Improving Adherence to Complex Medical Regimens through the Integration of Knowledge, Technology and Informatics.

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ABSTRACT
About 33.3 million people were living with HIV at the end of 2009. Over the past several years a significant investment in the scale up of antiretroviral therapy (ART) has contributed to both a reduction in AIDS-related morbidity and mortality and to a decline in new HIV infection. A total of 5.2 million people in low- and middle-income countries now receive antiretroviral therapy. Within several months of initiating ART most patients become asymptomatic and then must closely adhere to unforgiving drug regimens for life. Incomplete adherence to ART regimens results in treatment failure, the emergence of drug resistance and the transmission of drug resistant virus to uninfected individuals. This requirement for lifelong regimen adherence has proven to be the Achilles’ heel of antiretroviral therapy. Advances in the capability and affordability of mobile technologies present a new perspective on this paradigm. Combined with human and computer networks, mobile devices such as smart phones and tablets bring patients and providers together in previously impossible ways and may present real and lastingremedies for patient outreach and communication. In order to integrate the three major components of adherence: Information, Motivation and Behavioral Modification, we are developing open source pictographic software enabled for web and mobile platforms. We will use these tools to study ART adherence and motivation in low-literacy patients with the goal of enhancing patient comprehension and health. Cybernetic technologies utilizing mobile computing and pictogram interfaces can serve to communicate highly tailored information, evaluate regimen-specific knowledge and assess motivation and behavioral skills of patients requiring therapy. We expect this workshop will bring together all of the requisite expertise in informatics and cybernetics required to develop powerful computerized tools to ensure ART treatment success at the level of both individual patients and the population at large.

Key words: ART adherence, pictographic software, HIV adherence, tablets.

INTRODUCTION
The drug armamentarium developed to control HIV replication is unique in the history of medicine. Incomplete adherence to the treatment of HIV with the recommended drug regimens results in treatment failure, emergence of drug resistance and the transmission of drug resistant virus to uninfected individuals [1, 2]. Once treatment failure has occurred, the emergence of drug resistant viral variants usually requires the initiation of a new drug regimen that is selected on the basis of laboratory testing [3-5]. Unfortunately, after several rounds of treatment failure, more extensive drug resistance drives the selection of less well-tolerated and less convenient regimens. If patients are not able to adhere sufficiently to treatment, over time with successive treatment failures, multidrug resistant virus emerges and, ultimately, it is no longer possible to craft a fully suppressive treatment regimen [3, 4].

Several attempts have been made in the 30 years of the HIV epidemic to improve HIV adherence. Many studies have been performed and others are still ongoing to enhance adherence to antiretroviral treatment regimens (ART) [5]. The challenges to improving adherence to ART is based on several factors that have been categorized by Ickovics [6] into four groups: a) patients characteristics; b) patient-provider relationship; c) treatment regimen; and d) additional variables related to the treatment regimen (including associated illness, contextual or environmental factors). Other reports have emphasized additional challenges in antiretroviral therapy. Fear of disclosure of being HIV infected has been deterrent to starting therapy for many patients. Other factors that must be considered are the extent to which medications are perceived to interfere with daily life and the fact that both depression and forgetfulness are critical factors that affect adherence in medicine [7]. Today, over 30 different products in five different drug class targets are available for use in combinations designed to achieve optimal HIV viral suppression [8]. Although much progress has been made in simplifying drug regimens – especially first line therapy – antiretroviral therapy is unforgiving and it remains difficult for patients to adhere to drug treatment regimens. Many tools have been developed and tested that are designed to improve adherence. We are proposing a self-reporting electronic device that will be used by the patient and the providers to learn, instruct and evaluate patient readiness to begin and to adhere sufficiently to treatment to control viremia and improve immunological function over the longer term.

ATTEMPTS TO IMPROVE ART ADHERENCE
Nonadherence is a serious and challenging problem that complicates individual viral suppression in individual patients and compromises the global effort to prevent HIV transmission [9]. Several strategies it has been developed to enhance HIV medication adherence. These strategies can be grouped into five categories: 1-Cognitive strategies; 2- Behavioral strategies; 3- Affective strategies; 4-Drug treatment simplification.
1-Cognitive strategies: These are intervention strategies designed to instruct, clarify and teach the patient about HIV disease, how drug treatment works and why treatment interruption leads to treatment failure. This approach also, in addition, attempts to tailor specific education to ARV therapy (ART) intervention strategies. For example, nursing case management and individualized counseling by pharmacists have been reported to improve adherence above 90% in over 70% of patients in several clinical trials [10, 11]. Group education sessions appear to be difficult to implement because of high refusal rates [13-15]. A great challenge of cognitive aspect of a patient’s treatment adherence is the nature of the provider-patient dialogue in HIV care centers. A recently reported multisite study in a developed country revealed that only 10% of utterances were devoted to ARV treatment and only 23% of patients had any ARV problem solving with dialogue [12]. Apparently, single strategies are not enough to significantly improve adherence to ART. In Uganda, for example, a recent report of improving clinic attendance by comparing a standard adherence intervention package (SAP) and monthly self-monitoring of medication taking using adherence diaries versus a group that received additional treatment supporter initiatives that included regular individual and group education revealed no difference in the mean adherence between the two groups [13].

2-Behavioral strategies: These are designed to shape and reinforce the patient’s ability to take the treatment as recommended by their physician and to adapt this long term treatment commitment to their life style. It has been documented that HIV infected patients with substance abuse challenges, mental incompetence, dietary restrictions, homelessness and lack of education are often non-adherent to ARV treatment [14].

3-Affective strategies: These are designed to improve emotional and social support. Social economic factors such as social support from family and friends, psychological distress, depression and inadequate confidence in the treatment providers, which are the most common factors challenging adherence. Nonadherence to HAART was independently associated with worse depression rating scale scores, but not associated with neurocognitive impairment in a study of HIV patients in Europe [15]. Depressive symptoms were assessed among 324 people living with HIV/AIDS. Greater adherence to psychotrophic medication regardless of medication class of medication class was positively related to higher antiretroviral adherence [16].

4-Drug simplification: ARV therapy for HIV disease is used in a strategic order with a well-defined combination to ensure efficacy. The first line ARV currently available consists in one to three pills taken once daily [17, 18]. Regimens for individuals with drug resistance are usually require twice-daily regimens with a larger number of pills per day [8]. The ADONE (Adherence to ONE pill) study was performed to verify the effect of a reduced number of pills on adherence and quality of life (QoL) in HIV-infected patients on highly active antiretroviral therapy (HAART) [19]. Patients chronically treated with emtricitabine (FTC) + tenofovir (TDF) + efavirenz (EFV) or lamivudine (3TC) + TDF + EFV and with a HIV-RNA < 50 copies/mL were switched to the single-pill fixed-dose regimen (FDR) of FTC + TDF + EFV. The study revealed one month post switch to FDR the adherence rate increased significantly to 96.1% from a baseline value of 93.8% (P<0.01). ARV regimens design for multi-experienced patients are more complicated and third and fourth line regimens, in particular, often cause more side effects and toxicities [8] resulting in lower rates of adherence. In a cross-sectional study we performed in Brazil among 182 subjects on ARV therapy, 40% were highly adherent were in their first (and simplest) drug scheme compared to only 15% of those on the second or additional regimens [20].

As previously mentioned stigma about HIV can also be a barrier to adherence as can, food insecurity, health literacy and organization of the health care. In several African countries individuals who self-report missed medication over time also report higher levels of perceived HIV stigma [21]. In Malawi, hunger during HAART initiation emerged as a leading obstacle to ARV adherence [22]. Also, food insecurity is emerging as an important barrier to ARV adherence in Sub-Saharan Africa [23]. Similar data are reported in US peri-urban areas (defined as being at least 5 miles distant from a city) where 45% of participants with less than 85% adherence reported experiencing hunger during their ARV treatment [24]. The association between health literacy and ART adherence appears to be robust. Low literacy skills are closely related to understanding medication instruction and the need to plan for pharmacy refills in order to keep the long term commitment to antiretroviral therapy after AIDS symptoms disappear [25]. Evaluation of the effectiveness of ARV of countries such as Brazil that have implemented free access to ARV revealed that 24% of patients on ARV in a public clinic in Rio de Janeiro lacked supply of medication for more than a month at least once during the year [26].

METHODS FOR MEASURING ADHERENCE

An array of tools has been used to assess the level of adherence to ARV therapy [27]. Adherence has been measured in various ways: Two major categories are commonly employed: a) Patient-derived information (self-reported) and b) Methods for independently monitoring drug intake are electronic devices, pharmacy refill logs, pill counting or a combination of these methods.

a) Patient-derived information: Questionnaires are the most commonly used method in many intervention studies on adherence. The Patients Medication Adherence Questionnaire (PMAQ) is one of the most widely used questionnaires for assessing adherence in HIV infected patients, especially in clinical trials [28]. Patients may also self-report via interview with a member of the health care team. Walsh and colleagues [29] described a patient self-reported adherence instrument called the Medication
Adherence Self-Report Inventory (MASRI) that collects patient reports of missed doses electronically and a visual analogue scale that correlates with virological treatment outcome. SERAD (Self-Reported Adherence) questionnaire, a qualitative and quantitative self-reported instrument designed to provide an easier adherence measurement has shown good correlation with pill count, electronic monitoring, and plasma drug monitoring [30]. Several structured sets of questions on self-reported adherence are useful to measure adherence. However, the recognition of factors which are determinants of non-adherence must systematically be included in self-reported questionnaires; the most common of these factors are related to patient or medication-centered issues.

b) Patient independent drug monitoring techniques: There is no gold standard test for adherence monitoring. Directly Observed Therapy (DOT) is the most reliable one. It has been used with success in treating tuberculosis (TB) [31, 32]. It is less feasible in HIV since HIV requires lifelong daily drug therapy. It is thus extremely costly to fully apply DOT in clinical practice [33]. In addition, patient and family concerns about confidentiality also make it difficult to employ DOT for prolonged periods in HIV infection [34]. Community-based modified directly observed therapy (MDOT) is a promising approach that led to lower plasma HIV-1 RNA levels and higher CD4 cell counts in a cohort of HAART experienced substance users [35]. In one preliminary report six women with substance abuse and histories of poor adherence received daily antiretroviral directly observed therapy (DOT) and achieved undetectable plasma HIV-1 RNA levels by 6 months [36]. The Medication Event Monitoring System (MEMS) has been available for decades. A microchip housed in a plastic cap that fits on standard medication bottles records the date and time of each opening and closing of the medication bottle [29, 37]. MEMS adherence studies results were strongly correlated with concurrent viral load [38]. In one study, the mean self-reported 1-day adherence was 79% compared to electronic monitoring (MEMS) of 52%. However, MEMS correlated better with HIV viral load [39]. A major reason that MEMS adherence is lower than self-reported adherence is that the MEMS system is programmed to register opening the bottle. Unannounced pill counts conducted by telephone were demonstrated to be a viable alternative for objectively assessing medication adherence [40]. A high degree of concordance was observed between phone and home-based number of pills counted.

**READINESS FOR OPTIMAL ADHERENCE ART**

Several factors are correlated with the inability and ability of patients to take ARV medication. Many of these have been outlined in the manuscripts reviewed. Enriquez and Mckinsey [9] summarized in a table the majority of those factors divided in two columns:

**Barriers:** Substance abuse, Fear of disclosure of HIV status, Denial of the HIV diagnosis, Speaking a different language than the health care provider, Stigma, Depression, Forgetfulness, Suspicions about ARV treatment, Perceived unpleasant side-effects from ARV medications, High number of pills in an ARV regimen, Sleeping through medication dosing time, Decreased quality of life, Work and family responsibilities, Limited access to ARV medications, in addition to change daily routine, interference of ARV in their life, difficulties to understand prescriptions, inability to read written instruction, apathy, high stress, problems swollen tablets, inability to distinguish colors or identify makings medication are barriers to adherence ARV treatment.

**Facilitators:** Sense of self-worth, Seeing/feeling positive effects of ARV therapy, Strong will to live, Acceptance of the HIV diagnosis, Understanding the need for adherence, Making use of reminder tools such as pill organizers, Having an ARV regimen that “fits” into one’s daily schedule, Once daily dosing of ARV medications, ARV regimens that are considered to be too complicated, Presence of motivational readiness, Perception of a positive health care provider–patient relationship and Having social support.

Another important factor related to treatment success is the selection of the optimal time to initiate the ARV treatment. Most treatment guidelines strongly emphasize the need to fully prepare each patient for the initiation of therapy. Assessing the readiness for initiation of antiretroviral therapy has a special significance to physicians who provide daily care to people living with HIV/AIDS. Most HIV care providers already have a large file of patients with viruses that are resistant to most classes of ARV drugs. In the case of many of these patients treatment failure could have perhaps been avoided if a careful motivational readiness evaluation had been done. One challenge to the evaluation of Readiness is the lack of precise readiness measurement tools that can reliably predict which patients will fail therapy and, therefore, should delay treatment. In their comprehensive review of this topic Grimes et al., concluded that there is currently no viable predictor of adherence [41].

We have summarized the complexity of providing ARV therapy to people living with HIV/AIDS in the format of a Trilogy [27] that includes Information, Motivation and Behavioral skills.

**Information:** Information is the mainstay of adherence tools. Patients must have comprehensive knowledge of any disease including its cause and the undesirable consequences that will occur if no intervention is provided. In the case of HIV-1 infection the knowledge base includes the meanings of viral load and CD4 cell count as well as how ARV therapy will change the natural course of disease. Although the digestion of this information by a patient might appear to be very simple to the health care specialist, it is often extremely complex for individuals without a background in science. As treatments become more complex even more information must be explained to patient.

**Motivation:** Motivation is the second fundamental in the adherence trilogy. Even though a patient might know about
the disease, what HIV does to the immune system and how drugs will help control his or her disease, this knowledge will not necessarily lead to optimal adherence to therapy, if the patient is not also motivated. Motivation acts in the threshold limit of psychological disturbance. Depression is the biggest impediment to motivation. Often when a physician feels a patient is not motivated, the real problem is that the patient is depressed. A depressed patient is rarely enthusiastic about receiving therapy. Depression may be caused by external factors but it may also be an intrinsic aspect of the patient’s individual personality. Depression is common – nearly everyone has experienced a period or moment of low motivation or even a more profound depression. Depressed patients may fail to participate actively in care, may act negatively and may mirror the bad experience that they had with a friend or relative. Individual values are usually structured by motivation. In ancient times philosophers held that values are external to people. In the 1890’s a new philosophy concluded that values are intrinsic to each individual. Things have no value; people’s wishes are what give value to everything. Thus, the wishes built the values, and motivation transforms these values to action. In other words, patients define their values, and if they are treated with such a level of consideration in the hierarchy of his life, then they will be motivated to adhere to treatment.

Behavioral skills: Health care workers usually forget this third component of the trilogy. A prescription always is based on the most appropriate pharmacokinetics of the drugs, but often conflict with the patient’s habits. Usually a prescription will require that a patient change his life style. If the patient is able to adjust to this change in life style, the regimen may work temporarily. Dietary patterns, job activities and biorhythms are peculiar to each individual. For many individuals, these issues are considered to be private matters. Treatment must be adapted to the life style of the patient.

Thus, structuring treatment regimens to optimize adherence is quite complex and is far beyond the external attachment. Optimal adherence requires an integration of several critical factors that must thenceforth be part of life.

PATIENT COMPUTERIZED SELF-ADHERENCE TOOL (PCSA)

We are developing preliminary computerized software that includes three major parts Figure 1.

A-Patient evaluation of HIV knowledge. A series of questions related to knowledge of the disease and its therapy will be asked of each patient in a friendly manner using a computerized touch screen or a voice driven system. These questions will explore patient knowledge level about HIV infection and its therapy. What are the symptoms? How should it be treated? Which types of laboratory tests should be used and in what frequency? A fully validated questionnaire would also include measurements of motivation to fight against the disease as well as treatment preferences, beliefs and fears about the disease and its therapy. Each factor that might complicate adherence to a proposed ARV treatment will be specifically assessed.

B-Educational aspects for those living with HIV infection. The second aspect of the electronic interaction is constructed with a maximum of self-explanatory animated pictograms that patients can access as many times as desired. By the end of the electronic interaction the patient will understand the requirement of a minimum of 95% adherence for treatment success. When this is demonstrated, the patient is deemed to be ready to initiate therapy.

C-Proposed ARV treatment analysis. Based on the Bruin and Hospers [42] Theory of Planned Behavior (TPB), we will explore TPB by using specific pictograms with information of three determinants factors: Subjective Norm. We will explain subjective norms using animated pictograms that illustrate what the care team expects of the patient if treatment success is to be achieved.

Attitude: Using the same strategy we will access the patient’s beliefs in terms of how difficult it will be to start and maintain ARV treatment in the context of a personal cost and benefits outcome analysis. What are the required behaviors for successful adherence to therapy? The instrument, in short, provides the patient with objective feedback about self-perceived behavioral control. We will construct a structured algorithm using pictograms that will ultimately help each conclude either: “Yes, I can!” or “No, I am not yet prepared to successfully undertake optimal adherence behaviors for my own treatment regimen.

Feasibility. This system will be built on tablets that the patient can carry to his home or use at the hospital, clinic or public sector. This will allow each patient to take time necessary to assimilate the required adherence knowledge, motivation and behavior to initiate ARV treatment. Each patient will have access to a training assistant if needed to instruct in the correct operation of the tablet. In most settings, at 80% of patients are already proficient in the use of touch screen “smart” phones or computer interfaces and, thus, we expect that the ability to master use of the adherence assessment and instruction platform will be rather intuitive.

CONCLUSION

With this self-reporting tool for assessment of and instruction about the adherence trilogy we expect to have together all of the requisite expertise in informatics and cybernetics required to develop this powerful computerized tool to ensure ART treatment success at the level of both individual patients and the population at large
Footnote figure 1.

Promoting patient adherence and care through pictogram enhanced-tablet based communication. Above: Preliminary cloud tools will be based on the Pictogram Evaluation Authoring and Collaboration Environment (peace.ucsd.edu) currently under development by our US colleagues. 3.5, 5, 7 or 10.1 inch tablet devices (Android or iOS) with cellular connection may be used to access the system for patient assessment, pictogram validation or patient training. Future iterations will consist of native mobile clients specifically designed for HIV adherence. Bottom. Such a system will promote patient education and adherence through enhanced knowledge and ongoing feedback and communication. A cloud based database and reporting structure will enable efficient monitoring by providers as well as aggregate system reporting.

REFERENCES


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