.67	--	--	--	--
Very satisfied vs. very dissatisfied	1.34 (0.85, 2.12)	0.21	--	--	--	--
Substance use - Yes vs. No	0.94 (0.64, 1.39)	0.77	--	--	--	--
Binge drinking - Yes vs. No	0.93 (0.73, 1.17)	0.53	--	--	--	--
Unprotected sex - Yes vs. No	0.85 (0.61, 1.18)	0.33	--	--	--	--
Gender - Female vs. male	1.06 (0.76, 1.48)	0.72	--	--	--	--
Region - Africa vs. America	0.83 (0.53, 1.30)	0.41	--	--	--	--
Asia vs. America	0.86 (0.52, 1.42)	0.55	--	--	--	--
Pill count adherence (binary) – 95-100% vs. <95%	1.43 (1.15, 1.77)	0.001	**1.42 (1.14, 1.77)**	**0.002**	--	--
PCA Self-Report Adherence Score	1.19 (1.10, 1.30)	<.0001	--	--	**1.19 (1.10, 1.30)**	**<.0001**