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Prospective prediction of viral suppression and immune response nine months after ART initiation in Seattle, WA

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Abstract

Knowing at antiretroviral therapy (ART) initiation which patients might be at greatest risk for failure to achieve viral suppression would enable providers to target patients most in need and tailor their care appropriately. This study involved multilevel modeling of data from a randomized controlled trial among outpatients in Seattle, WA, USA. The 224 participants initiating or switching ART at baseline were 24% female, 34% heterosexual, and 47% Caucasian. Of 24 baseline demographic and psychosocial patient-level variables modeled in separate generalized estimating equations, only employment predicted changes in HIV-1 RNA viral load or CD4 lymphocyte count over the course of the 9-month trial. Although the findings require replication, they suggest adherence support strategies should emphasize close monitoring and support for all patients initiating ART.

Keywords

HIV/AIDS; HAART; viral load; antiretroviral therapy

Introduction

Identification at antiretroviral therapy (ART) initiation of patients most at risk for therapeutic failure would enable providers to target scant resources toward patients most in need. Overwhelming evidence demonstrates suboptimal adherence is the primary driver of therapeutic failure (e.g., Bangsberg et al., 2000; Lima et al., 2009). Studies have identified many patient-related variables associated with adherence that could readily be assessed at ART initiation, including socio-demographics and mental health factors (Ammassari et al., 2002; Machtinger & Bangsberg, 2005; Mills, Nachega, Bangsberg, et al., 2006; Ortego et al., 2011). However, adherence does not fully account for viral suppression and is unknown at treatment initiation. Research is needed, therefore, on other possible predictors of therapeutic nonresponse that would be suitable targets for early intervention.

Several studies have identified patient characteristics associated with viral suppression, including higher age (Cescon et al., 2011; Li et al., 2011), male gender (Cescon et al., 2011), White race (Carrico et al., 2011), homosexual identity (Lampe et al., 2007), and drug use (Fairbairn et al., 2011). This is supported by research (Ironson et al., 2005) indicating that a number of psychosocial factors, including depression, hopelessness, avoidant coping, and negative life events contribute to viral load (VL) over time; indeed, Carrico et al. (2011) found that a mental illness diagnosis predicted a sixfold higher HIV-1 RNA VL.

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Shortcomings of this literature include the use of cross-sectional studies, bivariate analyses, and patients at various stages of treatment.

In the present study we use generalized estimating equations (GEE; Liang & Zeger, 1986) to evaluate 24 patient-level variables assessed at ART initiation as possible predictors of VL and CD4 lymphocyte count trajectories over the course of 9 months of treatment.

Methods

Procedures

Data for the present study derived from a prior randomized controlled trial evaluating peer support and pager text messaging to promote adherence (Simoni et al., 2009), in which participants were recruited from a primary care HIV clinic using advertisements, provider referral, and a nurse dedicated to recruitment. To be eligible, patients needed to be at least 18 years of age, proficient in English, living within pager service range, and starting a new regimen with at least two medications of ART(i.e., naive to ART, off ART for at least 6 months and restarting, or switching to a new regimen). Patients with cognitive impairments, active psychosis, or a known history of harming others were excluded. Researchers collected psychosocial data at baseline, 2 weeks, 3 months, 6 months, and 9 months.

Participants

Of 224 total participants, 210 completed assessments at 2 weeks, 205 at 3 months, 195 at 6 months, and 202 at 9 months. Participants were mainly low-income, with about half reporting less than $552 per month in income; approximately 80% were unemployed, and 79% had graduated high school. There were more men than women (n=169 and 53, respectively), and the mean age was 40 years (SD=8.2). Forty percent of participants had a steady partner, and 34% reported a heterosexual orientation. The average number of years since HIV diagnosis was 8.5 (SD=6.7), and 38% were naive to Highly Active Antiretroviral Therapy (HAART) at the start of the trial.

Measures

We investigated 24 patient-level demographic, psychosocial, and mental health variables collected at baseline. These were originally included based on their hypothesized association with adherence or biological outcomes or their possible moderating role in intervention efficacy (Yard, Huh, King, & Simoni, 2011). All continuous variables were standardized to a mean of zero and a standard deviation of one to facilitate interpretation. The predictors, with respective item counts, citations for instrument source, and reliability coefficients (if applicable) are listed in Table 1.

Viral load in copies per milliliter and CD4 lymphocyte counts in cells per cubic millimeter were taken from patient medical records when available within 30 days of an assessment time-point. Otherwise, they were obtained from blood draws on the day of the assessment interview. Since VL data were not normally distributed, they were log transformed and the transformed data were used in all analyses. Both biological outcomes were analyzed as continuous variables to maximize statistical power.

Data analysis

Two sets of longitudinal analyses were conducted using GEE to evaluate whether baseline demographic, psychosocial, and mental health variables prospectively predicted (1) VL and (2) CD4 trajectories over time. The intercept and slopes of these trajectories were predicted by the baseline patient variable with intervention condition and previous ART experience as covariates. Preliminary GEE analyses evaluating moderation by previous ART experience

indicated no statistically significant subgroup differences in the association between any of the 24 patient variables and biological outcome. Consequently, the final analyses combined patients across all stages of treatment. In accordance with Carrico et al. (2011), we did not control for adherence as it is in a causal path between the predictors and the outcomes. We assessed each patient variable in a separate longitudinal model. For the analysis of VL, we used a piecewise linear approach to account for the more rapid decrease in mean VL from baseline to 3 months compared with 3–9 months. For the CD4 analysis, we modeled longitudinal trajectories as a linear effect since mean outcome levels increased at a constant rate. The statistical test of each predictor was the omnibus test of the longitudinal trajectory (i.e., the predictor and predictor × time parameters). Because of the number of comparisons, we used the Benjamini and Hochberg (1995) alpha correction across each set of 24 analyses for each outcome. A multiple imputation using chained equations approach (Van Buuren, Brand, Groothuis-Oudshoorn, & Rubin, 2006) was utilized to address missing data, with the final results calculated as a pooled average across 10 multiply imputed data sets using Rubin's (1987) methodology.

Results

Generalized estimating equation (GEE) results for each predictor for both the VL and CD4 outcomes are provided in Table 1. The VL slopes are divided into two segments, corresponding with the initial slope from 0 to 3 months and the change in slope from 3 to 9 months, respectively. The CD4 slope is defined as a single linear effect from 0 to 9 months. No baseline variables prospectively predicted VL over time after Benjamini-Hochberg alpha correction. Participants who were employed part- or full-time (vs. unemployed) at baseline had a 30 cell/mm^3 greater improvement in CD4 count at each follow-up assessment; there were no other significant predictors of CD4 count.

Discussion

This secondary analysis of data from an adherence-promotion trial revealed that, with one exception, no patient-level demographic, psychosocial, or mental health variable assessed at baseline was associated with VL or CD4 trajectories over the 9-month study period. The exception was that part- or full-time employment (vs. unemployment) at baseline was associated with a steeper longitudinal increase in CD4 count. Prior research generally confirms an association between adherence and employment (e.g., Carballo et al., 2004; Kyser et al., 2011), perhaps due to the confounder of overall good health, which allows one to maintain gainful employment (Amico et al., 2007).

The results stand in contrast to studies mentioned earlier that demonstrated the association of various psychosocial variables and viral response (Carrico et al., 2011; Fairbairn et al., 2011; Ironson et al., 2005). One possible explanation for this discrepancy is that our sample was more strictly limited to participants initiating or switching therapeutic regimens. Alternatively, it is possible that viral resistance in some participants accounted for a lack of therapeutic response, thus obscuring the significance of potential predictors. However, we conducted a moderation analysis by stage of treatment and there were no statistically significant subgroup differences. Other methodological limitations may explain the null findings, including the sample's diversity due to few exclusion criteria which may have inflated type II error; the self-reported nature of the predictors which perhaps limited their predictive power, and the efficacious peer and pager intervention strategies (http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm), which might have addressed patient needs and obscured any power to identify significant predictors of nonresponse.

Further research on virologic response may yet identify some baseline characteristics amenable to intervention. Overall, the findings reinforce calls (Simoni, Amico, Pearson, & Malow, 2008; Simoni, Amico, Smith, &Nelson, 2010; Thompson et al., 2012) for individually tailored adherence strategies with frequent assessments of adherence and clinical biomarkers to identify problems before resistance develops or virologic breakthrough occurs, increasing the odds of successful therapeutic response for all patients.

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Table 1

GEE results predicting therapeutic response at 9 months from demographic, psychosocial, and mental health factors assessed at ART initiation among 224 HIV-positive patients in Seattle, WA, USA.

				HIV-1 RNA viral load (log_{10} copies/mL)				CD4 lymphocytes (cells/ mm^3)		
Variables	**Name of scale**	**#Items**	**Reliability**	**Int**	**$Slope_{pre}$**	**$Slope_{post}$**	**p_{omni}**	**Int**	**Slope**	**p_{omni}**
Demographics										
Age in years		1	–	−0.09	0.07	−0.07	0.85	−24.02	−0.29	0.45
ART naive (%)		1	–	0.46*	−0.25	0.03	0.02	−6.19	21.96*	0.04
Employed (%)		1	–	−0.22	0.07	−0.32	0.05	61.41	30.37*	**0.003**†
Female (%)		1	–	−0.10	0.16	−0.09	0.83	−12.79	6.57	0.74
Heterosexual (%)		1	–	−0.04	0.16	−0.15	0.90	−17.86	−14.49	0.10
HS graduate (%)		1	–	−0.15	−0.39	0.48	0.16	56.74	4.27	0.16
Income <$553/ month (%)		1	–	0.07	0.14	−0.08	0.42	−17.68	−24.04*	0.003
Partnered (%)		1	–	−0.02	0.00	0.05	0.97	0.78	−1.99	0.96
Race		3					0.60			0.58
Black vs. White			–	0.06	0.15	−0.07		−61.86*	5.22	
Latino vs. White			–	0.11	−0.25	0.27		11.78	5.70	
Other vs. White			–	−0.27	0.61	−0.76		−59.25	−10.55	
Years since diagnosis		1	–	−0.05	0.31*	−0.34*	0.08	−11.03	−3.64	0.32
Psychosocial										
Alcohol abuse	AUDIT	10	0.88	0.17	−0.11	0.06	0.23	−23.28	5.87	0.04
ART knowledge	*Investigator's*	13	0.63	−0.17	0.09	−0.11	0.37	33.95**	1.16	0.11
ART self-efficacy	*Investigator's*	14	0.96	−0.26**	0.20	−0.26	0.03	37.17**	−5.48	0.14
Drug abuse	DAST	28	0.89	0.13	−0.11	0.14	0.55	7.39	−4.56	0.35
General social support	MOS-SS	20	0.47	−0.09	0.07	−0.13	0.52	−20.59	6.03	0.16
Network orientation	NOS	20	0.77	0.03	−0.03	0.12	0.13	13.44	−8.21*	0.03
Perceived stress	PSS	14	0.86	0.19*	−0.23	0.24	0.27	3.02	−7.59*	0.03
Physical health status	MOS-HIV	20	0.80	−0.25**	0.21	−0.19	0.15	32.27**	6.86	0.02
Social desirability	MCSDS	10	0.57	−0.01	0.13	−0.09	0.32	−12.87	2.49	0.62
Spirituality	SBI-15	15	0.97	−0.03	−0.12	0.22	0.19	−23.73	1.04	0.30

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				HIV-1 RNA viral load (log_{10} copies/mL)				CD4 lymphocytes (cells/ mm^3)		
Variables	**Name of scale**	**#Items**	**Reliability**	**Int**	**$Slope_{pre}$**	**$Slope_{post}$**	**p_{omni}**	**Int**	**Slope**	**p_{omni}**
Mental health										
Depression	CES-D	20	0.92	0.14	−0.09	0.06	0.52	4.94	−7.23 *	0.04
Mental health status	MOS-HIV	24	0.94	−0.21 *	0.14	−0.12	0.22	12.03	7.86 *	0.03
State anxiety	STAI	10	0.89	0.13	−0.10	0.14	0.49	−2.26	−4.44	0.33
Trait anxiety	STAI	10	0.89	0.14	−0.12	0.14	0.54	7.26	−6.61	0.09

* $p<0.05$.

** $p<0.01$.

† Statistically significant after Benjamini-Hochberg alpha correction (bolded). All continuous measures were standardized (i.e., mean=0, SD=1).

Int, intercept; p_{omni}, omnibus p value; ART, antiretroviral therapy; AUDIT, Alcohol Use Disorders Test (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993); DAST, Drug Base Screening Test (Skinner, 1982); MOS-SS, Medical Outcome Study Social Support Survey (Sherbourne & Stewart, 1991); NOS, Network Orientation Scale (Vaux, 1985); PSS, Perceived Stress Scale (Cohen, Kamarck, &Mermelstein, 1983); STAI, State-Trait Anxiety Inventory (Spielberger, 1983); MOS-HIV, Medical Outcome Study HIV Health Survey (Hays, Sherbourne, & Mazel, 1995); MCSDS, Marlow-Crowne Social Desirability Scale (Crowne & Marlowe, 1980); SBI-15, Systems of Belief Inventory (Holland et al., 1998); CESD, Centers for Epidemiologic Studies Depression Scale (Radloff, 1977).