

Adherence to Antiretroviral Therapy among Patients Attending an Inner-City HIV Primary Care Clinic: Non-obvious Factors are Most Important

Abstract

Patient adherence is arguably the most important factor determining both individual and public health benefits of antiretroviral therapy (ART). Adherence issues also appear to be central in understanding the large disparities between African Americans and Whites in terms of lower rates of ART utilization and adherence. In an attempt to understand factors which constitute barriers or facilitators of adherence, particularly in African American populations, seven studies are reviewed which focus on the largely disadvantaged and African American patients receiving HIV care through the University of Maryland Medical System in Baltimore. Analysis of these studies reveals that ART adherence is better understood and predicted by “non-obvious,” complex, and often underlying factors, including the adverse circumstances which describe the HIV-infected individual who ends up receiving care in an emergency room and inpatient setting rather than from the same clinician in an outpatient clinic, patients’ subjective perceptions of their health care providers, mistrustful beliefs about HIV and its treatment, and dimensions of forgiveness and how these affect attitudes and behaviors about being HIV-infected and relating to others, medical systems, and God or spiritual being. More “obvious” factors such as knowledge of HIV and its treatment, “pill burden,” or providing external incentives or methods intended to help patients take their prescribed medicines do not play a significant role in adherence, and moreover, may have counter-intuitive effects, as discussed in two studies. We present a model of biodisparity, as the biological entrenchment of socioeconomic and healthcare access disparities, resulting from the conjoint influence of suboptimal adherence and the transmission of drug resistant virus within isolated social networks and disadvantaged sub-populations.

Keywords: Adherence, Antiretroviral therapy; *Biodisparity*; Transmission risk behaviors; Biopsychosocial; Attributions; Forgiveness

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Abbreviations: cART/ART: Combination Antiretroviral Therapy; ARVs: Antiretrovirals; DOT: Directly Observed Therapy; IHV: Institute of Human Virology; HIVDR: HIV Drug Resistance; HIV+: HIV-Positive (HIV-Infected); PrEP: Pre-Exposure Prophylaxis; VSRM: Vignette Similarity Rating Method; VL: Viral Load; WHO QOL: World Health Organization’s Quality of Life scale

Introduction

Although new and ever more effective antiretrovirals (ARVs) for HIV/AIDS are continuously being developed, approved, and incorporated into HIV medical care in the US [1], it is increasingly clear that patient adherence is arguably the most important factor determining both individual and public health benefits of combination antiretroviral therapy (cART/ ART): durable viral suppression, improved CD4 cell count response, decreased drug resistance, sustainable treatment success, reduced hospitalizations, and decreased risk of HIV transmission [2-4]. Adherence issues also appear to be central in understanding the large disparities between African Americans and Whites in terms of HIV/AIDS diagnosis, disease progression, and treatment. African Americans not only have higher incidence and prevalence of HIV/AIDS and poorer survival times, compared to Whites

[5,6], but HIV-infected (HIV-positive, HIV+) African Americans also have lower rates of ART utilization and adherence [7-9]. Thus, it is critical to understand what factors constitute barriers or facilitators of adherence in different populations, particularly African Americans, in order to develop effective and appropriately tailored prevention and intervention approaches and integrate them into HIV medical care [10].

Although there is a large literature on adherence-related factors, most studies deal with “common-sense” or “obvious” factors such as “pill burden,” accurate knowledge about adherence and why it is important, or patients “forgetting” to take their prescribed medications, the problem with looking only at these factors is that there is often an unwarranted leap to implementing “common-sense” interventions. Many of these interventions, such as those involving educational curricula and methods to “remind” or “help” patients to take their medications are implemented, usually at considerable expense in terms of staffing, without conducting the necessary research to demonstrate that such “obvious” factors are indeed causally, predictively, or even concomitantly linked to ART adherence, and/or without conducting randomized controlled clinical trials to evaluate whether such “common-sense” interventions in fact enhance adherence, produce the desired

virologic, immunologic, and clinical outcomes, and are sustainable not just over a few months but for a year or more, considering the years (essentially, a lifetime) that successful ART entails.

To provide an apt illustration: the Division of Clinical Care and Research of the Institute of Human Virology (IHV) instituted a “treatment delivery program” intended to enhance adherence among the predominantly African-American inner-city patient population in Baltimore served by the University of Maryland Medical System. As described in a 2004 paper [11], what was called the JACQUES Initiative adherence program consisted of an intensive “pre-treatment interactive treatment preparation curriculum,” centered on information about HIV, concepts of resistance, and the importance of adherence, after which patients self-selected one of 6 tracts as a “treatment delivery” option. These included daily or weekly (with pillboxes) directly observed therapy (DOT), which were chosen by 96% of the first 70 patients enrolled in the program, treatment “coaches,” treatment or care “partners,” or the option of self-administration (standard of care), which turned out not to be selected by anyone. Although there were apparently no publications resulting from a formal evaluation of this “treatment delivery” program, anecdotal observations suggested that what seemed to be the short-term (3 and 6 month) success of this program in terms of viral suppression, which was reported as preliminary data in the 2004 paper [11] was not evident with longer-term follow-up, especially when intention to treat was considered. Ancillary factors which, in retrospect, appeared to be important in influencing short-term adherence to the DOT options, such as free meals, other incentives, and rewards for > 95% ART adherence were not taken into account. Without such assessment, it is not possible to determine conclusively what caused the longer-term adherence drop off, but it seems likely that the discontinuation of these incentives and rewards after a certain period of time played a role. External rewards tend to motivate patients only as long as they are in place; once the reward is withdrawn, adherence can be expected to decline, as previous research has found.

A less obvious, more psychological explanation may also be operating in this situation. Social psychological attribution theory [12,13] seeks to explain how people perceive, infer, and/or ascribe causes for their own and others’ motivations and behaviors in a given situation. For example, if I learned someone was taking a medication and being paid to do this, I might reasonably conclude that the drug is experimental, potentially risky, and/or has a number of side-effects for which the monetary incentive is meant to compensate or otherwise induce someone to take that drug. The same considerations would apply to self-attribution, i.e., the simplest, most readily available answer to the question, “why am I coming every day to get ART at this clinic?” would be “because I get a free lunch, as well as travel expenses, and other rewards which I really like,” rather than “because I understand that taking ART every day will lower my viral load (VL), prevent the development of resistance, and I really want to get my HIV under control.” Thus, when the meals and other incentives are discontinued, the individual who had been so incentivized does not have the same “reasons” for showing up every day at the clinic for ART. In fact, according to attribution theory, that individual would be less likely to develop an intrinsic motivation to take ART or to attribute effectiveness to ART precisely because the external motivation of monetary incentives was sufficient as a self-attribution. To

elaborate further, most adults have a lifetime of experience in which they pay often steep prices for effective medicines, rather than being paid to take them; therefore, if people are being paid to take a particular drug, they might reasonably conclude that its effectiveness has not been proven or that there is something wrong with it. All of the foregoing commentary is completely consistent with more than a half-century of social psychological research on attribution theory [14].

No results were published concerning the longer-term efficacy of the “treatment delivery” program described in the 2004 article [11], leading this observer to attribute the absence of publications to the absence of positive findings. There was a much later poster [15] which described a “supportive care delivery” model applied to patients seen in the same aforementioned JACQUES Initiative at the IHV. There was no mention of daily or weekly DOT, (although “peer support” and “integrated pharmacy” were listed as core services), so it is reasonable to conclude that DOT as an adherence intervention was discontinued. The later poster presented the following statistics: 630 patients were seen between 2007 and 2012, 77% (116) of the “retained clients” were placed on ART, of whom 89% (103) were “virally suppressed,” defined as having a viral load (VL) of less than 200, at > 1 year. While the 89% figure may sound impressive initially, it is important to point out that patients who were virally suppressed represent only a small subset of all the patients served by this program. Critical questions to ask include: What factors characterized patients lost to follow-up? Why were so many clients not retained in medical care? Why were 23% of the patients who were retained in care not receiving ART? What sociodemographic, clinical, and/or psychosocial factors characterized patients in care who received or did not receive ART? What factors characterized patients placed on ART who were not virally suppressed? And finally, why were the daily and weekly DOT programs discontinued?

This paper will summarize and discuss a series of studies focused on the less obvious and arguably more salient factors influencing ART adherence in this same predominantly African-American, inner-city Baltimore population (although not necessarily the same individual patients) as served by the treatment/ care “delivery” programs described above [11,15]. All these studies were conducted by the Behavioral Medicine Program of the IHV under the direction of the author in an HIV primary care outpatient clinic, The Evelyn Jordan Center, within the University of Maryland Medical System (UMMS), where most of the patients seen in the IHV’s treatment/ care delivery programs received their medical care. One study was also conducted in the UMMS inpatient infectious disease unit. Research was informed by a biopsychosocial approach [16], which examines a comprehensive set of biomedical, psychological, behavioral, sociodemographic, and cultural factors which could potentially influence adherence, including those factors which are non-obvious, complex, underlying, less available to conscious awareness, and thus difficult to self-report. Our research, which is congruent with other biopsychosocial research on adherence, found that the “non-obvious” factors which we assessed predicted adherence better than more obvious factors such as patients’ knowledge about HIV and treatment resistance, “pill burden,” or even their understanding of the details of their drug regimen.

All of the studies reviewed here utilized more complex

assessment methods which went considerably beyond self-report. Although accurate assessment is critical to the validity of adherence research—and indeed, any research, it is clear that many factors undermine the accurate reporting of nonadherence. Patients often misrepresent their medication usage for a variety of motives, including fear of negative consequences (e.g., disapproval, withdrawal of treatment), the desire to appear cooperative and compliant, and perceived physician expectations. One problem for accurate assessment in the “treatment delivery” program described in the earlier publication [11], which was focused on the same patient population is that there were serious disincentives for admitting to lapses in adherence, including loss of rewards or the risk of being dropped from the study. We found, however, that our Behavioral Medicine program investigators were able to create circumstances which facilitated more honest disclosure of adherence problems, for example, by establishing a neutral interview environment with someone other than an authority figure or a provider involved in the patient’s medical treatment, and reassuring patients that adherence issues are common, so it is OK and in fact important and useful to talk about this.

Most of the studies described below utilized an innovative assessment technique developed by the author, the Vignette Similarity Rating Method [VSRM], which reduces the social desirability bias of self-report questionnaires by presenting a series of vivid, accessible, and non-judgmentally worded one-paragraph vignettes depicting the thoughts and behaviors of sympathetic and culturally appropriate characters reacting to relevant medical situations [17-19]. In asking participants to rate their similarity to characters who, for example, have trouble taking their prescribed medications for various relatable reasons, an individual is more likely to endorse strong similarity to these characters in the vignettes than to provide truthful answers on a questionnaire which might ask, “how often in the past week did you miss taking your ART as prescribed? Why?”

It should be noted that all the research reported below was based on voluntary, fully informed consent, and participants were reimbursed only for their transportation costs and their time involved in answering research questions, not for participating in psychosocial or biomedical interventions from which they could derive some benefit.

Relationship factors related to art adherence: HIV+ inpatients vs. outpatients

It is an axiom of clinical practice in medicine that the patient’s relationship with his or her physician or main health care provider is critical for the patient’s adherence to prescribed regimens, including engagement in care, showing up for scheduled appointments, and ultimately, more favorable clinical outcomes [20]. Behavioral scientists have documented that the patient-clinician relationship influences patient and adherence to ART [21]. What about the HIV+ individual who does not regularly see the same healthcare provider for his or her HIV care, or who may not even have a main HIV clinician, who seeks HIV care in an emergency clinic only when symptoms are so serious that they can no longer be ignored, and who, consequently, may end up hospitalized as an inpatient? The first study described below

focuses on differences in ART adherence, patterns of seeking HIV care, and indicators of psychological, cognitive, and social functioning between HIV+ outpatients and inpatients. Most of the prior research on ART adherence has been with outpatients; little is known about adherence among HIV+ hospital inpatients.

In this study [22,23], 200 HIV+ inpatients and 132 HIV+ outpatients (53% male, 92% African-American) completed a one-half hour semi-structured interview conducted by an experienced clinical psychologist to obtain social and demographic data; health-relevant behavioral data on quality of life, psychological and social functioning, substance use, smoking, nutrition; adherence to ART, adapting the commonly used AIDS Clinical Trials Group (ACTG) adherence questionnaire [3], which asks about missed doses over the past 4 days, and defines optimal adherence as taking at least 95% of the prescribed medication over the 4 days prior to assessment, with lower levels of adherence defined as 90-94%, 80-89%, 70-79%, and < 70%; as well as potential co-factors found in the literature to be related to adherence (e.g., depression, stressors, cognitive impairment). This semi-structured interview was designed for, validated within, and used extensively in this clinic population.

Inpatients reported missing significantly ($p < .001$) more doses of ART in the week prior to hospitalization than did outpatients. The 40% of inpatients who were taking ART reported that they missed an average of 7.5 doses in the week prior to hospitalization, compared to outpatients, who reported missing an average of 1.8 doses of ART in the past week.

Inpatients reported a dramatic pattern of inadequate HIV treatment and lack of engagement in HIV care prior to their hospitalization. Inpatients were significantly less likely to have a regular HIV clinician ($p < .001$) or to have seen an HIV clinical specialist in the 6 months prior to hospitalization; 35% of inpatients had not seen an HIV clinician in the past 6 months, while all of the outpatients had. Those in care reported lower satisfaction and poorer relationships with their treatment providers ($p < .001$).

Although inpatients and outpatients were drawn from the same inner-city Baltimore population, inpatients demonstrated much higher levels of psychological problems, which previous research has shown to be associated with nonadherence, including social instability ($p = .05$), depressive symptoms ($p = .003$), symptoms of more severe mental illness, such as hallucinations and manic episodes ($p < .001$), recent heroin or cocaine use ($p < .001$), cognitive dysfunction ($p < .001$), and more severe life stressors ($p < .001$).

This study documented the confluence of variables reflecting adverse psychological, social, and medical circumstances which describe the HIV+ individual who ends up receiving sporadic inpatient HIV care, rather than more systematically organized and planned care from the same clinician in an outpatient setting. Given these circumstances, it is perhaps not surprising that HIV+ inpatients are significantly less adherent to ART, and report poorer relationships with their treatment providers. While this study was able to document a rather somber and concerning picture of these patients, it was not able to address questions

of causality. It is probably not necessary to definitely separate correlation from cause, however, in order to develop interventions to increase adherence to ART, engagement in care, and more successful treatment outcomes for individuals who have more social instability, and/or significant mental health / substance use concerns. This study underlines the need for such interventions to be comprehensive and integrated with HIV medical care [10], and to address the wider scope of psychosocial factors which affect ART adherence, including, importantly, relationships with treatment providers.

Patients' subjective perceptions of health care providers significantly predict adherence

Another study of patient-clinician relationship factors on ART adherence focused on the often-overlooked factor of the quality of these relationships [24]. Such research is inherently challenging, because (1) many clinicians, quite naturally, are often unwilling to view themselves as influential or even partly responsible for their patients' nonadherence to their prescribed medicine, preferring to blame, instead, patients' unstable living situation, substance use, depression, or lack of motivation; (2) measuring the important dimensions of the clinician-patient relationship is difficult and prone to social desirability bias, particularly when the patient is asked in an interview or on a self-report measure to be potentially critical of a powerful medical authority who is seen as making often literally life or death decisions about patients' health.

To address this second point, the author created a series of "clinician-patient relationship" vignettes, adapting her Vignette Similarity Rating Method (VSRM), such that study participants were asked to rate their similarity to characters who feel either more positive, trusting, and confident in their doctors or negative, mistrusting, and lacking confidence (e.g., "...Having to come to the clinic is just one more problem for Mary. It's not like the doctors can do anything for her anyway-- they keep pushing medicines on her, but she knows there still isn't a cure...Mary's doctor might pretend to care about her, but she feels that if he really did, he would find some way to make her feel better...").

Participants in this study were 70 HIV+ adults (90% African-American, 36% female, mean age 44, 56% infected through IHW drug use, 20% infected through heterosexual sex, 18% infected through male-male sex). In addition to assessing relationship factors using the Clinician-Patient Relationship Perceptions VSRM, participants also completed the World Health Organization's Quality of Life scale (WHO QOL). Missed ART doses, psychological symptoms, and life stressors were assessed using the same validated semi-structured interview described in the previous study.

Significant correlates of missed doses in the past week included depressive symptoms, social instability, life stressors, and severity of life stressors—all factors described in the wider ART adherence literature. The strongest and most significant correlates with missed ART doses in the past week, however, were trust and confidence in medical providers, as assessed by the VSRM ($r = -.434$, $p = .003$), and subjective satisfaction with physical health, as assessed by the WHO QOL ($r = -.55$, $p < .001$). The observed correlation between subjective health satisfaction

and missed doses was not found to be mediated by differences in objective indicators of health, such as CD4+ count or disease staging.

Both subjective physical health satisfaction and the quality of the clinician-patient relationship emerged as significant predictors of missed doses in the past week ($p = .015$), even after the usual culprits found to affect adherence (depression, stress, and social instability) were statistically controlled.

Important lessons to be learned from this study include the importance of patients' subjective perceptions of both their physical health and their relationships with healthcare providers. When non-adherence is a problem, it may be helpful to focus on enhancing patient-clinician relationships, and digging deeper into the reasons underlying patients' subjective sense of health concerns, even when so-called objective indicators do not reveal any problems.

Mistrustful beliefs about HIV and its treatment affect whether HIV+ patients elect to take ART

Understanding subjective perceptions and beliefs about HIV and its treatment among African Americans, particularly those in disadvantaged, inner-city sub-populations, is critical in order to address a long-standing legacy of mistrust of medical systems and doctors, which date back to the Tuskegee Syphilis study and beyond. Surveys of the general African-American population, which did not ask about HIV status, have found widespread endorsement of so-called HIV "conspiracy theories" and beliefs. These surveys revealed deep-seated mistrust of medical systems and providers, such as "the government is withholding information about HIV," "a cure is being withheld from the poor," and that people on AIDS drugs are "human guinea pigs" [25-27]. Although the U.S. HIV epidemic is increasingly concentrated in the African-American population, the extent of such beliefs among HIV+ African Americans and the implications for racial disparities in access to care, cooperation with medical providers, and ART adherence have not been well studied until relatively recently [8,9]. The study described below, conducted in the same Baltimore outpatient HIV clinic as in the previously described studies, was possibly the first to examine mistrustful beliefs about HIV and treatment among HIV+ African-American patients and the connection to initiating and/or adhering to HIV treatment [28].

The 111 HIV+ African-American adult study participants (45% female; mean age 43) completed a questionnaire assessing endorsement of common HIV "conspiracy theories," mistrustful and/or inaccurate beliefs about HIV treatment, as well as more positive views of HIV research and treatment. Participants' ART status and adherence were assessed using the previously described semi-structured interview. Optimal adherence was defined as taking at least 95% of prescribed medication over the week prior to assessment, following the most common usage in the HIV ART adherence literature at the time of the study [2-4].

Several "conspiracy theories" were endorsed by conspicuously high percentages of the sample: "the government created HIV" (34.7%); "a secret cure exists" (25.6%), "drug companies are not interested in curing HIV" (35.5%); "HIV is a genocidal plot against minorities" (18.2%); and "HIV has not been proven to

cause AIDS" (14.7%). The 47% of the sample who were not taking ART were significantly more likely to believe that the government created HIV ($t = 2.08, p = .04$), that a secret cure exists ($t = 3.31, p = .001$), that HIV doctors unfairly experiment on minorities ($t = 2.60, p = .011$), and that HIV has not been proven to cause AIDS ($t = 2.84, p = .006$). Participants not taking ART were also significantly less likely to report that they could trust their doctors ($t = -2.01, p = .047$). Among the 53% of the sample who were already taking ART, conspiracy beliefs were not significantly related to ART adherence, although one could hypothesize that new items written to reflect more nuanced, less stark, albeit still mistrustful beliefs might be better able to reveal differences in adherence. This finding can also be interpreted in light of the previous discussion of attribution theory. In other words, patients already taking ART are more likely to make self-attributions that they believe this treatment could work and that the prescribing clinician can be trusted.

Although mistrustful beliefs were more common among persons not on ART, such beliefs were endorsed by a surprising number of patients receiving ART, who were engaged in care to the extent that they had shown up for their scheduled medical appointments, and volunteered to be in this study. Patients receiving ART had been provided the most up-to-date education and informational resources about HIV and its treatment from their HIV healthcare providers at the IHV, several of whom were also African-American. These findings suggest that HIV+ African Americans from the same population who were not in care or only sporadically in care would hold even more mistrustful beliefs. Further research is necessary to determine whether and to what extent mistrustful beliefs cause some patients to reject or delay ART, or to avoid seeking care at larger health care organizations such as the University of Maryland in Baltimore. Our findings underline the importance of developing interventions and programs to address inaccurate beliefs and the associated mistrust of healthcare providers and organizations, so that more HIV+ individuals, particularly African Americans living in disadvantaged inner-city circumstances, are able to receive optimal HIV treatment.

Dimensions of Forgiveness and ART Adherence

Because of the intense fear and stigma still associated with HIV/AIDS, many persons living with HIV feel alienated from their families, communities, and places of worship. This sense of alienation is often intensified by feelings of shame or betrayal associated with stigmatized routes of HIV transmission (e.g., male-male sex, injection drug use). These factors combine to cast the multidimensional construct of forgiveness into a central role for HIV+ individuals [29]. This next study focuses on dimensions of forgiveness as rarely considered reflections of an individual's important relationships: with oneself, important others--including family and sexual partners, healthcare providers and the wider medical system, and God or spiritual being [30].

Forgiveness was conceptualized as a multidimensional construct involving aspects of both forgiving and of feeling forgiven, considered across multiple contexts: Intrapersonal (e.g., forgiving oneself or not for risk behaviors or circumstances of infection); Interpersonal (e.g., forgiving or not the person believed to have infected one with HIV; feeling forgiven or not by family

members who may feel burdened and/or stigmatized in having an HIV+ family member); Medical (e.g., forgiving or not one's doctors and the medical system for the inadequacy of treatment and medicine's failure to find a cure; feeling forgiven or not by one's doctor for missing appointments and ART doses); Spiritual (e.g., feeling forgiven, as opposed to punished, by God; forgiving God for allowing HIV to exist in the world, or blaming and not forgiving God for one's infection) [29].

Participants were 131 HIV+ patients attending the same Baltimore HIV primary care outpatient clinic as in the studies previously described. The sample was 44% female, 91% African-American, mean age 42, with an average of 8.5 years since their HIV diagnosis. Reported routes of transmission were intravenous drug use (50%), heterosexual sex (28%), and male-male sex (14%). At the time of study entry, 91% of the participants were currently being prescribed ART.

Forgiveness was assessed using the VSRM [17-19], with 12 scenarios adapted to depict forgiving-or not, and feeling forgiven-or not, in different contexts (intrapersonal, interpersonal, medical, and spiritual). In addition to the semi-structured interview previously described, participants also completed the Religious Commitment Inventory, a measure of involvement in religious institutions and depth of personal religious commitment, and the previously described WHO QOL.

Of the participants who were prescribed ART, high ratings of similarity on the VSRM to characters who felt unforgiven by important others were associated with significantly more missed doses of medication in the past week ($r = .295, p = .005$). A complementary finding was that participants who identified more strongly with the vignette characters who were more forgiving of the person believed to have infected him or her were significantly less likely to have unprotected sex ($r = -.189, p = .03$), and thus, less likely to transmit HIV to uninfected partners.

Participants who rated themselves as more similar to characters in the forgiving vignettes and less similar to those in the unforgiving vignettes also reported fewer depressive symptoms ($r = -.435, p < .001$). They identified fewer life stressors ($r = -.233, p = .007$) of lower severity ($r = -.318, p < .001$). On the WHO QOL, both global QOL ($r = .322, p < .001$) and health QOL ($r = .341, p < .001$) were correlated with higher similarity ratings to the forgiveness vignettes. Thus, forgiveness was broadly associated with more positive psychological functioning and greater life and health satisfaction.

Participants who described themselves as more deeply involved in religious communities and activities, as measured by the Religious Commitment Inventory, reported fewer depressive symptoms ($r = -.243, p = .005$), higher global quality of life ($r = .264, p = .002$), and higher subjective satisfaction with health ($r = .322, p < .001$), as measured by the Health QOL subscale of the WHO QOL. Although they did not report fewer life stressors than other participants, the stressors they described tended to be of significantly lower severity ($r = -.307, p < .001$). Participants who reported a higher degree of religious involvement reported significantly fewer sexual partners in the past two years ($r = -.18, p = .04$).

For this sample of largely disadvantaged African-American

patients, feeling forgiven, particularly in the context of important others, was associated with better ART adherence. The multidimensional construct of forgiveness was strongly associated with depression, life stress, and quality of life, all variables associated in our studies, as well as in the wider literature, with poorer adherence. This suggests that it would be important to elucidate the larger pattern and underlying connections among all these variables in order to develop more effective interventions to enhance ART adherence in this population. Another implication of these findings is that it would be a mistake to treat each variable associated with adherence in isolation, for example, prescribing poorly adherent patients anti-depressants, without understanding and addressing the possibility that an individual feels depressed, with the consequent feelings of unworthiness, because he or she feels guilty about having acquired HIV and feels unforgiven by significant others. Until patients feel that they deserve to feel better, deserve the best possible HIV treatment, and certainly do not “deserve” to be stigmatized or blamed-including by themselves-because they acquired HIV, they will probably not be optimally adherent with their prescribed regimen, no matter how many times they are lectured about its importance or “reminded” to take their pills.

This study’s findings regarding the association of forgiveness factors and religious involvement with reduced transmission risk behaviors have important implications not only for the patient’s own health, but also for preventing the spread of HIV to others. The close relationship between better ART adherence and preventing HIV transmission is highlighted in the next study described below.

Suboptimal adherence and transmission risk behaviors: implications for developing *biodisparity*

Although nearly all HIV behavioral prevention research in the first decade of the HIV epidemic focused on primary prevention, i.e., reducing the risk of exposure to and acquisition of HIV, research on secondary prevention-reducing the risk of HIV transmission by already infected individuals began to emerge in the late 1990s [31]. A number of studies in different populations documented the concerning levels of HIV transmission risk behaviors, even among individuals who knew their HIV+ status [32].

HIV+ individuals who continue to engage in transmission risk behaviors, including unprotected sex and sharing needles/ drug equipment, place their negative partners at high risk of infection with HIV, including drug-resistant HIV (HIVDR). Studies have documented concerning numbers of treatment-naïve patients presenting with HIVDR [33], which they could only have acquired from an HIV+ partner who had such resistance. Suboptimal adherence to ART facilitates the selection and emergence of mutated and drug resistant strains of HIV, a significant and by now, extensively documented problem which compromises effective ART, leading to treatment failure and ultimately, disease progression [34]. Moreover, HIV drug resistance (HIVDR) complicates ART, in that resistance to some drugs may confer cross-resistance to other classes of ARVs [35].

Although the risk of new HIVDR infections have received the most attention, researchers have documented the growing problem of “HIV-1 superinfection,” defined as the reinfection

of an HIV+ individual with a second heterologous strain of HIV [36,37], which could be drug-resistant [38], and/or co-infection with other sexually transmitted infections which can further complicate treatment and exacerbate disease progression [39].

Studies by our Behavioral Medicine team in Baltimore [40,41] revealed that both sexual risk behaviors and suboptimal adherence were common among a sample of 131 patients (91% African-American, 44% female; mean age 42.4; mean 8.6 years since diagnosis) from the same inner-city Baltimore HIV clinic described previously. Among the 70% of patients who were being prescribed ART at the time of the assessment, 46% fell below the 95% adherence level considered minimally necessary to prevent the development of drug resistance. Participants missed an average of 3.7 doses of ART in the previous week.

A clinically significant proportion of participants reported engaging in sexual behaviors which could result in HIV transmission to uninfected partners or “super-infection” of HIV+ partners: 34% had inconsistent condom use during vaginal sex; 70% had inconsistent condom use during oral sex; 66% reported a recent partner of negative/unknown serostatus; 19% admitted concealing their HIV status from a partner. Inconsistent condom use was more common with HIV+ partners, in those with less education, and in those reporting higher levels of unsupportive social interactions. Participants whose sexual partners were all HIV+ had higher levels of sexual risk behaviors than those with one or more HIV-negative partners ($p=.004$). Risk-relevant behaviors were far more common with HIV+ partners than with partners of negative or unknown serostatus. A majority of these participants reported that they believed that having sex with seroconcordant partners constitutes effective prevention.

Our findings of the complex associations between HIV transmission risk behavior and suboptimal adherence among largely disadvantaged and African-American HIV+ patients in Baltimore were also reported independently by several other groups of US behavioral investigators around this same time [42-45]. Mathematical modelers predicted that the HIV epidemic would become increasingly difficult to control with even the best ART if there were increased transmission of drug-resistant HIV [46,47].

To the extent that both suboptimal adherence and transmission risk behaviors may be more common in socially isolated inner-city populations, sub-populations, or neighborhoods which are characterized by social, economic, and healthcare access disparities, multi-drug resistant HIV is more likely to spread within these segregated sexual networks [31,40,41]. Consequently, the observed socioeconomic disparities, reduced access to optimal ART, and poorer HIV outcomes may become biologically entrenched, as HIVDR that is more difficult to treat becomes differentially more common within disadvantaged sub-populations. We have coined the term *biodisparity* to refer to this potential scenario, in which a convergence of factors results in the epidemic spread of HIVDR within socially isolated sexual networks [31,40,41]. Hypothetically, with increasing HIV *biodisparity*, HIVDR will become concentrated within certain sub-populations, groups, communities, and/or neighborhoods,

resulting in biologically limited treatment options for their constituents (Figure 1).

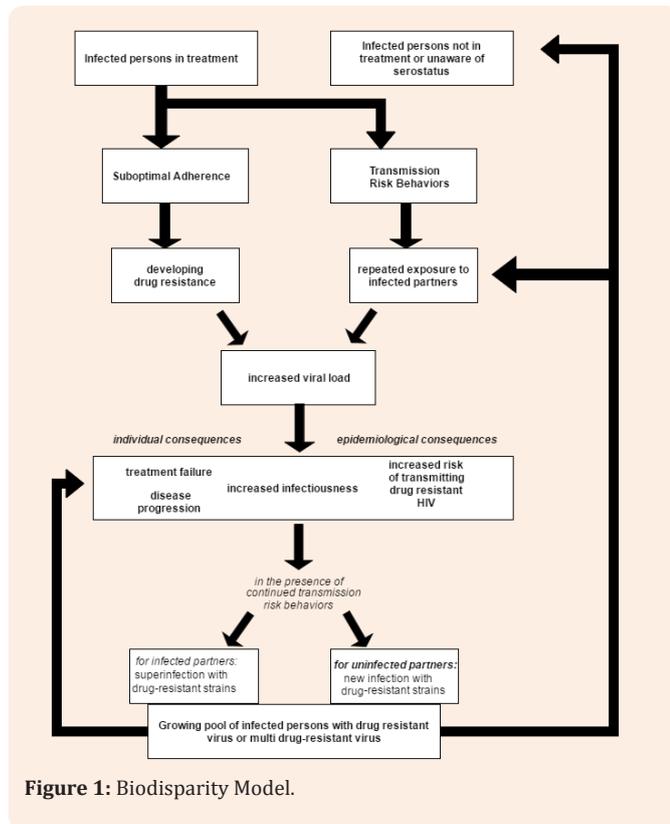


Figure 1: Biodisparity Model.

Number of medicines in one pill vs. doses taken predicts key indicators of clinical outcomes

“Pill burden,” i.e., the number of pills prescribed, has long been assumed by HIV clinicians to be a contributing factor to nonadherence. In response, the pharmaceutical industry has developed pills combining two or three medications (e.g., Truvada, Trizivir, Atripla), so that patients only have to take a single pill (or two) rather than several. Perhaps because this seemed to be such an obvious improvement, there have been no studies (which we could find) testing this assumption and its impact on adherence and clinical outcomes [31].

The last study conducted by our Behavioral Medicine program to be reviewed here evaluated adherence and clinical outcome indicators (VL and CD4+ cell count [cells/mm³]) at baseline and 6-month follow-up in 395 largely (96%) African-American HIV+ men (N =204) and women (N =186) in the same Baltimore HIV outpatient clinic and inpatient infectious disease unit as in the previous studies described above [48]. There was no difference in adherence defined as number of missed doses over the previous 4 days between patients taking one pill containing 2-3 ARVs and those who took more pills at the same time, each with a single ARV; however, those taking 2-3 ARVs combined into one pill missed more medications in total. For all patients with available

6-month follow-up data (N = 177), defining suboptimal adherence as the total number of missed medicines (vs. the number of missed doses) was the most significant and predictive measure of both log VL (p =.05), and log CD4+ cell count (p = .004).

These findings call into question the prevailing idea that pill burden is one of the primary causes of suboptimal adherence and treatment failure. Instead, this study documents that HIV+ patients who have trouble taking three pills at the same time are just as likely to have trouble taking 2-3 medicines combined into one pill. Moreover, results suggest that missing one pill combining 2-3 ARVs, particularly Truvada, will result in unfavorable clinical outcome indicators (detectable VL and lower CD4+ cell count) at 6-month follow-up.

Although this study did not examine the reasons why taking one pill (containing 2-3 ARVs) was functionally and apparently psychologically equivalent to taking 2-3 separate ARVs at the same time, one hypothesis is that once someone is mentally and intentionally prepared for the action of taking pills, the effort to remind oneself to do this, find the pill box or bottles, get a glass of water, overcome the unpleasant thought that one has to take these pills because of being HIV+, and prepare for possible side effects, it really doesn’t matter at that point whether there are one, two, or three pills to take. A related hypothesis is that the person who misses taking one pill may think, “It’s just one dose,” forgetting that it contains 2-3 medications. On the other hand, the impact of missing a dose of three separate pills is psychologically greater, leading the person to think, perhaps, “oh no, I forgot to take my meds this morning! Well, I’ve got two of them here with me—I should just take these now and the other one when I get home.” It is not difficult to see how this might make a difference in clinical outcome indicators over time.

The seemingly counter-intuitive finding that missing one dose when this was a pill combining 2-3 medicines, rather than missing a dose consisting of 3 ARVs, results more quickly in unfavorable indicators of poorer clinical outcomes has important implications for other HIV “treatment as prevention” strategies, such as Pre-exposure Prophylaxis (PrEP) using Truvada, in which the effectiveness in reducing the risk of HIV infection is directly related to adherence [49].

Discussion

Antiretroviral therapy has improved dramatically the quality and quantity of life for people living with HIV; yet, many patients still view these medications with suspicion, and fail to take them as prescribed. There are now highly effective HIV medicines, but, in a quote attributed to the former US Surgeon General Dr. C. Everett Koop, “Drugs don’t work in people who don’t take them.” The studies described above, conducted in an HIV primary care clinic serving a largely African American and inner-city population, are remarkably consistent in showing that such “common sense” or obvious factors as pill burden, “forgetting,” knowledge of HIV-related information, and understanding the consequences of not taking one’s medicines as prescribed did *not* predict adherence. What all our studies showed was that it isn’t so much that patients “forget” to take their medicines and therefore

need to be “reminded” or to have their treatment “delivered” via some technology or method, it’s that they don’t want to take their medicines for various reasons, or they run up against more subtle but powerful psychological barriers. The factors that *did* predict more optimal adherence were non-obvious and complex, including mental health factors, little-researched concepts such as forgiveness, psychological attitudes and perceptions of taking medications, and underlying attitudes, attributions, and ways of perceiving, thinking about, and relating with health care providers and medical systems. Certainly, if the answer to why many patients and African-American patients, in particular, do not adhere well to ART were obvious and simple, it would have been addressed by now, deployed in the design of effective intervention programs, and ART adherence would not be such a problem today.

Optimal adherence depends on other non-obvious factors that go beyond trusting one’s healthcare provider, medical establishments, and authorities. Patients cannot be just educated or lectured into taking their medicines. Most of us, including people living with HIV, generally know what we should and should not be doing. The research described above by the IHV’s Behavioral Medicine program was aimed at understanding *why* people so often don’t do what is good for them, so that we can better help people to make healthier choices and take healthier actions. Real and lasting behavioral change in terms of optimal ART adherence can only come from helping people find the internal motivation to change what isn’t working for them, to better understand and address the obvious as well as less obvious obstacles to taking medications as prescribed, and to work in partnership with trusted medical providers to choose the course of treatment that is right for them, recognizing that they are not merely complying with what someone is telling them they should do.

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