

## Speech by David Barr

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Last night I was out at dinner and then some friends and I went on for a few drinks. We got to the bar at about 11:00 and as one drink led to another and more people came and went, the time rolled by. I was having a good time. I wasn't on drugs. I wasn't drunk. I was just happy to be out socializing and getting a feel for a new city. At one point, I looked at my watch and realized it was 2:30. I was over two hours late for my pills. I'm not really much of a party kind of guy. At home, I am quite happy to stay in. My routine is pretty set. I am also a very adherent guy. Sometimes I am late or early for my pills, but very rarely is it more than an hour either way. In almost three years of HAART, I've missed maybe five doses. Here a slight change of routine and I forgot about my medication and was later than I should be. Probably not a catastrophe and not the most compelling adherence story. But, it is telling as to how something as simple as hanging out with your friends can interfere with **HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY**.

I was thirty-three when I found out I was infected. I am forty-three now. I had under 350 t-cells ten years ago. Had I started HAART then, there would have been lots of opportunities for staying out too late, or crossing one too many time zones, or having an argument with my boyfriend or forgetting to get to the pharmacy before it closed or simply just falling asleep in front of the television. And these are pretty simple and luxurious examples. I don't also have to take care of children. I don't worry that someone at work is going to discover my HIV secret because I am taking pills in the middle of the day. I have a home and a refrigerator. I have a doctor who takes the time to explain my medication and answer my questions. And I have uninterrupted access to health care. Adherence to treatment is the issue where the wonders of science come face-to-face with every day life, where randomized controlled studies come face-to-face with chaos theory. The extraordinary work done by scientists and physicians and the massive investments of time and money from industry, can all be undone if the patients can't take the pills. Clearly, HAART is a remarkable treatment strategy. But, it is also an extremely fragile and unforgiving strategy. If we all don't give this issue the respect it deserves, then it will eat us. Each time therapy fails a patient, either because of side effects, or the difficulties of adherence, or because of sub-optimal pre-treatment, or because the physician and patient were never taught how to use the drugs properly – every time therapy fails a patient, we lose a little ground to the chaos, we move closer towards HAART becoming irrelevant. We can only withstand so much treatment failure until we are spending so much time dealing once again with late stage AIDS, that anti-viral therapy loses its impact and value.

So, what do we know about adherence to treatment? A year ago, the Forum for Collaborative HIV Research, along with the NIH Office of AIDS Research and the National Minority AIDS Council held a conference about research into adherence to therapy. The conference brought together HIV clinicians, bio-medical and behavioral researchers, community educators, industry and government representatives and third-party payers. We presented an overview of the literature in treatment adherence and scoped out the issues in HIV care and treatment. The participants were then put to work and developed a research agenda for adherence to HIV treatment. We focused on the bio-medical and behavioral research issues that can lead to a better understanding of (1) the factors that affect a patient's ability to adhere to therapy, (2) the interventions that can assist a patient in treatment adherence, and (3) the methods to measure adherence. The research agenda, summaries of the conference presentations, and a background paper on adherence research with a bibliography is in the Conference Report, which I am happy to make available to you.

We know that patients have a hard time taking pills. We know that the more complex the regimen, the harder it is to comply. Adherence levels fall as the number of pills, the number of drugs, and number of times per day you take pills increases. Required changes in diet and the length of time a patient is expected to be on therapy will effect adherence levels. Research shows that adherence gets harder the longer the patient is on treatment. Changes in routine, depression, beliefs about health care and medicine, and self-esteem will all affect adherence levels. Communication between the physician and the patient is cited as a key factor in adherence, as is good patient understanding on the logistics and purpose of therapy.

In HIV, the challenge is particularly rough. The regimens are complex, and patients are expected to start therapy early in the course of the disease and stay on therapy for the rest of their lives. The side effects of therapy will interfere with quality of life, if not life itself. For late-stage patients, the large numbers of drugs and their interactions can be particularly difficult to manage. And, for the largest group of patients for which therapy is now indicated, their first experience of feeling physically ill will often come from the pills they are taking, not from HIV disease. For the asymptomatic patient, HAART won't make you feel better, but it can make you feel worse. The motivation for good adherence can be lacking. Numbers on a piece of paper from a test result are not always the best motivators. The challenge of adherence is confronted when the patient is far from the office visit getting viral load results.

Adherence rates are lousy in every disease. Even where the regimen has been made as simple as possible – one pill a day for hypertension, for example the adherence rates are very poor. One ACTG study showed that 11% of patients in the controlled setting of a clinical trial missed a dose in the past 24 hours, 36% missed a dose in the last two weeks. 43% of patients said they forgot to take their pills, 36% said they fell asleep, 27% cited a change in routine. Are these surprising reasons? Not to me. If I am expected to take these pills forever and I am supposed to be leading a normal life, then the pills become a part of every day life. We will forget to take the pills, like we forget our keys or forget to turn off the coffee pot. We will fall asleep. We will have other crises or other joys in our lives that

will make us forget for a moment that we have a life-threatening illness and must take our pills every day on time or else we will develop irreversible cross-resistant viral mutations and die.

Can we predict who will be adherent? Overall no. The research is clear that demographic characteristics, including education levels, income status, race, gender, age and a history of drug use are not predictors for adherence. There is good data from San Francisco showing that homelessness is not per se cause for non-adherence. Active alcohol or substance abuse is a predictor for poor adherence. The research suggests that the only demographic group that seems to be per se non-compliant to medication are physicians. The development of a good tool for doctors and patients to predict adherence is an essential and missing element of good care. The work that is done to determine if one is ready for therapy may be the most important work for successful long-term treatment. Buzzers, beepers, timers, calendars, phone calls, multi-compartmental pill boxes ö these can all help create a structure for adherence. But, while I think there is an important role for these tools, we shouldn't think that these gadgets are the answer alone. Yes, simpler regimens will help. Yes, reminders will help. But, we can't escape the psycho-social complexities of this issue, even though we'd like to.

I remember two counseling sessions I did back when I was running a treatment education program. Two guys came in on separate occasions, both had known they were positive for years. They were knowledgeable about HIV treatment and had never been on therapy before. Their t-cells were mid-range, but stable. The viral load test became available and for both of them, the reading came in high. Both their doctors suggested that they begin treatment. They were devastated. The recommendation of therapy meant to them that they were now sick and were facing death. They still felt fine. The pills, for both of them, was really their first physical manifestation of AIDS. Most of the day, they felt fine. But, every time they reached for the pill bottle, they had AIDS. So, if you are in that situation, and you don't want to have AIDS for a few days, then a drug holiday has a certain rationale.

When you adhere to therapy, you are taking good care of yourself. But, sometimes, we don't want to take good care of ourselves. Sometimes, it is our self-destructive behavior that feels most comfortable and familiar. What better way to self-destruct than to not take the medication.

I view the challenge of adherence to treatment as similar to that of primary HIV prevention. Both issues require that patients make significant behavioral changes in their lives. Personally, I think incorporating safer sex into one's life may be easier than living in a fasting state nine hours a day. Ice cream at about 11:30 at night is a drug that works, too. And like prevention, the consequences of poor adherence can be devastating. As I said earlier, this is a very fragile and very unforgiving treatment strategy.

Having good information and a good support system is cited as one of the most important factors in achieving good adherence. From my experience in treatment education, I feel strongly that it is essential for patients to understand the concepts of viral replication,

how the drugs affect replication and how drug resistance develops in order to understand why adherence is so important. Not only is it essential to teach these concepts, it is possible. Already, models for teaching these ideas to patients in a simple and clear fashion are available. And all patients, regardless of education level can learn from them if they are presented properly and, most important, respectfully.

Certainly, the physician has a role to play in patient education. But, that is not enough. Patient education and support is essential and doctors are often under too much pressure to take the required time. Also, patients may not feel comfortable asking questions or raising their concerns with their doctor. Every person who has contact with people living with HIV has the opportunity to engage in an adherence intervention. The case manager, the drug treatment counselor, the peer educator, the nurse, the pharmacist, the receptionist: they all have the opportunity to ask how it is going, answer a question, help the patient design a routine and strategy that is useful for them.

Developing individualized structures to assist patients in their daily lives is important. Find the things that motivate the person – you take your pills just before you pick your daughter up from school or right before you make her lunch for the next day. It will be different for each of us. And most important, preparing the patient for treatment before starting is essential. You really have to be ready to make the commitment to this regimen. I can't imagine ever giving a patient a script to start treatment on the same day as they got their first viral load count.

The infrastructure of HIV social services can be put to work to address this issue, provided that training in treatment issues is offered for the staff and volunteers at the community-based organizations and for all staff at health care delivery centers. Yes, this is all a lot to ask for. But without it, this treatment strategy—which we have all invested so much of our lives and our hopes—will fail. Talk to your patients, listen to them. And know that so far, as we have done time and again in AIDS, we're doing something remarkable. The adherence rates in HIV treatment are unbelievably good—even if they are not good enough.