

The Forum for Collaborative HIV Research

Examining the Risk and Benefits of Directly Observed Therapy for Treatment of HIV Disease

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**A Workshop sponsored by the Forum for Collaborative HIV Research and
the U.S. Health Resources Services Administration (HRSA)**

The Forum for Collaborative HIV Research, founded in 1997, is a public-private partnership project of the Center for Health Services Research and Policy at the George Washington University. The Forum's mission is to address emerging issues in HIV clinical research and the transfer of research results into care. Through our work, we identify gaps and impediments in the efforts to optimize medical management of HIV disease, develop recommendations to fill those gaps and serve to catalyze constituents to implement of those recommendations

The Forum is a coalition of representatives from five constituency groups—government, industry, patient advocates, health care providers, and researchers. An Executive Committee made up of members from each of those groups governs the Forum. The Executive Committee determines which projects the Forum will undertake and the scope of those projects. Most projects involve the development of a Planning Committee of experts who identify the issues for discussion and the appropriate structure for the project. We usually start by collecting and distributing background materials on the particular subject. Then, we bring together a group of experts from each of our constituency groups in a workshop to discuss the current state of knowledge, identify gaps in that knowledge, and develop recommendations to further efforts in research and quality care provision. Finally, Forum staff work with constituents to help implement those recommendations.

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For more information about the Forum and/or to download reports from this meeting or prior ones, visit the Forum's website at:

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Forum for Collaborative HIV Research

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Executive Summary

At the request of the Health Resources Services Administration (HRSA), the Forum for Collaborative HIV Research held a two-day workshop to discuss the potential risks and benefits of directly-observed therapy (DOT) for HIV treatment. The workshop brought together approximately 75 experts including physicians, clinical researchers, patient advocates, community service providers, health care providers, ethicists, and representatives from state and federal government and the pharmaceutical industry. The workshop agenda was developed by a diverse Planning Committee of experts in HIV care, research and drug development.

Participants first heard background information about the possible applications of DOT for HIV disease, the use of DOT in tuberculosis, ethical considerations of DOT, the current state of development of once-a-day antiretroviral treatment regimens, and methods to evaluate DOT programs. There were then a series of presentations describing current DOT or modified DOT efforts in different settings and targeting different populations. Finally, there were presentations about the needs of different populations when considering the implementation of a DOT program. Workshop participants also spent time in break-out sessions at which they discussed if and how DOT should and should not be designed to best meet the needs of HIV-infected patients. This report includes summaries of all workshop presentations and a summary of the breakout group sessions along with the participants' recommendations for the further development of HIV/DOT programs. The meeting agenda and participant list are included at the end. The participants' recommendations are summarized below.

The participants agreed that DOT could be useful for some people to ensure better treatment adherence. However, the rationale for and the application of DOT in HIV will differ significantly from TB. In TB, the rationale for DOT is to protect the public health from the further spread of a communicable illness. While preventing further spread of HIV, in particular drug-resistant HIV, could be one rationale for utilizing DOT, the participants agreed that DOT will more likely be used in HIV care to provide assistance and support for patients on antiretroviral therapy. The one overarching recommendation in this report is that DOT programs should be voluntary and flexible. HIV DOT will differ significantly from TB programs for many reasons including the need for flexibility of chosen treatment regimens, the amount of time spent on therapy, and the side effects of treatment. HIV DOT will often not include the observation of

every dose. Modified DOT, where only some doses are regularly observed will more likely become the norm when DOT is utilized in HIV care.

The consensus view was that there is no way to predict who will be adherent to therapy. Rather, many participants believed that DOT should be offered as a treatment option to everyone who meets the criteria for commencing antiretroviral therapy. The participants strongly cautioned against presumptions about particular populations per se needing or not needing DOT; an uneducated homeless person may have better adherence levels than a clinical researcher.

DOT programs can be developed in multiple settings to best meet the needs of different patient populations, including AIDS service organizations, meals programs, outpatient clinics, methadone centers, correctional facilities, day care centers, etc. DOT should be built into established programs providing care and support to people with AIDS. It is essential that patients see the DOT program as a support mechanism. The programs, therefore, should not be mandatory, should be tailored to meet the needs of varied populations, should respect and protect patient confidentiality, and should be made available to patients if and when they need them.

There was concern that DOT programs will be designed around the use of once-a-day regimens. Participants agreed that any treatment program must provide the best possible treatment for patients. Once-a-day regimens should only be used when proven to be as effective as the current standard of care. Further, because different patients will have different treatment histories and different side effects, DOT treatment regimens must be tailored to provide optimal and individualized treatment to patients.

Participants agreed that DOT programs should be coordinated among health care providers and community service providers. Peer-support programs were strongly emphasized as a feasible and cost-effective approach. Because HIV treatment is lifelong, finding ways to taper off from DOT will be an important part of many programs. Because good treatment adherence is not constant, DOT should remain available to people when needed. Programs that taper off the use of DOT need to be evaluated to determine the effects on adherence levels.

The participants urged government funding for demonstration projects and evaluation to determine how best DOT can be used effectively to assist in the medical management of HIV disease.

Creating a context: Why is DOT now an important topic for discussion in HIV treatment? – Richard Moore, MD – Johns Hopkins Medical Center

Clinical benefits of HAART

The rationale for using DOT for treating HIV disease must be based upon sound evidence that highly active antiretroviral therapy (HAART) confers a clinical benefit for the individual and benefits for public health. Dr. Moore reviewed ways by which HAART combats HIV disease and its transmission. Among the benefits offered by HAART are the following:

- decline in rates of opportunistic illness and death (figure 1)
- durable HIV-1 RNA decrease
- CD4+ cell count increase, with recovery of naïve and memory cells
- potential decline in HIV transmission
- cost effectiveness.

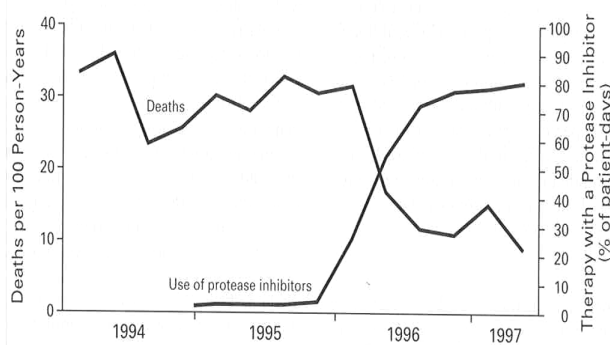


Figure 1. Mortality from AIDS before and after advent of protease inhibitors. Source: Palella FJ Jr, et al. N Engl J Med. 1998;338:853-860.

Recent data from Africa demonstrates a decrease in HIV transmission associated with a reduction in HIV-1 RNA (figure 2). In the U.S., an increase in outpatient service utilization associated with the use of HAART has been offset by decreased hospitalization (figure 3). Freedberg et al. (NEJM 2001;341:824), demonstrated that the incremental cost of HAART per life-year ranges from \$13,000 to \$23,000.

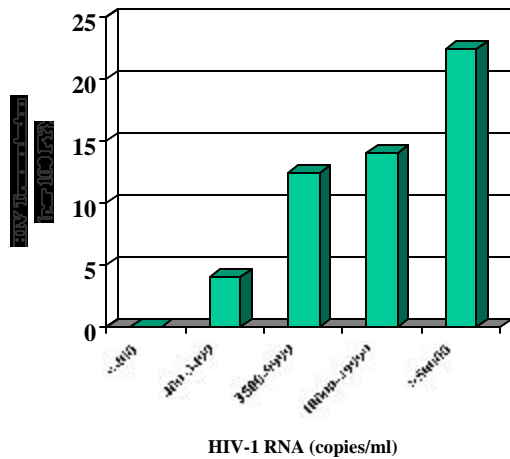


Figure 2. High viral load is associated with heterosexual HIV transmission. Quinn T, et al. NEJM 2000:342-921.

Importance of adherence to HAART

Despite its proven benefits, HAART is “unforgiving” of less than near-perfect use because of HIV’s high replication and mutation rate. The medication has a short half-life and limited potency, and it exhibits broad class resistance. Important factors that must be considered for maximum clinical benefit include adherence, drug levels (trough, area under the curve, peak), prior use of antiretroviral therapy, and viral resistance.

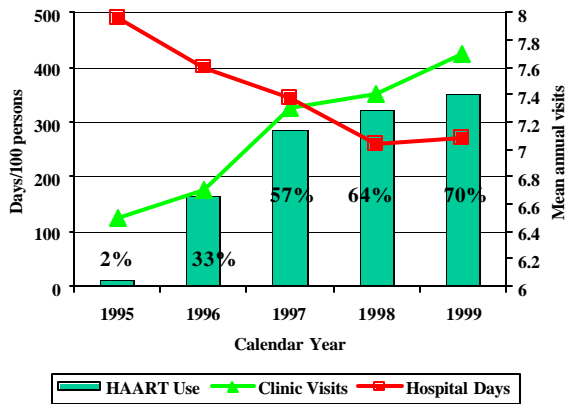
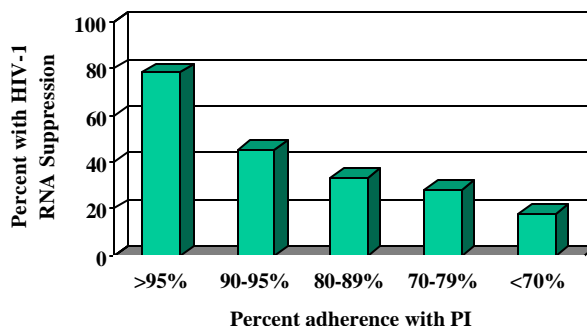


Figure 3. Health care resource use in HIV-infected persons from the Johns Hopkins HM Clinic in Baltimore. Source: Richard Moore, Johns Hopkins University, 2001.

Figure 4 demonstrates how critical patient adherence to HAART regimen is for maintaining suppression of HIV-1 RNA loads. Bangsberg et al. (8th CROI, 2001) showed that poor adherence was associated with new AIDS-defining illnesses. In his study, those who had

better than 95% adherence had a near-zero rate of progressing to AIDS-defining illness, whereas some 38% of patients who have only 50% or less adherence developed a new AIDS-defining illness.

Figure 4. HIV-1 RNA and adherence to highly active antiretroviral therapy. Source: Paterson et al. Ann Intern Med 133:21-30.



Factors that affect adherence

What affects adherence? According to Cheever (11th Johns Hopkins AIDS Clinical Care Conference, 2001), these factors fall into three main categories: patient-related, medical care system-related, and treatment-related.

Patient-related factors include:

- sex, age, and race.
- level of education, socioeconomic status
- stage of disease
- alcohol, illicit drug use
- depression and other mental illness
- health beliefs and attitudes
- knowledge
- self-efficacy
- tolerance of treatment and side effects
- previous adherence patterns.

Medical system-related factors include:

- doctor-patient relationship
- patient education
- accessibility of care providers, appointments, and medications
- support services.

Treatment-related factors include:

- number of doses per day
- number and size of pills

- duration of therapy
- dietary restrictions
- adverse side effects.

Interventions to improve adherence should be multifaceted and repetitive, and the interventions should be implemented before viral resistance develops.

Interventions that have been tested include patient counseling, diaries, special pill containers, reminder telephone calls and emails, and DOT. In classical DOT, all dosing is observed. In modified DOT, some dosing is observed, and in DART (or DAART), the dose is given to the patient (administered) but ingestion is not necessarily observed. Still another term is enhanced DOT, which refers to DOT enhanced by supportive social, behavioral, and clinical services.

The tuberculosis model

DOT has been a successful means of treating another infectious disease: tuberculosis (TB). It is more effective. The incidence of tuberculosis was cut by 64% between 1981 and 1992 by implementing DOT in Baltimore, improving from a rank of sixth to 28th among U.S. cities in terms of case rates (Chaulk et al., JAMA 1995;274:945-951). Development of resistant *Mycobacterium* strains can be avoided with DOT.

However, HIV treatment has differences with TB treatment. For example, HAART usually involves dosing at least twice a day as opposed to once a day for TB. Treatment of TB is not lifelong, as it is for HIV, and the side effects of the treatments are quite different. In many settings, the HIV patient volume is larger than the TB patient volume.

The promise of once-daily dosing

The pharmacology of HAART influences the feasibility of using DOT, because the dosing schedule depends on the drugs' half-life. Among the therapies being evaluated are once-daily HIV therapies such as non-nucleoside reverse transcriptase inhibitors (RTIs), FTC, 3TC, and ddI (Maggiolo et al., 8th CROI, 2001) and once-daily regimens of dual protease inhibitors (e.g., ritonavir plus saquinavir, lopinavir, or amprenavir).

As more drugs become available for once-daily use, DOT becomes more attractive. However, potential risks exist. Once-daily dosing may produce lower trough concentrations of

drug. The consequences of missing a dose may be more ominous than for twice-daily dosing with the risk of developing viral resistance greater. DOT may be most appropriate in settings such as prisons, drug treatment programs, mental health programs, other residential programs, and community-based programs.

Meeting goals and topics

Our goal for this meeting is to address these questions:

- Is there a place for DOT in HIV therapy?
- How can DOT be used to meet patient needs, assist with adherence, and fit into the comprehensive array of needs of our patients?
- Which patients are the best candidates for DOT?
- What are the setting and programs in which DOT should be used
- What are the right ways—and wrong ways—to use DOT?

The presentations for the meeting will address several important topics:

- use of DOT in other diseases
- pharmacology of HAART and the status of once-daily dosing
- methods for DOT program evaluation
- current DOT programs
- definitions of DOT
- ethical considerations for DOT
- practical considerations
- special needs and concerns of communities where DOT may be used
- costs and cost effectiveness of DOT
- patients (and patient care settings) that are the best candidates for DOT
- drugs that may be most suitable for DOT.

Discussion

The discussion following Dr. Moore's presentation touched on several different themes. We may have to vary treatments throughout patients' lifetimes; sometimes they may need DOT and other times self-administration may be sufficient. One way is not necessarily the only way for a patient. We must use care is when we talk about what patients require.

Others expressed reservations about the assumption that 95% adherence is necessary for optimal treatment and that the data of Paterson et al. may not generalize. Some treatments may allow for less than 95% adherence. Dr. Moore responded saying that the data depicted in the

slide was based on 2-3 times-daily therapy with a protease inhibitor-containing regimen. The impact of adherence may differ for other regimens and dosing.

Another participant asked whether viral resistance is something we need to avoid at all costs. We may have to strike a balance of abridging civil liberties and avoidance of resistance. Some patients even do well even with resistant strains. Dr. Moore responded that viral resistance is very important, although other considerations warrant discussion.

Another participant spoke from the perspective of TB experience. There was a time when the literature indicated that resistant bacteria were highly transmissible. We had better be sure that resistant HIV is not promoted by DOT regimens. As we develop recommendations, we must look toward factors that affect DOT as an adherence intervention. We must consider program guidelines and ways to conduct DOT programs.

A participant noted that when we look at the list of patients who may be best served by DOT, we are looking at the list of patients who are already underserved by the system. We are dealing with vulnerable populations who may have already failed several treatments and have resistant HIV. DOT must involve education and support. We must be absolutely sure that DOT is effective and the best therapy for these patients.

She also raised the specter of confidentiality issues, which could be a significant barrier to the success of DOT programs. By its very nature, DOT is intrusive. Even though we have predictive factors, such as substance abuse history, we cannot always know what are a patient's barriers to adherence. We are already studying DOT in certain structured settings like prisons and programs; we must translate this to the community.

Another participant said that although some indicators exist, we cannot reliably predict who will adhere to treatment and who will not. We always tend to think of DOT in certain settings: prisons, for example. We must also consider how to use DOT in the community.

One other question posed by a participant dealt with the issue of public funding. We must keep in mind how HIV is transmitted. With TB, transmissibility is an environmental issue; this is not true with HIV. How can we justify need for funding support?

One participant discussed once-daily HIV therapy. The pharmacokinetics of non-nucleoside RTIs are known and are becoming clearer with combination protease inhibitors. Although most studies have been noncomparative, single-arm studies show that these regimens are effective for at least 52 weeks. Optimally we want to have the same strength of evidence as

for HAART regimens administered twice daily—decreased viral loads, increased CD4+ cell counts, decreased mortality and incidence of opportunistic infections—to demonstrate that these once-daily regimens are efficacious. This would entail a large comparative trial of once-daily regimens to other regimens. We will have to be careful about interpreting data from DOT studies as we do not have these rigorous data available on once-daily dosing.

Another participant noted that there has been no discussion of who will administer the DOT. If registered nurses are used, how will we manage the clinics? It is possible to use nonprofessional providers for DOT. Some reports indicate that community health workers can be used, but we may need to change the legal requirements such that medical professionals are not needed. Another participant said that in his jurisdiction, a licensed professional (RN) must pack the medicine, but another community-based outreach worker can observe the DOT in home-based models. The patient is still responsible for taking the right medications at the right time. Someone who is not medically trained cannot offer advice about the medications.

The role of DOT in TB control: How we can apply our experience to HIV-related DOT research and programs- *John A. Sbarbaro, MD, MPH, University of Colorado*

“In medical school, physicians are given the vision that patients will follow their physicians’ advice and secondly, that patient behavior can be changed through education and the exercise of physician authority. But vision without reality is hallucination,” cautioned Dr. Sbarbaro. “And the belief that patients follow their physician’s advice is indeed an hallucination. As we have learned through our experience with TB, many patient do not take their prescribed treatment, and equally troubling, *nobody* can really identify those patients, either before or during treatment.” As we contemplate DOT for treatment of HIV, what lessons can we learn from our experience with tuberculosis DOT?

Dr. Sbarbaro explained the role that DOT has come to play a dominant role in the control of TB throughout the United States. Without treatment, 66% of patients with active pulmonary TB would die within 5 years. This situation is not so different from that of HIV infection. Beginning in 1952 with the development of the first really effective combined treatment of TB using isoniazid (INH) and para-aminosalicylic acid (PAS), a 95% to 98% cure rate could be achieved. However, in 1957, when a study was conducted to see what percentage of daily treatment doses were missed, the researchers found that 57% of outpatient doses of PAS were

not being taken. The explanation was thought to be the high incidence rate of side effects to PAS. But when adherence with INH, a drug with minimal side effects, was studied, the rate of medication default was also high- 31% of inpatients and 40% of outpatients did not take their medications. Later, following his exhaustive review of the literature, Davis estimated that overall, 30% to 35% of patients fail to take their medications.

Many physicians still feel that they are able to identify which patient will, and which patient will not, take their medication. Unfortunately, the reality, as indicated by Weintraub's study, is that there is no relationship between patients' knowledge of their disease and compliance with treatment. In fact, in one study, a patient educational intervention produced an untoward outcome: a dropout rate higher than that for patients receiving only routine clinic care. (Swain and Steckel, *Res Nursing Health* 1981 Mar;4(1):213-222.)

As members of the executive branch of government, public health officers are held legally responsible for protecting the community. Historically, physical quarantine (restrictions placed upon a person's activities or communication to prevent spread of a disease) has been used to protect the public from the spread of contagious diseases – especially tuberculosis. In 1965, the City and County of Denver became the first in the United States to use the combination of chemical quarantine and Directly Administered Therapy in place of physical quarantine. Although quarantine, per se, may not apply to the control of HIV infection and disease, our experience with this program may provide important insights to those concerned with insuring consistent and effective treatment and preventing the emergence of resistant organisms.

The following provisions characterize the implementation of chemical quarantine in the place of physical isolation:

- As with all decisions related to quarantine, a legally responsible public health physician makes a determination whether or not the individual's tuberculosis condition is contagious to others.
- An official letter of quarantine is issued to the individual advising him or her of the decision to impose quarantine isolation and the responsibility of that individual to cooperate with public health authorities.
- Chemical isolation is offered in place of physical isolation– with the admonition that failure to appear or be available for direct observation of treatment is evidence that the individual has broken chemical quarantine.
- Failure to meet the terms of chemical isolation will result in immediate physical isolation with the legal right to judicial appeal.
- The government bears responsibility for costs of those being treated under any form of quarantine.

During the years 1965 to 1975, 165 patients anticipated to be non-adherent were assigned to a DOT (Directly Observed Therapy) regimen that relied upon high doses of medication given to the patient twice a week doses over an 18-month period. The initial patient group missed only 37 of 2,445 doses (1.5%) (Chest 1997 111:1168). The staff of the Denver Health Department ultimately came to the recognition that indeed it was impossible to predict which patients would adhere to therapy; therefore, in Denver and subsequently throughout Colorado, DOT became universal for all TB patients. Since that time an average of only 8.5% of patients have had a poor outcome -- an average made up of the 3.3% of those who cooperated with DOT compared with 32% of those who recurrently exhibited non-adherent behavior.

What makes for a successful DOT program?

Based on Denver's experience with DOT for tuberculosis, the following measures help ensure success of DOT programs:

- Obtain a detailed social history when the patient first learns the diagnosis. At this time, patients are focused on their well being and tend to be most truthful about their contacts, life-style, relatives, and even barriers to adherence. This information is vital because a treatment program must be able to locate the patient in order to insure treatment.
- Assign the patient to the care of one professional, who becomes their "friend" and advocate. When necessary, the professional should be assigned to go to the patient.
- Treatment locations must fit into the patient's life style and include clinics, homes, homeless shelters, and even skid-row bars - anywhere the patients are. If patients are available only late at nights or weekends, arrangements may be made with local emergency rooms to dispense medication.
- Missed treatments must be immediately and intensively pursued.
- Provide enablers—individual appointments, bilingual staff, transportation, speaker telephones for accessing interpreters, children's play areas—to surmount any barriers to DOT.
- Inducements (incentives) to keep treatment appointments should be tailored to each patient (e.g., alcohol, tobacco, vouchers, cash, food, bus tokens).
- Any failure to show at appointment should result in the patient being made very aware of the staff's concern combined with strong encouragement of the patient to cooperate and further emphasized by having the patient sign a contract agreeing to cooperate with the treatment regimen.
- In TB, continued failure to keep treatment appointments led to the brief imposition of physical quarantine. Notably, following such incarcerations in Denver's locked medical unit, 50% of these patients became adherent with treatment; 25% required a second incarceration; and 25% remained non-adherent.

What can be learned from Denver's 30-year (1965-1995) experience with Directly Observed Therapy?

- It is important to recognize that DOT does not completely eliminate non-adherence
- It is still essential to use a spectrum of strategies that encourage adherence (Chest 111:1151; 1997).
- Authority and enforcement alone are insufficient to ensure patient adherence but may be necessary for up to 20% of patients.
- To be maximally effective, DOT requires culturally appropriate incentives and enablers, personal and social support, and, above all, assignment of a single health professional (or nonprofessional) to sustain a relationship with the patient.

The most difficult step in implementation of DOT is creating organizational change. To be successful the program must:

- be well organized before it is implemented and consistently well run
- have an effective, energetic leader – both initially and over the long haul
- involve dedicated and committed personnel
- possess sustainable resources
- enjoy the support of political entities, media, the general population, and patient advocate groups
- help the community understand the program is for people, not against people.

Dr. Sbarbaro summarized by stating that the vision of all patients following their physicians' advice and changing their behavior through education is not realistic. But if well designed and carefully implemented a treatment program that relies on DOT can very effective in sustaining long-term patient treatment and result in:

- A sustained focus and effort on the part of both patients and program staff because there is constant measurement of outcomes
- Recognition that non-adherence results in savings both in terms of drug costs and in the avoidance of organism resistance
- A means of meeting more of the needs of "difficult" populations than can be achieved by relying on the self-administration of drugs
- A reduction in the risk of infectiousness within the community
- Enhancement of the patient's right to health.
- A community wide understanding that DOT is not an infringement of civil rights of a patient; rather it is a service, designed to help patients through a crucial time in their lives.

DOT for TB: Recent experiences in the United States - *Kenneth Castro MD, Centers for Disease Control*

Dr. Castro reviewed trends in U.S. tuberculosis infection rates since 1953, when national surveillance began, and the subsequent resurgence of TB during 1985 to 1992. He also discussed

associated factors and the interventions used by the U.S. Public Health Service to combat the resurgence, with a focus on DOT. Finally, he enumerated some characteristics of successful TB-DOT programs, some of which may apply to DOT for the treatment of HIV.

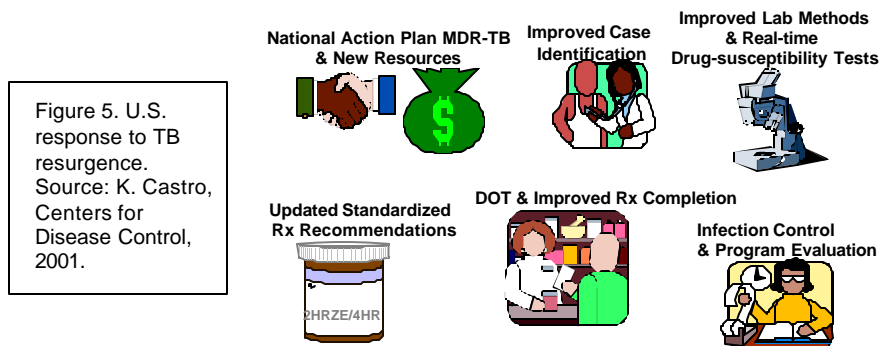
Since national surveillance for TB started in 1953, rates of TB infection decreased steadily at a rate of 5% to 6% per year until 1984. During the period 1972 to 1982, categorical funds for TB control—received by the public health service to support state-based TB research and control—dried up. Public health block grants became available in 1982, but at a time of competing needs and limited resources, several states redirected TB funds, significantly reducing TB clinical services. The states reduced TB clinical services, closed sanatoria, and generally adopted an attitude of complacency. The result of this laissez-faire policy was a loss of TB knowledge and expertise, lax infection control procedures, and a commensurate 20% increase in TB cases during the years 1985 to 1992.

Brudney and Dobkin tracked outcomes of 178 TB patients within 12 months of discharge on TB treatment (*Am Rev Respir Dis* 1991 Oct;144(4):745-9). In their eye-opening report, they described how only 11% of the discharged patients were either cured, died of other causes, or remained on therapy for the year following discharge. The other 89% either never received follow-up or were lost before completing the prescribed treatment. Perhaps most important, they identified noncompliance with TB treatment as a crucial issue that had to be addressed to improve patient outcomes and reduce TB transmission. (Some 40% of all TB patients seen then had AIDS or AIDS-related conditions.)

Outcomes of nonadherence to TB treatment were relapses, persistent infectiousness leading to ongoing transmission, and emergence of drug-resistant organisms resulting from the selective pressure exerted by prescription of inadequate regimens and treatment interruptions. In fact, Brudney and Dobkin documented that 27% (48/178) of their nonadherent TB patients had to be rehospitalized with recurrent TB. Another 20% required a third hospitalization for TB care.

In response to the resurgent tuberculosis, the Federal Tuberculosis Task Force joined forces with other partners and promptly developed the National Action Plan to Combat Multidrug-Resistant TB. The Task Force received new resources (a budget increase from \$40 million to \$104 million) to begin the implementation of several action steps outlined in that plan (figure 5). The plan called for increasing the proportion of patients who completed their treatment regimens; DOT became the centerpiece of that effort:

“A component of case management that helps to ensure that patients adhere to treatment,...DOT means that a health care worker or other designated individual watches the patient swallow every dose of the prescribed drugs. DOT should be considered for all patients because it is difficult to reliably predict which patients will be adherent. Even patients who intend to take their medicine might have trouble remembering to take their pills every time.” (*CDC self-study modules on tuberculosis. Patient adherence to tuberculosis treatment. Module 9. 1 999, Oct.*)



Directly observed therapy entails substantial labor-intensive efforts and major investments to improve TB services. Such improvements included extended clinic hours for improved access, free access to drugs if patients were unable to pay, and outreach activities. Additionally, state-specific statutory provisions address nonadherent patients with TB. All states require documentation that less-restrictive measures have been exhausted before instituting mandatory confinement of patients who do not adhere to TB treatment. This measure is uncommonly used and is justified by a public safety argument, given that persons with untreated active TB pose a health threat to others.

Dr. Castro went on to review reports that have correlated the use of DOT for TB with specific outcomes of interest:

- In their report entitled “Turning the Tide,” Frieden and colleagues showed that as the number of patients on DOT increased in New York City, from fewer than 100 before 1992 to 1,200 by the end of 1994, the number of TB cases fell by 21%. The authors calculated that approximately 4,000 infections and 800 cases were prevented during this time (Frieden et al. NEJM 1995; 350-666).
- A brief report published by Chaulk and Iseman (Lancet 1997;350:666) corroborated the relationship between DOT and decreased morbidity and mortality due to TB. In Baltimore,

where near-universal DOT was started in 1981, TB cases decreased by 62% between that year and 1995.

- Weis and his colleagues (NEJM 1994;330:1179) correlated the implementation of near-universal DOT in 1986 with pre- and post-DOT TB incidence, relapses, multidrug-resistant (MDR) TB, primary and acquired drug resistance. There were statistically significant decreases in the rates of relapses (from 20.9% to 5.5%), MDR -TB relapses (6.1% to 0.9%), primary resistance (13.0% to 6.7%), and acquired resistance (10.3% to 1.4%). These improvements occurred despite a temporal increase in frequency of injection drug use, homelessness, and HIV seropositivity in their patient population.
- Chaulk and colleagues (JAMA 1998; 279:943) led a public health guidelines panel to evaluate the evidence on the relative effectiveness of DOT in achieving treatment completion for pulmonary TB. Twenty-seven studies with original data were reviewed. The range and median completion rates are stratified in figure 6 by the type method of treatment administration. The lowest median completion (61.4%) was seen in studies reporting the use of unsupervised therapy. When only selected doses were observed (modified DOT), median completion was 71.8%. In fully supervised settings, median completion was 86.3%. The best median completion (91.0%) was observed in settings that used a patient-centered approach, described as enhanced DOT.

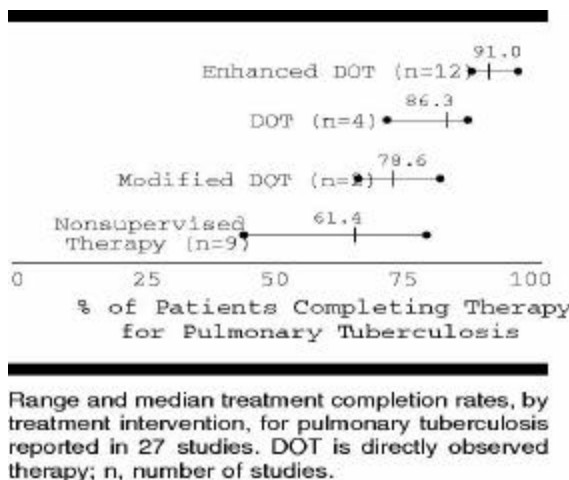


Figure 6. Review of 27 reports of TB treatment completion rates. Source: Chaulk et al. Public health TB guidelines panel consensus statement. JAMA 1998; 279:943.

Elements of enhanced DOT. Dr. Castro listed the elements of enhanced DOT for TB treatment as Chaulk et al identified them.:

- health education for patients and their families
- bilingual staff

- incentives (free medication, food, fast-food coupons)
- enablers (transportation tokens, taxi fare)
- temporary housing
- clothing
- extended clinic hours
- other health services
- referrals (drug rehabilitation)
- contracts, warning letters, incarceration.

In addition, Dr. Castro described several tools that complement DOT. These include administration of fixed-dose combination drugs to discourage selective drug discontinuation, thus reducing the likelihood of resistance development. Another complementary tool is the Medication Event Monitoring System (MEMS) cap, which consists of a microchip built into a medicine cap to monitor and sustain adherence. The system reports each time that the medication cap is removed.

Moore et al. (Am J Resp Crit Care Med 1996; 154:1013-9) showed that the cost per person treated, relapse averted, and lives saved were lower with DOT than with self-administration (table 1). For 1,000 TB cases, DOT was associated with 31 relapses and 3 deaths; fixed-dose combination drugs were associated with 96 relapses and 8 deaths; and, among those self-administering treatment, there were 133 relapses and 13 deaths.

Table 1. Cost effectiveness of DOT for treating tuberculosis.

| | Self-administered treatment | Fixed-dose combination | DOT |
|--------------------------|-----------------------------|------------------------|----------|
| Cost per person treated | \$15,000 | \$13,960 | \$13,930 |
| Cost per relapse averted | \$17,310 | \$15,450 | \$14,380 |
| Cost per life saved | \$15,200 | \$14,070 | \$13,970 |

Source: Moore et al. Am J Resp Crit Care Med 1996;154:1013-9.

Directly observed therapy has been used for TB in HIV-infected patients. Alwood and colleagues (AIDS 1994;8:1103) published a retrospective analysis demonstrating that, compared with patients not receiving DOT, those who received DOT were significantly more likely to complete 6 months of treatment (96% versus 76%) and to survive after therapy (85% versus 57%). In this study, TB was diagnosed before other AIDS-defining conditions in 31%, at the time of AIDS in 32%, and after AIDS in 37%

Limitations of DOT. Although DOT is a very useful component in TB prevention and control, it is not a panacea. One study (Burman et al. Chest 1997;111:1168-1173) showed that

some TB patients fail to complete their treatment even with the support of DOT. Both alcoholism and homelessness significantly correlated with nonadherence in the DOT program.

Zwarenstein et al. (Lancet 1998;352:1340-3) reported no significant differences in completion rates in a randomized, clinic-based evaluation of DOT versus self-administered therapy. Their report stands in sharp contrast to other assessments of DOT and has elicited much controversy within the TB community. Zwarenstein and colleagues described the following drawbacks associated with DOT for TB, including:

- high cost of the staff's and patients' time
- loss of patient autonomy
- need for structured training of observers
- pessimism in ability to change "deeply ingrained" staff-patient relationships
- lack of clarity regarding optimal patient populations or amount of DOT necessary.

This perspective argues that DOT is authoritarian and leads to decreased responsibility for self-care. At the same time, this perspective fails to acknowledge the multiple other problems plaguing our patients, for whom TB may be the least of their immediate concerns, given the need to secure a meal, the next drug fix, or shelter.

Have the gains in TB control been sustained beyond the years of the published reports cited above? With deliberate efforts to understand and apply the effective patient-centered components of case management, and guard against the limitations of DOT, we continue to observe decreases in TB as evidenced by recent data from New York, where DOT support has peaked at around 69% of patients. Tuberculosis rates have fallen commensurately. Nationwide, the proportion of persons receiving either DOT or a combination of partly observed and self-administered therapy has increased to 71% in 1997, the last year for which complete program management data are available. Although completion rates have remained stable—around 90% since 1993—the number of persons completing therapy within 1 year or less has increased from 63% in 1993 to 77% in 1997. This probably reflects improved ability to follow patients and reduce treatment interruptions. As demonstrated by Steve Weis in Tarrant County, Texas, national MDR-TB rates have fallen from 2.5% to less than half, 1.1% from 1993 through 1999.

The steady decline in the incidence of TB over the last 8 years is a great success story, and provisional figures for the year 2000 show that this decline is continuing, accounting for a 39% decrease in TB incidence from 1992 through 2000. No doubt, DOT has remarkably

enhanced the number of TB patients completing therapy, reduced the occurrence of MDR-TB, and decreased TB incidence, including the proportion of HIV-associated TB.

Directly observed therapy, however, is no panacea and requires labor-intensive activities. By now, it should be quite clear that successful DOT is shorthand for the provision of a creative array of services in a patient-centered case-management system. Finally, DOT appears to be complemented by adjunct measures, such as the MEMS cap and fixed-dose combination drugs.

For DOT to succeed, it is crucial to openly discuss and help overcome the perception of “big brother,” loss of autonomy, and infringement upon individual rights. If treatment success is documented to reduce HIV transmission, there will be a compelling public health argument for treatment as a prevention method. Dr. Castro invited the community of those involved in HIV research and care of HIV-infected individuals to learn from the lessons of TB-DOT to overcome obstacles and improve patient care.

Issues of civil liberties in HIV treatment – Ron Bayer, Ph.D., Columbia University

Legal authority behind TB-DOT

The question of DOT for TB necessitates an appreciation of the legal, constitutional, and ethical contexts for treating infectious diseases in the United States. No doubt, those who have infectious TB can be required to undergo therapy or face the prospect of isolation after a due-process hearing. The authority of the state to isolate individuals with TB is well established constitutionally and by statute. Less well known is the ethical foundation for such intervention. Consider these words of John Stuart Mill, the father of contemporary liberalism, in his essay *On Liberty*: “The only purpose for which power can be rightfully exercised over any member of a civilized community against his will is to prevent harm to others. His own good, either physical or moral, is not sufficient warrant.”

Those words assert that the state can intervene to prevent an individual from harming others but cannot intervene when the purpose is to protect a person from his or her own foolish choices. The harm principle of Mill can be restated thus: “My right to swing my arm ends where your nose begins.” The questions are, then, whose arm? whose nose? how close?

An expanded mandate for TB-DOT

In the early 1990s, it became apparent that ultimate challenge of TB treatment and control was not to respond to acute cases of TB, but was rather the treatment of individuals until

they were cured. In fact, individuals can be rendered asymptomatic and noninfectious, soon after treatment begins. The trick is to get people to continue their therapy for an additional 6 to 9 months until they are cured. Failure to do so entails the risks that the TB can reoccur and become resistant to treatment. Essentially, the state mandate to prevent transmission of TB was expanded to prevent the *potential* threat of resistance and reactivation. It was in this context, that DOT was rediscovered. Dr. Bayer noted that the concept of DOT had been around for decades, going back to the United Kingdom, Hong Kong, and Madras, India. These early efforts showed that DOT could accomplish what self-administered therapy could not; it increased the likelihood that people would complete their therapy. DOT began to be embraced in the United States with the emergence of multiply drug resistant TB. Used for patients selected for their propensity to be nonadherent.

The doctrine of DOT

In San Francisco, DOT was used for people who were deemed to be most likely to be nonadherent (e.g., alcoholics, clients of methadone maintenance clinics). Using this selective approach for DOT, they were able to achieve very high rates of regimen completion (around 90%). This was not true in most parts of the country; adherence rates remained abysmal with selectively applied DOT. The conclusion was that physicians could not accurately predict who would be adherent and who would not. From these findings was born the doctrine of universal DOT for TB patients backed up with the ultimate threat of isolation or incarceration. Furthermore, in the early 1990s, it was argued that for the sake of nondiscrimination, DOT for HIV should have been universalized. But, according to David Hansell, a former policy director at Gay Mens' Health Crisis:

I cannot see how mandatory directly observed therapy can be reconciled with the principle of the least restrictive alternative in the exercise of government power. It would require the imposition of a coercive treatment regime in a class of people without any showing that they, as individuals, will fail voluntarily to follow a course of medical treatment. Nor does it comport with the basic constitutional due-process principle, which requires individualized determination before state sanctions are imposed.

The data are actually very complicated and do not necessarily indicate that everyone has to be on DOT. Some places in the United States achieve high rates of adherence without high rates of DOT. There is no question that offering DOT is a good way of assisting those who

acknowledge problems with adherence. Indeed, the failure to make that offer represents a moral problem that must be remedied. Care must be appropriate to the individual.

The differing landscape of HIV

For TB, individuals have no choice about treatment, but voluntarism has been the standard—indeed the centerpiece—for HIV diagnosis and treatment throughout the epidemic. Protection of civil liberties through informed consent, voluntary testing, and choices of treatment has been at the core of public health efforts to stem HIV infection. Despite these important differences from the doctrine of TB treatment, some who are involved in the HIV epidemic, nevertheless, have looked to the TB model for guidance in treating HIV.

Some ethical problems

Could HAART be made conditional on acceptance of DOT? That is the question before us.

What should the physician do if a patient states that he will not take medications as required? Because the physician “must do no harm,” should the doctor warn about the risks of developing resistance and say, “Then I won’t prescribe for you”? This is an act of paternalism that embodies an element of coercion—a situation that is not very tolerable in the United States, according to Dr. Bayer. The emergence of resistance may justify this action if *transmission* of resistant strains via risk behaviors could harm others.

One thing is important here: In the context of TB, we have discussed the use of universal DOT from both empirical and moral grounds. No one is speaking of universal DOT for HAART. If we are not talking about using DOT universally for HIV-infected individuals, whom are we talking about? Should DOT ever be imposed on those who have demonstrated nonadherence? Or, should DOT be imposed on those who *might* be nonadherent?

Focusing on subsets—alcoholics, drug users—may lead to “underinclusiveness.” Why focus on drug users when we know that middle class, white men are also nonadherent sometimes? This is especially a problem if you believe that DOT is a burden rather than a service.

Food for thought

Dr. Bayer then posed more questions for the group to ponder:

- What do we know about the relationship between adherence and the social context in which patients find themselves?
- Is effective DOT inevitably linked to provision of social services designed to enhance the prospect of adherence to treatment?
- Does the moral and legal principle of the least restrictive alternative impose a duty on government to provide such social services to enhance adherence?
- Would the provision of such social services minimize the necessity of DOT?

It is one thing to speak of DOT for people who will be in treatment for 6 to 9 months; it is quite another to talk about people who will be in treatment for a lifetime. There is no evidence that we can be sanguine about getting people weaned away from DOT. In fact, becoming asymptomatic may increase the prospect of nonadherence. Duration of treatment seems to increase the prospect of nonadherence. If that is the case, we cannot say that DOT is only necessary for a brief period. We do not know the answer to this dilemma. This is an empirical question at the root of the problem of using DOT in the context of antiretroviral therapy.

Discussion

One participant commented about new data, which indicate that a significant percent of transmission comes from people who know they are HIV-infected. That finding plus the knowledge that antiretroviral resistance is on the rise gives more impetus to the push toward DOT. In addition, DOT can be voluntary in many settings when patients state that they need help.

Another participant asked Dr. Sbarbaro about methods to measure adherence with TB-DOT. How do you know records at the local level are accurate? Relapse rates and communication with co-workers are the two main measures of adherence. The centers must have committed, dependable, altruistic staff who immediately follow up on missed appointments.

Other participants commented on the limitations of our ability to measure adherence. Physicians have only a poor idea of who is taking their medication and who is not. It is impossible to predict who is likely to adhere. Whatever measures we use to enhance adherence, we need to apply them to everyone. We must keep costs and benefits in mind, and these will vary for the individual.

Other participants noted that universal HIV-DOT is also unwieldy because the number of HIV-infected individuals is much higher than the number of TB cases. With HIV, we are also hemmed in by two realities: first, our ability to measure adherence and the second relates to the biology of the virus. When we see patients only every 3 to 4 months on average, if they have lapsed during the interim, their virus may have become resistant because of the rapid viral replication rate. We cannot afford to make that mistake. We have to weigh benefit versus cost for each patient.

Another participant discussed another conference in Geneva on care for HIV patients in the developing world. This conference (WHO) called for ways to treat HIV/TB dual infections. He also discussed use of HAART in developing countries. We must consider the developing world, too, not just the United States and Canada.

Directly observed treatment has many different faces, according to another participant. In his program, the term means enhanced DOT, which is voluntary. The incentives and enablers include transportation, culturally acceptable social services, free clothing, and so forth. There must be studies of enhanced DOT in TB without the default action of incarceration. The response was that we must not confuse DOT with a robust set of social services. It all boils down to a person having to take his or her medication in the presence of a witness.

There has been a huge groundswell of movement since it appears that cheaper antiretroviral drugs will become available in developing nations. But, little thought has been given to how to administer these drugs because of the great fear of widespread resistance. Several participants reiterated the need for more of an international focus.

Big differences prevail in the epidemiology of HIV and TB patients in the United States. Therefore, the acceptability of treatment modalities is likely to vary greatly, especially regarding illegal immigrant populations, which add a level of complexity. The whole cultural context may be very different between the HIV and TB populations.

Another participant asked about what is known about completion rates of TB therapy when stratified by route of HIV infection? The data have not been stratified thus.

We still do not know when to commence therapy, noted another participant. The provider-patient relationship is critical to this decision. Whatever schema comes from this meeting, we must consider that people may delay treatment based on a potential loss of freedom

posed by DOT—a real catch-22. The response was that some will consider DOT to be a burden. Once one begins therapy for HIV is when the issue of freedom comes in.

Another participant asked about the window of adherence during which resistance may emerge. Those with less than 50% nonadherence do not develop resistant genotypes; higher levels of nonadherence are required to develop resistance.

Why did TB resistance increase in New York City during the 1980s? There were too many barriers to acceptance to DOT. Some 69% of those on DOT were achieving a 90% completion rate. We have talked about patient reasons, but also important are provider reasons behind patients' failure to adhere: Fewer than 30% of patients with private providers were being offered DOT. In clinics, 80% of patients end up on DOT. Private providers are not convincing patients that this is important to them. Private patients are requiring longer times to complete the regimen. It may be difficult to convince private providers that patients are nonadherent. Providers must put many checks into place to preclude fraud. In Colorado, all TB patients receive DOT; private providers can lose their license if they fail to put patients on DOT or provide an acceptable reason for not doing so.

Another participant highlighted the fact that in prison populations, good and bad DOT programs exist. In prison settings, men have been more willing to forego confidentiality than are women. Patients on DOT are easily identifiable because they have to stand in line to receive medications twice a day.

A universal offer of DOT should be instituted, suggested one participant, but do we need the “stick” behind the “carrot” for patients who refuse this offer? When DOT is discontinued, will the patient return to old habits? We are already rationing treatment by saying “come back in a few weeks when you have things more together.”

Once-daily HAART: Are we there yet? - *Alice K. Pau, Pharm D. NIH Clinical Center Pharmacy Department*

Dr. Pau discussed the pros and cons of once-daily dosing, the ideal properties of drugs for once-daily dosing, approved and investigational agents with once-daily dosing potential, clinical trials to date, and issues to ponder as we design DOT programs based upon once-daily dosing of antiretroviral drugs.

Once-daily dosing

The goal of once-daily dosing, according to Dr. Pau, is to improve virologic and immunologic responses of HIV-infected individuals who are on antiretroviral therapy. The advantages and disadvantages of once-daily dosing are listed in table 2.

| Advantages | Disadvantages |
|--|---|
| <ul style="list-style-type: none">• Feasible for DOT• Ease of administration• Ease of patient education• Simplified dosing regimens• Improved adherence• Improved quality of life | <ul style="list-style-type: none">• Inter- and inpatient variability in pharmacokinetics• Implications of missing doses• Unknown risks of prolonged use of pharmacokinetics enhancers and boosted agents• High pill burden |

Source: Pau AK. NIH Clinical Center Pharmacy Department. 2001.

Ideally, antiretroviral drugs for once-daily dosing would have the following properties:

- *Long plasma and intracellular half-life:* It is quite difficult to measure intracellular half-life. The drugs' half-lives also vary depending on which other drugs the patient is taking in conjunction with antiretroviral therapy.
- *Minimal intra- and interpatient variation* in pharmacokinetic parameters.
- *High C_{min} : IC_{50}/IC_{90} ratio* at 24 hours and preferably at 48 hours. Another consideration is whether patients have wild-type virus or a very resistant virus. What level do we need for these different viral types? What is the optimal ratio? Should we do specific testing for patients in addition to monitoring drug levels? What happens after 48 patients in patients who have high IC_{50}/IC_{90} ratios?
- *Reasonable pill burden*, ideally no more than 5–10 pills should be taken at one time.
- *All drugs in the regimen should be compatible* so that they can be taken together and administered without a food limitation.
- *Drugs for once-daily dosing should be well tolerated if taken during daytime hours.* Some patients, to avoid side effects, are in the habit of taking their medications at bedtime, but this would be less than ideal for DOT programs.

Target population for once-daily dosing

Dr. Pau next turned to the question of who is the target population for once-daily treatment. Are we talking about a salvage regimen or are we speaking of patients who are treatment-naïve? Would once-daily dosing be a good idea for those with a history of nonadherence? Would it be a good choice for those who are homeless, for those who are participating in methadone programs, for children or people with mental disorders who may be

unable to manage complicated regimens? Once-daily dosing may be the answer for anyone with a busy lifestyle who has trouble finding more than one time in the day to take medication.

Antiretrovirals for once-daily dosing

At this time, didanosine (ddI) and efavirenz (EFV) are labeled for once-daily dosing, and the efavirenz 600 mg capsule formulation has been submitted to the Food and Drug Administration for approval. In addition, some drugs may be able to be administered together once a day. The list of investigational drugs that are being evaluated for once-daily dosing includes:

- tenofovir DF
- FTC (emtricitabine)
- BMS-232632 (a protease inhibitor)
- T-1249 (fusion inhibitor)
- VX-185 plus ritonavir
- fozivudine tidoxil
- stavudine extended -release formulation.

Moreover, some approved drugs may find new applications with once-daily dosing. For example, lamivudine (3TC) has a fairly long half-life and is under investigation for once-daily dosing. This is also the case for nevirapine (NVP) and abacavir. Ritonavir (RTV) has been studied in conjunction with a host of other protease inhibitors, including amprenavir, saquinavir, indinavir (IDV), lopinavir, and nelfinavir in the quest for a combination that may be appropriate for once-daily dosing.

One potential limitation of once-daily regimens is the number of pills that patients have to be taken at one time. Most NNRTI-based regimens involve five or six pills, whereas boosting regimens involve 13 to 15 pills. Some combinations cannot be taken together because of food requirements. Additionally, efavirenz may not be suitable for daytime dosing for some patients because of neurological side effects.

Dr. Pau then proceeded to describe some clinical trials that are underway. The combinations presently under investigation for once-daily dosing are:

- [NVP or EFV + ddI + 3TC] QD
- [NVP + EFV + ddI] QD
- [FTC + EFV + ddI] QD
- [RTV + IDV + ddI + EFV] QD

The first three regimens listed above do not include protease inhibitors. Other studies are investigating the use of boosting agents once a day plus an NRTI given twice a day, but these would not qualify as a true once-daily regimen.

Dr. Pau described a prospective, open-label study of once-daily [NVP 400mg + ddI 400mg + 3TC 300mg] in Frankfurt, Germany (Staszewski S et al. Antiviral Therapy 1998). She noted that few such studies are carried out in the United States. Preliminary results for 45 active intravenous drug users (44% female, 9 antiretroviral-experienced). The results are shown in table 3. Dr. Pau also noted that most of the participants were on methadone maintenance. Approximately 30% of the participants required higher methadone doses while they were on NVP. This is a phenomenon of which clinicians must be aware, but one that may present difficulties in a methadone clinic setting because of confidentiality issues.

Table 3. Virologic and immunologic responses of patients receiving once-daily [NVP 400mg + ddI 400mg + 3TC 300mg]

| | Week 0 (N = 45) | Week 12 (N = 23) | Week 24 (N = 18) |
|-------------------------------|-----------------|------------------|------------------|
| Median CD4+ cell count | 269 | 390 | 413 |
| Median viral load | 103,000 | < 500 (90%) | < 500 (90%) |

Source: Staszewski S et al. Antiviral Therapy. 1998.

Dr. Pau related the results of another study presented at the recent meeting in Amsterdam. This study compared the CYP3A4 induction effect of NVP administered once-daily and twice-daily to see if there was any difference (Crommentuyn KML et al. 2001). The study involved eight patients on a regimen of NVP (200 mg BID or 400 mg QD) plus a protease inhibitor for more than two weeks. Pharmacokinetic profiles were generated on days 15 and 29 of the study. The investigators found lower values for the AUCs for RTV, indinavir, and saquinavir when taken with NVP 400 mg QD as compared to the 200 mg BID dosing regimen. Conflicting data were reported with nelfinavir. The clinical significance of this phenomenon is still unknown, but this is something we must keep in mind as we design DOT based on once-daily dosing.

Another study by Maggiolo et al. (8th CROI, 2001) involved 75 antiretroviral-naïve patients who received [EFV 600 mg + ddI 300 mg + 3TC 300 mg] once daily. Sixteen of the patients had a prior AIDS diagnosis, and some 41% were coinfecting with hepatitis C. At baseline, the median HIV-RNA was 123,000 copies, which subsequently fell to 399 copies at week 4. By week 48, 78% of the patients had viral loads below 50 copies. The mean CD4+ cell

count rose from 251 to 467 cells/ μ L. Fourteen of the patients interrupted the treatment: four experienced virologic failure, six had adverse events, one died, and three wished to discontinue.

The next study she described had been presented in Durban, South Africa, last year (Jordan W, et al. XIII International AIDS Conference, 2000). The idea here was to combine two NNRTIs with ddI for once-daily dosing. Few studies have looked at NNRTIs in combination. The regimen consisted of [NVP 400 mg + EFV 600 mg + ddI 400 mg] administered to 15 antiretroviral-naïve and 11 antiretroviral-experienced patients. The results are shown in table 4.

| | Antiretroviral-naïve | Antiretroviral-experienced |
|-------------------------------|-------------------------------|-----------------------------|
| Mean viral load at baseline | 4.59 log | < 400 (9/11 patients) |
| Mean viral load at 9 months | < 400 copies (12/12 patients) | < 400 copies (9/9 patients) |
| Mean baseline CD4+ cell count | 351 | 368 |
| Mean CD4+ change | + 351 | + 203 |

Source: Jordan W, et al. XIII International AIDS Conference. Durban, South Africa; 2000.

Dr. Pau noted that five of the 26 patients discontinued the treatment: two because of rashes and three because of central nervous system symptoms.

She also highlighted the ANRS 091 (Montana) prospective, open-label study of a once-daily, protease-inhibitor-sparing regimen [FTC 200 mg + ddI (buffered tab, dose by weight) + EFV 600 mg] being conducted at 12 centers in France (Molina et al. J Infect Dis; 2000 and 8th CROI; 2001). This was initially to have been a 24-week pilot study, but data out to 64 weeks are available for 40 antiretroviral-naïve patients. The entry criteria were as follows:

- CD4+ cell count \geq 100
- HIV-RNA \geq 5,000 copies

The mean age of the study group was 33 years; 88% of the participants were male, 69% were men having sex with men (MSM). The median baseline CD4+ cell count was 373 cells/ μ L, and the median HIV-RNA was 4.77 log₁₀. The percentage of patients with fewer than 400 copies/mL is shown in figure 7. The participants' CD4+ cell counts are shown in figure 8.

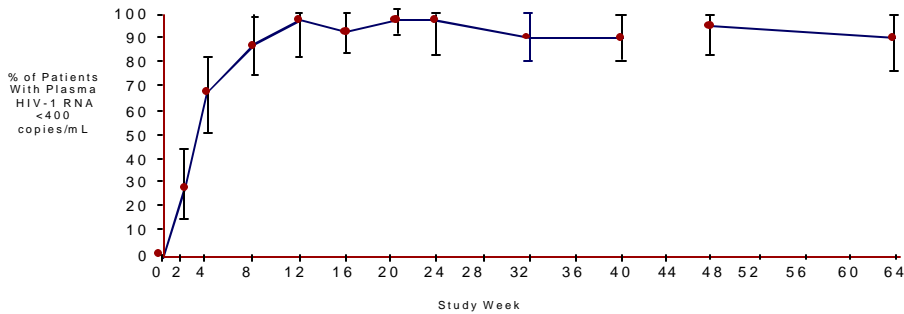


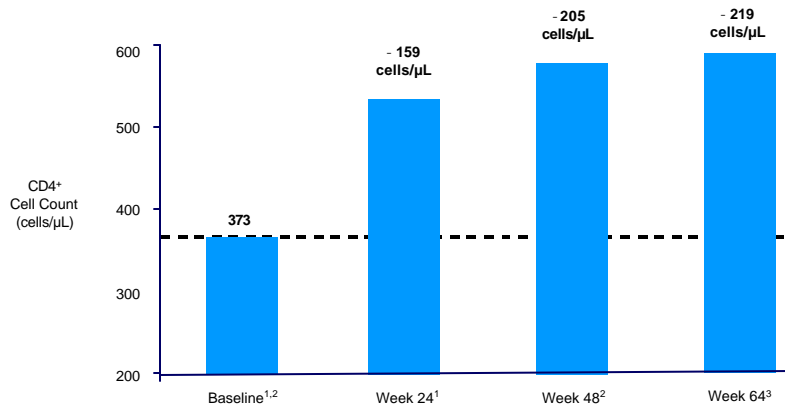
Figure 7. Montana Study (ANRS 091): Intent-to-treat analysis of 64-week results, Molina JM, et al. Presented at 8th Conference on Retroviruses and Opportunistic Infections; February 4-8, 2001; Chicago, IL. Poster G111e.

Pharmacokinetic (PK) enhancers

Dr. Pau then turned to the topic of pharmacokinetic enhancement, a topic that is predominating many meetings these days. Ritonavir and delavirdine seem to be the most often used in recent studies. The advantages of PK enhancers include the following:

- less frequent dosing
- lower pill burden of boosted drug
- increased AUC and C_{min} concentrations
- prolonged half-life
- in regimens involving high doses of ritonavir, some synergistic or additive antiretroviral effects.

Figure 8. Montana Study (ANRS 091): Median CD4⁺ cell count at baseline and at weeks 24, 48, and 64.



¹Molina JM, et al. *J Infect Dis.* 2000;182:599-602.

²Molina JM, et al. Presented at: 38th Annual Meeting of the Infectious Diseases Society of America; September 7-10, 2000; New Orleans, La. Abstract 562.

³Molina JM, et al. Presented at: 8th Conference on Retroviruses and Opportunistic Infections; February 4-8, 2001; Chicago, Ill. Poster G111e.

“Baby doses” and viral resistance

The concern is whether potential exists for the development of resistance with low levels of drug exposure and, if used over a long period, whether the boosted drugs may exhibit increased toxicity. The first question we must ask is “Does “baby dose” ritonavir select for resistance mutation?” She highlighted the results presented by Chaillou S, et al., who presented a retrospective review of data from the Viradapt study at ICAAC 2000. Thirty-four patients received a regimen consisting of [RTV 100mg BID (baby dose) + SQV-hgc 600mg TID] as a salvage regimen. Viral loads and genotypic testing were performed at baseline and each three months thereafter. The resistance mutations of most concern in this study were V82A/F/T and M46I/L, which confer cross-resistance to IDV and partial resistance to APV, NFV, and SQV. At baseline, slightly less than 10% of participants’ viral strains had mutations that conferred resistance to ritonavir, but by 12 weeks, some 30% to 40% of the viral strains had ritonavir-resistance mutations. We must keep these results in mind as we design boosting regimens for our patient populations.

Dr. Pau then went on to highlight studies of PK-boosting regimens:

- Hsieh S-M, et al. (JAIDS 2000) conducted an open-label study of 10 antiretroviral-naïve patients who received [RTV 400 mg (5mL) + IDV 1200 mg + EFV 600 mg + ddI (200mg <60kg, 300mg > 60kg) QHS. Nine patients remained on the treatment by week 12; gastrointestinal symptoms were the most common complaints. Fifty percent of the participants experienced cholesterol and triglyceride levels exceeding 200. The median CD4+ cell count increased by 165 from a baseline median of 211. Viral loads decreased by 1.7 log₁₀ from the baseline of level of 4.3 log₁₀. This was the only study of a once-daily, protease-inhibitor boosting regimen that Dr. Pau could identify in the literature.
- Suleiman J et al. (8th CROI, 2001) studied a regimen of [RTV 200 + IDV 1200] QD + [d4T 40 + 3TC 150] BID in an open-label, phase II (Merck 103/104) clinical trial. (This study built upon the Merck 089 healthy volunteers study, which showed favorable indinavir pharmacokinetics using a once-daily regimen of [RTV 100 mg + IDV 1200] QD.) Forty antiretroviral-naïve patients were enrolled who had a median CD4+ cell count of 329 and HIV-RNA of 4.91 log₁₀. Eight patients withdrew from the study, but none cited adverse

events as the reason although one patient developed nephrolithiasis and five experienced rapid alopecia. At week 24 of the study, the results were:

| Week 24 | HIV-RNA < 400 | HIV-RNA < 50 |
|---------------|---------------|--------------|
| Observed data | 87.5% | 65.6% |
| NC=Failure | 71.8% | 53.8% |

When the PK data for HIV-infected individuals taking 200 mg ritonavir QD were compared to the PK data from health volunteers taking the same regimen, it is apparent that the C_{min} value is significantly lower in the HIV patient population (156 nM versus 273 nM). This is another factor that we must consider in the design of once-daily regimens. A new study arm is to be introduced [RTV 400/IDV 1200] QD to attempt further PK enhancement and assess tolerability.

Summary of reports from the 2001 Amsterdam Conference

Dr. Pau highlighted the presentations on clinical trials of once-daily ritonavir/saquinavir. Six PK, safety, and/or efficacy trials were reported at the April meeting. The ritonavir doses studied ranged from 100–200 mg in combination with saquinavir soft gel caps, 1600 mg QD. Two trials were conducted with PI-experienced patients, who showed improvement in virologic responses. Pharmacokinetic studies that compared PK parameters of African Americans to Caucasians revealed no significant differences. Adequate PK parameters were observed in Thai patients, although large interpatient variations were seen with 24-hour saquinavir levels (27-fold difference).

Role of drug monitoring in once-daily regimens

Dr. Pau listed some possible benefits of such monitoring:

- to compensate for wide inter- and inpatient variability, especially with use of combinations in which one drug may inhibit or induce metabolism of the other drug(s)
- to assess changes in plasma levels over time, as has been seen with ritonavir/saquinavir data
- to apply with phenotypic data to determine $C_{min};IC_{50}$, primarily in salvage regimens
- to individualize dosing regimens
- to detect drug-drug interactions
- to include among parameters monitored during initial trials of DOT regimens so that we can discern reasons for clinical failure.

Dr. Pau recommended that the group consider a few additional issues regarding the design of DOT regimens based upon once-daily dosing. First, current regimens are generally not adequate for 48-hour dosing. This means that if a patient misses a dose, that drug levels may not be adequately maintained. When and how should the missing doses be made up during DOT? Second, clinical trials to date have not targeted highly antiretroviral-experienced patients, rather they have focused on antiretroviral-naïve patients. Do we want to target naïve patients for DOT programs, those who are experiencing their second failure, or should DOT be for salvage regimens? Third, we do not know the long-term risks of using PK enhancers. Fourth, we need to identify safe and effective non -antiretroviral PK enhancers (CYP and/or P-glycoprotein inhibitors) so that we can reduce the incidence of side effects and other problems, including development of viral resistance.

Discussion

One participant discussed a presentation (Montana) of four patients who had missed doses. One patient at 38 hours still had a level of 70 ng, which is 20 ng above the EC₅₀.

Another participant stated that we have a high comfort level with low-dose ritonavir and have not seen unduly high levels of resistance.

One concern expressed by another participant is that trials based on virologic and immunologic markers may not be reflective of clinical outcomes. We may be exposing the patients to unknown risks. Do we want to throw DOT into the variable mix, too? We need to dissect out these issues.

Another participant noted that although there may be a greater risk involved with missing a dose in a QD regimen than with a BID or TID regimen, with the theoretically higher compliance level with a QD regimen, would these risks be offsetting?

Assessment of DOT for HIV - *Tim Flanigan, MD, Brown University*

Dr. Flanigan suggested that the primary goal of DOT is to reduce morbidity and mortality from AIDS. Additional goals for DOT include:

- decreasing development of viral resistance
- improving adherence to primary care
- enhancing outlook and attitudes toward HIV treatment
- improving ability to self-administer medication
- increasing self-sufficiency

- improving referral, access, and utilization of mental health treatment and substance abuse treatment
- reducing risk behaviors.

Dr. Flanigan reported on a pilot, community-based program of DOT to enhance adherence to HAART. He discussed the outcomes for the 22 participants and articulated some lessons learned that should be considered in the design of future DOT programs.

Program design

The program targeted a small minority of individuals who had significant social disruption in their lives—those who had ongoing substance use, had mental illness, or were homeless. In general, HIV infected individuals with such disruption are not offered antiretroviral therapy by many practitioners. DOT in this setting was completely voluntary and was done in conjunction with the participant's primary care physician. Physicians were asked to identify patients who had demonstrated poor adherence to antiretroviral regimens and who self-reported ongoing substance abuse in the past 90 days. The decision to start therapy was made by the primary care provider and the patient.

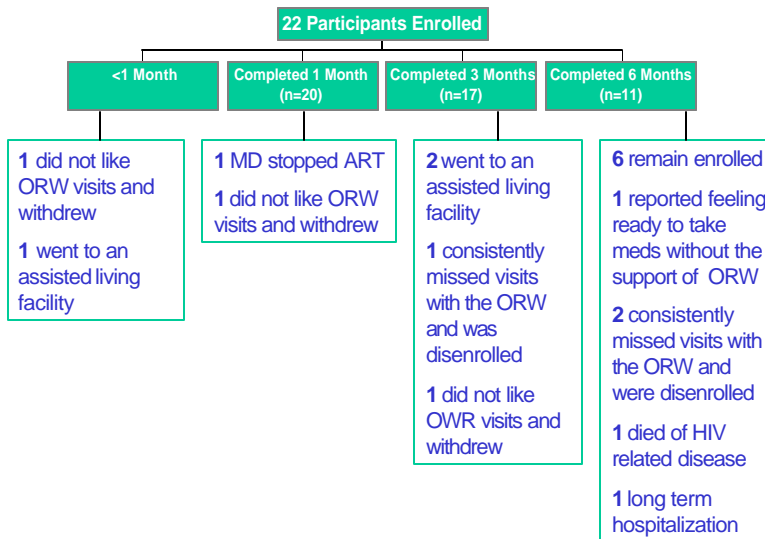
Participants underwent a baseline interview to collect demographic data, information about substance use, availability of social support, and patterns of adherence. Follow-up interviews were conducted at 1, 3, and 6 months after the baseline interview. Once enrolled, participants met with an outreach worker every day in a location selected by the participant, most commonly the participant's home. Half of the participants were on methadone maintenance; none of them chose to receive DOT in the methadone clinic. One reason cited for avoiding HIV-DOT in the clinic was the difficulty of maintaining confidentiality in that setting. In addition, participants expressed negative feelings about methadone maintenance and did not want their antiretroviral therapy associated with it.

The outreach workers were not medical professionals; usually they had high-school diplomas and a year or two of college. Usually they came from the inner city community. Nurses packaged the medications. At each visit, the outreach worker delivered the daily, prepackaged doses of medication and observed the participant taking the daily dose 7 out of 7 days. In addition, the outreach worker:

- assessed participant concerns regarding medications and makes appropriate referrals

- reminded patient of upcoming clinic appointments and medication refills recorded self-reported adherence for any missed observations due to cancelled or missed appointments.

Figure 9. Six-month participation in a pilot-DOT program. Source: Flanigan T. The Miriam Hospital/Brown University, 2001.



Characteristics of the participants

Table 5 lists the characteristics of the study population. Viral genotype and phenotype studies were not performed as a part of this pilot study because at that time it was not standard of care. Two participants with resistant virus did not achieve a potent antiretroviral effect. Currently all patients initiating DOT undergo resistance testing.

| | |
|---|---|
| Age (mean) | 40 years |
| Female | 50% |
| Race/ethnicity | African American 36% White 36% Latino 27% |
| Employed | 5% |
| History of incarceration | 68% |
| Antiretroviral-experienced | 100% |
| Mean CD4+ cell count | 177 cells/ml (range 2–548) |
| Mean plasma viral RNA | 4.66 log ₁₀ (range 2.58–5.88) |
| Source: Flanigan T. The Miriam Hospital/Brown University. 2001. | |

Participants received a once-daily regimen with two or three nucleoside reverse transcriptase inhibitors (NRTIs) plus an NNRTI, or a PI combination. Some participants were disturbed by the upregulation of methadone metabolism, which necessitated increased methadone doses. Some patients received daytime doses of efavirenz, and neurological side effects were tolerable. Even a daily ritonavir/saquinavir regimen that involved nine pills was well tolerated. After 6 months, participants were assessed for readiness to taper their number of weekly outreach worker visits.

Outcomes. Twenty-two participants were enrolled in the pilot study. The participants' participation outcomes are shown in figure 9.

At 3 months, the mean decrease in viral load was 1.96 log₁₀. At 6 months, the mean decrease in viral load was 2.24 log₁₀. At baseline, none of the 22 participants had viral loads less than 50 copies/mL, but after 3 months in the program, 50% of participants had viral loads of less than 50 copies/mL, and at 6 months, 70% of participants had viral loads of less than 50 copies/mL. The mean baseline CD4+ cell count was 60, but it rose to 188 at 3 months and was 183 at 6 months.

Perhaps one of the most significant outcomes is the participants' overall reactions to the program (table 6). The daily visit by an outreach worker was a great motivator and improved attitudes toward HIV treatment. At 3 months, 36% of participants said they would take HIV medication daily even without outreach visits; this number increased to 91% at 6 months.

| | 3 mo (N = 16) | 6 mo (N = 10) |
|--|------------------|------------------|
| 1. The outreach worker has helped me to take my medicine. | 100% | 100% |
| 2. The outreach worker visits are an invasion of my privacy. | 0% | 9% |
| 3. The program has helped me to not miss my clinic appointments | 88% | 73% |
| 4. I like the outreach worker visits. | 88% | 91% |
| 5. I would take my HIV medications every day even if the outreach worker did not visit me. | 35% | 91% |

Source: Flanigan T. The Miriam Hospital/Brown University. 2001.

Lessons learned

These data are subject to a few caveats because it was a pilot program involving a small number of participants and lacking a control group. The eligibility criteria were broad; therefore, baseline CD4 counts, baseline viral loads, and prior antiretroviral exposure varied widely. Below are listed a few lessons learned, which may help in the design of DOT for HIV:

- Participants preferred morning dosing.
- Seven-day-per-week staffing is challenging (5 days/week is easier)
- Outreach worker safety must be considered.
- Emphasize strict confidentiality and minimize intrusiveness
- Decrease participant dependency on an individual outreach worker by rotating route schedules.
- Do not use overqualified personnel; use community personnel and train them well.

Assessing DOT

This pilot study suggests a number of outcomes and indicators for evaluating DOT. Among them are the proportion of observed doses, changes in viral load and CD4+ cell count, percentage of patients with viral loads under <50, <500 or <1000, incidence of opportunistic infections, mortality rates, and cost-benefit analyses. Dr. Flanigan emphasized the significance of CD4+ cell count changes. Increases in CD4+ cell counts correlate well with reduced rates of opportunistic infections, decreased mortality, improved quality of life, and increased neurocognitive function.

Resistance testing should be included in assessments of DOT programs. Although the primary goal of DOT is improvements in morbidity and mortality, we need to assess if DOT will decrease the development of resistance. Even for naïve patients, resistance testing is important because some 14% to 16% of those patients will have strains with resistant mutations. For antiretroviral-experienced patients, such testing is critical.

Dr. Flanigan also suggested some other possibilities for clinical trials: Should we evaluate the number of outreach worker contacts and treatment adherence? Is there a dose response? Can we gauge the acceptability of DOT by determining how many patients are willing to try DOT and how many are willing to continue DOT? Will DOT help HIV-infected individuals increase self-reliance in regard to taking medication on their own? Will this intervention improve access to other primary care, including mental health substance abuse treatment? Will risk behaviors decrease, thereby reducing secondary transmission?

We need objective criteria for tapering based on virologic and immunologic criteria rather than arbitrary (time-based) criteria. For a randomized trial being designed by Dr. Flanigan's group, three criteria will be applied: First, the viral load must be below 500; second, the patient must make two consecutive appointments with his or her primary care provider; and, third, the patient must want to taper off DOT.

We must certainly consider the intrusiveness factor because HIV is lifelong. Tapering or modifying DOT is necessary for acceptability and cost. This pilot study suggests that we can view DOT as a relatively short-term, very intense strategy (at least 5 of 7 days) that can be tapered down or "ratcheted back up" again as necessary. Dr. Flanigan emphasized the necessity of designing flexibility into DOT programs to ensure that such programs will meet patients' needs as they wax and wane through the course of HIV as well as substance abuse and mental health illness.

Discussion

One participant questioned the assumption that HIV and TB must be treated differently. It is difficult to predict who will adhere and who will not. Every day, we are getting new medications with higher potency and longer half-lives. We must look to genotype and phenotype testing to design regimens. Maximal support is necessary for those who have resistant or partially resistant strains.

Another participant emphasized the importance of privacy issues; to bring HIV treatment into methadone clinics will entail some physical plant changes to ensure privacy. It is not easy to incorporate HIV treatment into methadone treatment although it sounds like it should be a simple matter.

An additional study is being planned with three study arms: self-administration, DOT, and enhanced DOT with case management. The randomized control trial will be powered for viral load and CD4+ counts. Patients will be tracked for 6 months of full DOT or will be offered tapering process at 6 months. All patients will be followed for 12 months.

One person questioned the inclusion of antiretroviral-experienced patients because it will be more difficult to show differences in this group. For such patients, DOT is essentially a salvage regimen, and they are the ones least likely to show a virologic response no matter how adherent they are. Dr. Flanigan responded that if DOT is to be implemented on a broad scale in this nation, that it is not likely to be widely used only for initial therapy. It will be most likely to be used with experienced patients, so this study reflects reality.

Program Descriptions

Frederick L. Altice, MD - Yale University AIDS Program

Dr. Altice reported on an M-DOT program at a needle exchange site. Out-of-treatment, HIV-positive drug users have many unmet social and medical needs that may affect adherence, among them:

- Poly-substance use, which leads to a chaotic lifestyle
- Co-morbid mental illness in 40% to 70% of the population
- hepatitis C infection in 60% to 80% of the population
- other chronic medical conditions in 40% to 60% of the population
- chronic or transient homelessness.

In addition, access to and utilization of medical care is limited for this group, largely because of mistrust—on the parts of this population and the traditional health care system. Multiple studies in the United States and Canada show that active drug users are less likely to be offered antiretroviral therapy, and they are less likely to adhere to treatment once prescribed. We need alternatives for this group.

Needle exchange programs reach active drug users at sites proximate to drug use and are being adopted as a means of community-based outreach for IDUs. These programs do much more than just exchange used needles for new ones; they can provide a link to medical care and act as a conduit to drug treatment and social services.

Dr. Altice and his colleagues developed a model—the Community Health Care Van—that builds upon the success of other mobile health care programs started in 1993 in New Haven.

By moving the needle exchange program throughout and linking it to other community health care, it may be possible to reduce stigma associated with particular “drug scenes” as has occurred in Europe. It also grants some feeling of autonomy to those who can procure health care in their own neighborhoods.

The 36-foot Community Health Care Van has one counseling room and two fully equipped exam rooms. It operates 5 days per week in tandem with the needle exchange program. Services include medical care provided by an on-site clinician, DOT for HIV and psychiatric medications, HIV prevention, and linkages to an array of community services. All services are free; pharmaceutical firms provide various medications free.

The clients interact constantly with the outreach worker as kind of a “primary companion tool,” but the client also lives within a community where they can interact with case managers and community providers. The outreach worker can coordinate with drug treatment coordinators, community providers, and Community Health Care Van liaisons.

Dr. Altice described a study, a randomized, controlled trial of M-DOT versus standard of care (self-administered regimen) among HIV-positive, active drug users. They are recruiting from sites of clinical care through providers who have ART-naïve clients who are ready to begin ART and ART-experienced clients who are judged to be poorly adherent based upon clinical outcomes. The primary outcomes to be monitored are

- adherence
- HIV-1 RNA
- HIV-1 genotype
- HIV quality of life
- utilization of health care
- linkage to service (e.g., drug treatment)

Randomization criteria are being applied to ensure that the two study arms will be balance with regard to:

- ART-experienced versus ART-naïve
- residence based on geocoding
- alcohol and addiction severity
- mode of drug use (IDU versus noninjected drug use)
- demographic characteristics
- once-daily versus twice-daily regimens if standard of care changes during study.

The outreach worker works with the client to establish a routine. Often this entails visiting living, copping, and other hangout areas with the client so that the outreach worker can locate the client if he or she fails to show at an appointment. The outreach worker also conducts an in-depth survey about health and medication beliefs and drug use patterns.

Preliminary data have indicated how important it is to exploring health beliefs with clients. Some believe that mixing chemicals (HAART with methadone or street drugs) is harmful and therefore avoid taking HAART on days when they get high. These surveys also give insight into clients' past experiences with HIV medications and give them a chance to express concerns about HIV medications. They also talked about worries about anticipated side effects and pill burdens. (Anticipatory side effects are definite predictors of nonadherence.)

The outreach worker also programs a MediMombeeper to remind the client to come to the van, to take additional doses on time, and to remind the client of upcoming appointments. The worker records all interactions with the client, and, if the client experiences a medical problem (e.g., side effects), the outreach worker immediately refers the client to the Community Health Care Van clinician for evaluation.

Outreach worker administers one dose as DOT. The second daily dose or weekend doses are placed in MEMS cap and given to the client to self-administer. Self-administered doses are coated with a riboflavin tracer to monitor adherence.

Enrollment had just begun as of the date of this meeting (5 patients enrolled), so few data were available, but some important insights were gleaned from a pilot intervention. They found that in 13 subjects:

- By month 9:
 - 10/13 (77%) had undetectable HIV-RNA
 - 9/13 (69%) entered drug treatment but only after achieving a viral load <400
 - The remainder had viral loads of 1,000 to 3,000 copies
 - Two had problems with adherence secondary to alcohol use
 - One was incarcerated seven times during the 12 months, usually for just a few days at a time
- By month 12:
 - Only 7/13 (54%) had undetectable HIV-RNA.

Perhaps having a positive outcome (achieving an undetectable viral load) prompted some of the clients to enter drug treatment. Only one person who had not entered drug treatment by

month 9 persistently maintained an undetectable viral load. At month 12, viral failure correlated with continuing drug use.

Joshua Bamberger, MD, MPH, of the San Francisco Department of Public Health- Action Point Adherence Project

Dr. Bamberger reported on his group's storefront project, which has been in place for a little over 2 years. It offers a modified HIV-DOT program and other services. It is open from 9 a.m. to 5 p.m. Monday through Friday. The project has enrolled more than 160 HIV-positive, urban poor (somewhat synonymous with homeless or transiently homeless). Funding for the first site was via local tax revenues, funding of a second site was via CSAT. The cost is about \$4,000 per client per year.

Clients come in weekly or daily, depending on how things are going with their adherence. Clients receive a \$10/week incentive for the first 13 weeks of enrollment. Clients are offered individualized care plans, which include doctor visits and methadone maintenance (methadone available only through the CSAT funded site). In addition, the project staff advocate on behalf of the clients with other treatment providers. The project also provides nurse and social worker case management and acupuncture. Action Point also adheres to a harm reduction philosophy; so long as a client is merely intoxicated and does not pose a danger to others, he or she will be admitted to receive medication.

A pager system, which is programmed through the Internet, reminds clients about appointments and medications. The center also has on-site medication storage and dispensing. Prefilled Medisets have been a great boon because staff no longer has to count out and package pills.

About half the patients reported sleeping on the street the night before enrollment. Some 55% receive psychiatric medications, but many more could benefit from such intervention. Virtually all the clients suffer from heavy drug addictions (cocaine, heroin, amphetamine, alcohol). This is the biggest issue from an adherence standpoint in this setting.

Seventy-nine percent of the clients are male, 14% female, and 7% male-to-female transgender. Most are between the ages of 30 and 50 years. Forty-seven percent are white, 37% are African American, 13% are Latino, and the remainder is Native Americans and Asians.

How long do people stay in the Action Point program? Thirteen percent stayed in the program for 1 to 2 months. Eighteen percent stayed 2-6 months, 24% stayed 7 to 12 months, 23% stayed 13 to 18 months, and 22% stayed 19 to 25 months.

What is being accomplished during the client's exposure to the program? Three clients have died in 118 patient-years—all male, white, amphetamine injectors. All three entered the program with CD4+ cell counts around 100 and died from pneumonia and/or wasting, and not from more classic AIDS related opportunistic infections. When this mortality rate is compared to the REACH cohort, which experienced 7.8% deaths per 100 patient-years, it looks like something significant may be happening. This is a potentially important outcome.

Dr. Bamberger expressed concern, though, that only 16% had a persistent viral load of < 400 while enrolled. Forty percent had at least one viral load determination of <400 while enrolled. Other encouraging data includes that only 13% reported being homeless, medical hospitalizations were reduced by 65%, and psychiatric hospitalizations were cut by 25%. Can some of these results be explained by CD4+ cell counts? The majority of clients (52%) had no change in CD4+ cell counts, 30% had increased counts, and 9% had decreased CD4+ cell counts.

Dr. Bamberger also had a list of lessons learned for the meeting participants to consider as they design DOT programs:

- If a program relies upon financial incentives for amphetamine or cocaine users, this may provide an incentive not to return as they will likely use the money to get high and then not return, undermining the DOT program. The story may be different with heroin users, especially if the program links to methadone maintenance.
- Evaluation staff must be different from service staff (preferably geographically distinct if possible) because the clients seek approval from the service staff and do not wish to acknowledge any lack of adherence to them. The idea is to administer DOT at one location and then provide significant incentives to motivate the client to appear at another site for evaluation of adherence.
- Biologic outcomes and adherence measures must be collected regularly and separately from clinical care.
- Adequate biologic outcomes need to be established. Our goal is to help people have better, healthier lives, and not necessarily to avoid development of viral resistance. In this complex population, people may live longer and live better even if they do not achieve undetectable viral loads. Improvement in life expectancy may be more profound than improvement in viral markers
- We desperately need a randomized, controlled trial of adherence case management versus DOT versus controls. We need funding to adequately assess the differences between these interventions.
- Financial incentives initially engage clients but do not consistently support adherence and may establish dependence and encourage inadequate adherence reporting.

- Substance abuse and a dearth of substance abuse programs are major obstacles to adherence. Amphetamines may have a more detrimental effect on adherence than abuse of other substances.

Daniel Barth-Jones, MPH, PhD, of the Center for Health Effectiveness Research, School of Medicine, Wayne State University

Dr. Barth-Jones discussed a pilot study that is underway in Central City Detroit. The Wayne State University/Detroit Medical Center program serves approximately 1,600 HIV-positive individuals annually. The population is 75% male and 75% African American. Sixty-one percent receive public assistance, 32% are employed, and 25% have a history of injection drug use (IDU) within the past year.

Dr. Barth-Jones and study principal investigator, Paula Schuman, MD, MPH, conducted a pilot study to evaluate adherence in an IDU population receiving modified DOT with cash incentives (\$5 per day of modified DOT plus a \$15 bonus for completing 7 days of M-DOT).

The primary outcome of interest was the percentage of M-DOT visits completed during the first three months after enrollment. Secondary outcomes were plasma viral loads, CD4+ cell counts, self-reported adherence, percentage of clinic appointments kept, and results of the SF-12 quality of life measures. These parameters were assessed prior to enrollment and again at the end of the study.

Twenty-seven patients enrolled, but two patients dropped out because of transportation problems. In all, 25 patients began the M-DOT program. Their characteristics were as follows:

- 73% were between the ages of 41 and 50 years
- 60% had not completed high school
- 90% were African Americans
- 68% reported crack use within the past year, 23% injection drug use, 23% alcohol abuse 45% had received treatment for IDU.

The 25 patients who embarked on the M-DOT program logged 1,166 days of potential DOT observation; 1,048 days were completed by these patients, yielding a figure of 90% adherence. Two patients have completed 90 days of M-DOT to date. Additional follow-up is slated for 3 and 6 months post-M-DOT. In addition to these preliminary statistics, Dr. Barth-Jones noted that the patients were very enthusiastic and appreciative of the structure offered by the program.

Maryrose De Fino, RN, Adherence Coordinator for the Montefiore Medical Center

Ms. De Fino explained the center's HIV-DOT program in the broader context of all the adherence programs and strategies that are ongoing at Montefiore. Three counselors apply a case management model for HIV-DOT.

The HIV-DOT program is very small; it was meant as a back door component to the adherence service models that they use. It was geared after the TB-DOT program, which started in 1992 and provided much experience, quality control measures, and strategies for developing the HIV-DOT program.

Patients can volunteer for the DOT programs through direct referrals from the providers. Experience has shown that patients tend to self-select out of the program. If they can keep the patients engaged for the initial three or four visits, they tend to stick with it. According to Ms. De Fino, patients tend to either like or not like DOT; their preferences dictates whether they will be in it for the long haul.

Several factors have contributed to Montefiore's success with TB-DOT. First, they offer to visit participants at 18 different sites, including offices, home, school, methadone clinics, dialysis locations, and medical offices. Second, they rely on an incentive model based upon 100% weekly compliance. No cash is given, but incentives offered include certificates for Sears stores, Keyfood supermarkets, McDonalds, WIZ electronics stores, pharmacies, as well as movie tickets, telephone cards, tickets for sports events, and travel reimbursement or taxi fare.

Case management, though, is what makes the TB-DOT program work. The staff establish strong rapport with the patient through education and advocacy, follow up for treatment and lab testing, medical visits, provider communication, and early intervention. The team model for the DOT program includes dietary counseling, a new mental health component, peer-education program, social workers to help with entitlement issues, and a pharmacy back-up to help with adherence counseling. The staff complete many data collection forms to create individualized plans for the participants. All these components tend to keep patients engaged in the program.

To meet state requirements, the TB-DOT program must maintain 80% or better adherence. If individual participants fall below this level, they are referred to the department of health for return to service or court-ordered DOT.

The participants come to the centers for 8 weekly visits and are then seen quarterly thereafter. Patients may remain in the program up to 12 months. Patient appreciation days are

held quarterly during which participants receive recognition and give testimonials. Upon completion of the program, participants receive certificates.

The HIV-DOT program is modeled closely after the TB-DOT program. It is a 3-month model but patients may opt to continue. Adherence is monitored via MEMS caps, pill counts, and self-reports. Patients and staff must sign the medication log. The program also relies on use of adherence tools, such as beepers, watchers, alarms, reports to providers. Incentives are given for 100% weekly compliance as determined by the medication log. If patients do not appear for 2 weeks, they are deemed lost to follow-up, they are discharged from the program, although they may reenroll later.

Evaluation of the HIV-DOT program looks promising, although the sample size (11 participants) is too small to demonstrate statistical significance. Upon entry, the mean viral load was 96,762 copies; after 1 year in the program, the mean viral load was 535 copies. The mean CD4+ cell count at entry was 232; after 1 year in the program, the mean CD4+ cell count was 226. These results indicate that the participants achieved a stable condition with their HIV infection through the HIV-DOT program.

This small program has demonstrated that HIV-DOT is

- a timely early intervention, which facilitates communication with providers and patients
- measurable via laboratory testing, devices, and adherence tools
- affordable compared to the alternatives
- doable from participant and staff perspectives
- replicable
- effective as indicated by research and outcomes.

Barriers exist, too. HIV-DOT is labor-intensive for the staff, and intrusive and burdensome for the participants. DOT involves expenses of travel, incentives, and space. Not all treatment regimens lend themselves to DOT because of drug and food interactions, dosage timing, and other restrictions. No standards yet exist for DOT programs. Funding is problematic because third-party reimbursement does not apply, necessitating reliance upon grants. And, the question still remains: When are patients ready to stop DOT, especially when they are doing well?

Montefiore plans to expand the HIV-DOT program by offering it at additional locations. The plan is to accept all referrals and make the program open-ended. Also in the works are

standardized HIV-DOT criteria and guidelines for treatment regimens. Also needed is reinforcement of responsibilities and boundaries for both staff and participants.

Shannon Hader, MD, MPH, of the Centers for Disease Control

Dr. Hader spoke about use of DAART in New York City residential treatment facilities. This project is a collaboration of CDC and the Control Community Research Initiative on AIDS (CRIA). In New York, DAART has been provided routinely in the more than 12 large residential AIDS treatment facilities, each of which has 100–200 beds. All people with AIDS are eligible. New York Medicare/Medicaid reimburses costs. These sites provide comprehensive, on-site HIV care and services. Most patients have mental illness, drug abuse problems, or otherwise lack adequate social support. The study described by Dr. Hader sought to

- quantify adherence under DAART
- describe virologic, immunologic, and clinical outcomes under DAART
- assess factors associated with treatment failure.

To achieve these goals, Dr. Hader and her colleagues performed a historical prospective study through chart reviews at two facilities. DAART at these facilities consisted of each dose of antiretrovirals being handed to the patient and a per-dose medication record being kept. The primary outcomes tracked were virologic and immunologic stability. Treatment failure was defined as an increase in viral load of more than 0.5 log, a viral load of more than 100,000 copies, or a 30% decline in CD4+ cell count. Secondary outcomes were clinical events, including HIV-associated illnesses, hospitalizations, or death.

A total of 148 individuals, most of whom were very treatment-experienced (75%) and in advanced stages of HIV infection, were enrolled. All patients had CDC-defined AIDS. They were predominantly male (77%), with a median age of 45. Most (66%) had acquired HIV infection through IDU. The baseline characteristics of the population were as follows:

| | | |
|--------------------------|---|----------------------|
| CD4+ cell count | - | 88 cells/microliter |
| Viral load | - | 15,591 copies |
| Baseline viral load <400 | - | 22% of participants. |

The participants logged a total of 60,017 person -days of observation time, with a median follow-up of 366 days per person. Overall adherence was 99% with no significant differences attributable to the class of ART prescribed. In terms of the primary outcomes, 64% of

participants achieved viral loads < 400 copies at least once during the observation period. Forty - two percent failed treatment at least once. Univariate analysis of factors associated with treatment failure showed

- no significant correlation with baseline viral load, CD4+ cell counts, or past antiretroviral treatment
- antiretroviral treatment interruptions of more than 7 days were significantly associated with an increased risk of treatment failure.

Dr. Hader then described the results of multivariate analysis (semi-Markov stages of change model), which was split into two components: (1) likelihood that people failing treatment would transition to response; and (2) likelihood that someone who was responding to treatment would transition to failure.

There were 85 intervals during which people were in a failure state; of those, 50 transitioned to response. In this analysis, being treatment-experienced did significantly decrease the chance of responding to treatment. Having a treatment interruption of more than 7 days also significantly reduced the likelihood of responding to treatment; ART-experienced individuals were only one-third as likely to respond as those who were ART-naïve.

The second component examined the likelihood that a patient who was responding to treatment would then transition to failure. Dr. Hader identified 173 intervals when patients were responding to ART, with 62 subsequent transitions to failure. With this model:

- being ART -experienced and nonadherent were significantly associated with the risk of failure
- patients who were doing well and stable on their therapy did not have an increased risk of transitioning to failure if they interrupted their treatment.

An examination of the study's secondary outcomes revealed that 53 people (36%) experienced 81 episodes of HIV-related illness. Twenty-two people (15%) became ill enough to require hospitalization for HIV-related illnesses. Forty-four people (30%) experienced 89 hospitalizations, of which 33 (37%) were HIV-related, indicating that comorbidities were a significant factor in this population. Sixteen percent died during follow-up.

Dr. Hader concluded that DAART was very effective for ensuring that patients took their antiretroviral medications. Ninety-nine percent of ART prescribed doses were taken. Two -thirds of patients on DAART achieved undetectable viral loads at least once. However, almost half failed at least once, and one-third experienced HIV-related clinical events. These data suggest

that a practical level of response is attainable in an ART-experienced population with AIDS. Some factors, including resistance and treatment interruptions, may have limited the practical level of response. For patients who are not optimally controlled, it is important to avoid treatment interruptions.

Dr. Hader outlined some next steps being undertaken by CDC:

- Compare outcomes for patients on DAART to matched patients receiving intensive adherence support at adult day health centers in New York.
- Compare outcomes for patients on DAART to matched patients receiving standard of care in comprehensive HIV clinics.
- Proceed with prospective interventional trials of DAART in conjunction with Johns Hopkins and the Los Angeles Department of Health.

Brian Harrigan of the University of British Columbia and the British Columbia Centre for Excellence in HIV/AIDS

Dr. Harrigan described a program that provides ART and other drugs to HIV-positive people living in British Columbia. In the area, there are about 12,000 injected drug users, about 4,000 of whom are HIV-positive. The epidemic peaked in 1995–1996. Approximately 400 of these people are receiving treatment through this program. IDUs are underrepresented in the group receiving treatment. Most are in Vancouver's downtown east side where other epidemics—drug addiction and hepatitis—often overlap with HIV infection.

The research that they have done indicates that for successful treatment, people need stable housing and user-friendly treatment regimens. People who are coinfecting need special assistance. To address these needs, a pilot program was established in 1999 with the Vancouver Health Board. The program was called DOT and MAT (maximally assisted therapy), in essence, a version of M-DOT. The setting for the program is a storefront office located in the downtown east side. The office is open 7 days a week, 8 hours a day, and 365 days a year. It is staffed with nurses, doctors, pharmacists, and health care counselors. To enhance adherence, participants are offered inducements, usually in the form of a free breakfast or lunch on site. The program is based on a harm-reduction model; participants feel free to stop in and stay all day if they wish. Coffee, newspapers, and a free telephone are all available, as well as an on-site generic pharmacy.

To promote adherence, the program initially had a significant outreach component, but it was financially unsustainable. Subsequently, they converted to a drop-in setting and rely on outreach only about 5% of the time.

The DOT/MAT clients range in age from 26 to 56 years. Eighty-four percent are men, and 54% are aboriginal. More than 90% report current, active drug use. Upon enrollment, most were in unstable housing situation, but 59% transitioned to stable housing during course of DOT/MAT program.

Fifty-six have been enrolled in DOT/MAT as of June 2000. Adherence is estimated to be 95%. Significant decreases in viral loads and increases in CD4+ cell counts have been observed.

The pilot program will continue for another year. One barrier is cost, which is \$5,000 to \$6,000 per client above the cost of the drugs. Another challenge relates to the setting as plans are forming to move this program into a multidisciplinary clinic where issues of confidentiality will likely arise. This program, like many others, faces questions about tapering patients off DOT or graduating them from the program entirely. As it is, some clients pick up a week's worth of medications but still spend every day at the center.

In terms of future directions, they will be looking at the possibility of capturing clients at local emergency rooms where they sometimes go at night to get medicines.

Christina Hill Zabala, PharmD - Glaxo SmithKline

Dr. Hill Zabala described an upcoming clinical trial of once-daily HAART administered in a modified, home-visit DOT program. This 48-week trial is an open-label pilot study being conducted with the Duval County Health Department (Jacksonville, FL). Two hypotheses underpin this study:

- Once-daily HAART therapy with lamivudine/abacavir/amprenavir/ritonavir will provide durable viral suppression and be well tolerated.
- Twelve-week DOT will improve long-term adherence to HAART in antiretroviral-naïve patients.

The 25 participants are ART-naïve and have CD4+ cell counts greater than 50 cells/mm³ and viral loads exceeding 5,000 copies/mL. Most important, they must be willing to have daily home visits. The once-daily regimen will consist of lamivudine 300 mg (1 tablet), abacavir 600 mg (2 tablets), amprenavir 1,200 mg (8 gelcaps), and ritonavir 200 mg (2 capsules)—a total of 13 pills.

The first dose will be administered in the clinic during the baseline visit. From baseline through week 8, medications will be administered during home visits five days per week. For weeks 8–12, home visits will continue three days per week. Home visits will be supplemented

with reminders delivered via alphanumeric pager through week 12. All DOT will be discontinued at week 12, but the monthly clinic visits will continue for 48 weeks.

The investigators will evaluate the efficacy of this DOT regimen by (1) determining the proportion of participants who have viral loads below 400 and below 50 copies per milliliter at weeks 24 and 48; and (2) assessing the participants' immunologic response at weeks 24 and 48. Other objectives include gauging the regimen's safety and tolerability, and assessing participants' adherence to and acceptance of DOT.

A patient medication adherence questionnaire, a measure of retrospective adherence for past 3 days and the previous weekend, will be used for self-reporting of adherence at weeks 8, 12, 24, and 48. Likewise, the participants' acceptance of DOT will be evaluated using a DOT acceptance assessment (exhibit 1), which consists of six questions that call for responses on a 5-point Likert scale.

Exhibit 1. DOT satisfaction questionnaire.

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| Protocol code ABCD1234 | Session number <input style="width: 40px; height: 15px;" type="text"/> | Subject number <input style="width: 100%; height: 15px;" type="text"/> |
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Satisfaction Questionnaire

Satisfaction With DOT Program
The following statements are about your satisfaction with the Directly Observed Therapy (DOT) program over the past 4 weeks. ✓ only one answer after each statement.

| | Strongly agree (0) | Agree (1) | Don't know (2) | Disagree (3) | Strongly disagree (4) |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. I feel I can take my HIV medications on my own. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. My DOT worker helps me manage my HIV disease. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Since I started the DOT program, I understand my HIV disease better. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. I feel comfortable with the number of times the DOT worker comes to my house. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. The DOT program is helping me take my medications better. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. I would recommend the DOT program to others who are HIV positive. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Satisfaction With HIV Medications
The following questions are about your satisfaction with the HIV medications you've been taking over the past 4 weeks. ✓ only one answer after each question.

| | Very satisfied (0) | Satisfied (1) | Somewhat satisfied (2) | Neutral (3) | Somewhat unsatisfied (4) | Unsatisfied (5) | Very unsatisfied (6) | |
|---|--------------------------|--------------------------|---------------------------|--------------------------|-----------------------------|--------------------------|--------------------------|--|
| 1. Overall, how satisfied are you with the HIV medications you have been taking during the study? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| 2. How satisfied are you with the convenience of the HIV medications you have been taking during the study? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| 3. Would you use the HIV medications you have received in the study again? | | | | | | | | |
| Yes, I would ask my doctor for it | <input type="checkbox"/> | | | | | <input type="checkbox"/> | | |
| No, even if my doctor thought I should take it | | | | | <input type="checkbox"/> | | | |
| Yes, if my doctor thought I should take it | <input type="checkbox"/> | | | | | <input type="checkbox"/> | | |
| No, I would ask my doctor for something else | | | | | <input type="checkbox"/> | | | |
| Not sure, I might or might not | <input type="checkbox"/> | | | | | | | |

SAT (US English) 1

Source: Christina Hill Zabala, Glaxo SmithKline, 2001.

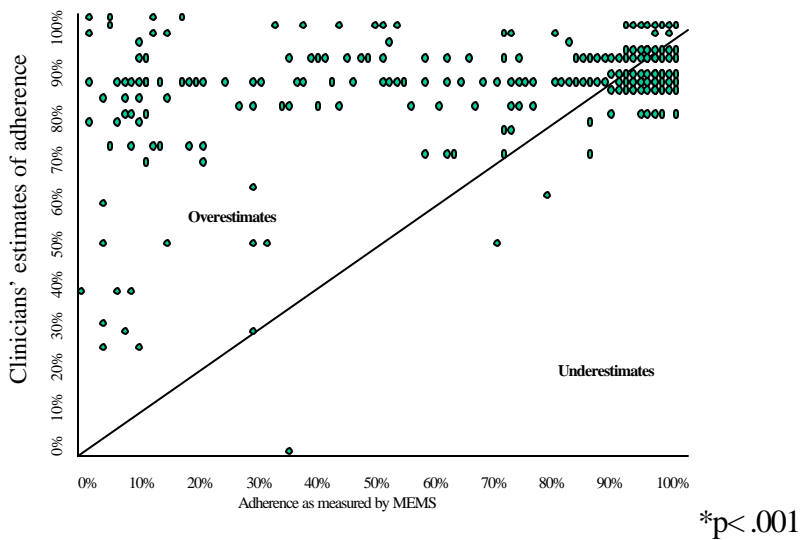
Andrew Kaplan, MD, of the University of North Carolina, Prison Research Group

Dr. Kaplan first reminded the group that physicians are not good at predicting which patients will or will not be adherent to treatment or at estimating individual adherence rates. He presented results of a prospective study of 200 antiretroviral-naïve patients. Clinicians were asked to estimate how adherent patients had been over the previous 4 weeks. A combination of MEMS cap data, serum drug levels, pill counts, and self-reporting was used as an index of adherence. In almost every case, clinicians overestimated adherence (figure 10).

This study also showed that adherence increases in naïve patients over the first two months then decreases by about 10% per patient over the course of the yearlong follow-up.

In the North Carolina Department of Corrections, direct observation of ingestion of protease inhibitors has been the policy. Non -PI antiretroviral therapy can also be prescribed as

Figure 10. Comparison of adherence estimates versus adherence measurements as determined by MEMS cap.* Source: Andrew Kaplan, MD, University of North Carolina, Prison Research Group, 2001.



DOT if clinicians think that the patient-inmate is nonadherent. Patient -inmates receive a 30-day supply at a time.

Dr. Kaplan's group designed a prospective observational pilot study of adherence to antiretroviral therapy in this setting. Adherence was assessed with a combination measure of MEMS caps, pill counts, self-report, and medication administration records (MARs). The goals of the study were to assess HAART adherence, compare adherence to DOT and self-administered ART, and compare measures of adherence within a correctional setting, and assess patient-inmate attitudes regarding health care delivery, adherence, stressors, and quality of life.

The subjects were HIV-positive incarcerated women and men who were receiving three antiretroviral drugs, at least one of which was administered via DOT. Of the 51 patients screened, 41 consented to participate, five discontinued DOT, three discontinued HAART, and two were transferred out of the facility. In all, data were collected on 79 ART prescriptions. The study showed that:

- Thirty-two percent of subjects demonstrated 90% adherence or better to every ART prescribed.
- For 91% of DOT-administered ART, MARs recorded adherence as greater than that measured by eDEM caps.
- There was no change in median HIV-RNA levels from entry to exit.
- CD4+ cell counts increased by a median of 53 cells/mm³ from baseline.
- Five of 28 subjects with follow-up viral load data experienced a rise in viral load, and in all but one of these patients adherence was less than 85%.

From this study, Dr. Kaplan and his colleagues concluded that adherence to HAART by all objective measures was less than optimal for durable HIV suppression in more than half of patients. There was no significant difference between DOT and self-administered ART by any objective measure. This study is also significant in that it was the first to attempt to validate MARs with objective data. Their data suggest that MARs may overreport adherence.

As a next step, the group is starting a randomized, controlled trial of DOT in the North Carolina Department of Corrections called DOT-KOM (Directly Observed Therapy—Keep on Medicine Study). For this study, they are randomizing 200 HIV-positive patient-inmates to either DOT or self-administration for all their retroviral therapy. A secondary randomization will then assign participants to receive motivational interview intervention or standard counseling. Patients will be followed for a year with monthly measures of adherence, as well as monthly viral load and resistance testing.

Adherence will also be assessed at each home visit. The worker will record if the patient took the medication and list reasons for nonadherence (e.g., participant unavailable, DOT worker

unavailable, holidays, self-administered without observation, medication unavailable, participant refusal). On weekends, the pager will remind the participant when to take medications, and adherence will be self-reported.

Gregory Lucas, MD, of Johns Hopkins University

Dr. Lucas discussed a study of DAART in conjunction with methadone maintenance, which is being conducted in collaboration with the CDC. The first patient was enrolled in April.

Why target injecting drug users (IDU)? They constitute an important part of the HIV epidemic. IDU account for 26% of reported AIDS cases in United States; at the Johns Hopkins HIV clinic, where some 3,000 patients are seen, 55% of patients report injected drug use as their primary risk factor. Injected drug users generally experience inferior HIV treatment outcomes compared to other exposure groups, largely because of underutilization of therapy, delayed initiation of therapy, poorer adherence to treatment, and lower rates of viral suppression.

Methadone maintenance—a very effective treatment modality for opiate addiction — features important benefits in terms of reduction of illicit drug use, reductions in criminal behavior, and better socialization and integration into medical care. At first blush, methadone treatment centers seem to offer a convenient venue for DOT within a community setting. If such a model were to be successful, it would be applicable to numerous urban drug treatment centers.

The setting for the study is the Johns Hopkins Methadone Maintenance Program, which is located 3 blocks from the HIV clinic on the East Baltimore campus. The program has about 200 active slots, including Slots dedicated for Ryan -White-eligible individuals.

Some 40% of the methadone clients are HIV-positive. More than half the clients are women. Most are between the ages of 21 and 50 years, African American, and have incomes below the federal poverty level. To be included in the protocol, participants must be receiving HIV treatment through the Hopkins AIDS service and be on methadone maintenance for at least 4 weeks. Both ART -naïve and ART -experienced individuals are being enrolled, although people who have had heavy exposures to all three classes of antiretrovirals are being excluded. The choice of ART regimen is determined by the patient's HIV provider and individualized based on past antiretroviral experience, results of resistance testing, and history of adverse effects. The only stipulation is that the regimen be administered no more than twice a day.

All doses are packaged in labeled plastic bags. When patients present for their methadone dose, they also receive a directly administered dose and a bag with their evening dose.

Participants will self-administer ART for evening doses and on methadone “take-home” days, when they do not have to come into the clinic. When participants return to the clinic, they are queried about their adherence with the self-administered doses. Directly administered doses and self-reported adherence are recorded on a daily log. Each participant also receives a 3-day emergency supply of medication.

Dr. Lucas and his colleagues will prospectively collect data on viral load and CD4+ cell counts, clinical disease progression, mortality, and development of ART resistance. For program evaluation, they will also collect data on retention rates and reasons for discontinuation. In addition, they will examine data on costs and resource utilization.

This DAART intervention is nested within the Hopkins HIV Cohort Study, which has been in place for the past decade, and which routinely collects clinical and cost data. For the DAART project, the investigators will compare relevant HIV treatment outcomes with matched patients who have received standard care at the AIDS clinic.

The goals of this study are:

- to develop a DAART strategy within a methadone setting
- to compare HIV treatment outcomes with similar, matched patients receiving care in the Hopkins AIDS clinic
- to provide a basis for carrying out larger clinical trials.

One of the early concerns that is being addressed is confidentiality. A focus group of about 15 patients expressed a wide range of opinions; some were clearly concerned about taking ART at the methadone window. Logistical problems exist, too. Rapidly swallowing 5 to 10 pills quickly, while standing at the methadone window may be a daunting challenge for some. To address this problem, Dr. Lucas is looking into the possibility of administering ART in a nearby office. This measure, however, separates DOT from methadone and may compromise the ability to translate this study’s results to methadone programs at other centers.

Again, the question arose about how long DAART should continue. Funders, including HRSA, may be interested in continuing the program beyond 12 months if the system proves effective. Weaning from DAART is a secondary consideration, according to Dr. Lucas. The primary concern should be to determine whether the DAART intervention has short-term positive effects.

Kathy McCallum, RN, ACRN, of AIDS Services of Dallas

Ms. McCallum described a program that started in a simple way. Her initial intent was just to increase the amount of information to physicians before clients' appointments. She started counting pills that remained in clients' pillboxes and let the physicians know that not all medicines were being taken as prescribed. The physicians came to appreciate this service and requested that she institute short-term DOT with the clients. Subsequently they embarked on longer-term monitoring.

Ms. McCallum fills pillboxes for about 20 clients each week and then checks the boxes weekly to see which medications were taken. She then follows up with physicians. If a pattern of non-adherence emerges with certain medications, she will adjust medication combinations to see if adherence improves. The emphasis is on empowering clients by helping them to understand how important their medications are for their health. She also shares with clients the results of their viral load assays and CD4+ cell counts to provide some positive feedback.

Ms. McCallum offers this assistance to any client who desires it. The service is particularly helpful for clients who are psychiatrically compromised, either because of medical problems or true mental illness. So far, she has served 62 clients, maintaining 15 to 20 pillboxes at any given time.

By looking back over the past 3 years, she was able to determine that 39% became adherent and ultimately did well; 35% were deemed non-adherent but expressed a desire to enter hospice care for end-stage illness; and 24% quit for other reasons. Overall, being able to observe clients and communicate with them and their physicians was a rewarding experience for Ms. McCallum and an empowering phenomenon for her clients.

Elinor McCance-Katz, MD, PhD Albert Einstein College of Medicine

Dr. McCance-Katz described a study of DOT for HIV disease in a methadone maintenance setting in operation for about a year. She described some of the challenges in setting up and carrying out the program.

The first challenge involved working with clinical staff. A full year was necessary to get clinicians to accept the new program. Physicians feared that this system would erode their authority, and they were reluctant to refer patients into the program. This familiar tension between clinical programs and research often exists because of the difficulty convincing

clinicians that research programs may benefit participants. Over-burdened staff may also fear that research programs will result in additional workloads. Building a therapeutic alliance between research and clinical staff requires time and some convincing.

Other challenges arise from working with participants. The participants must:

- make a lifelong commitment to HAART
- decide if they want to take their medications in a clinic setting
- adhere to all prescribed medication
- deal with the potential stigma of an HIV diagnosis
- address the lack of privacy in the clinic
- overcome their fear of withdrawal symptoms associated with taking HAART

Dr. McCance-Katz stressed the importance of closely monitoring patients for signs of methadone withdrawal. If withdrawal symptoms are not managed effectively, the patients may turn to illicit opiates to alleviate their symptoms. Providers must weigh this ethical consideration so as not to impede patients' progress in turning away from opiate addiction.

Abuse of other substances is a huge problem in this special population. Virtually 100% of the population has some other substance use disorder. In addition, 80% have psychiatric comorbidities, mainly major depression. These are common and must be dealt with via medication and psychosocial interventions.

DOT must be viewed as more than pill-taking observation. Alliances between the patients, clinic staff, and research are necessary to provide the best possible care for people on methadone maintenance. HIV care and psychosocial needs must be well coordinated to monitor and manage withdrawal that may result with HAART and to diagnose comorbidities (e.g., other substance abuse, psychiatric disorders, other medical problems). In addition, the staff may have to arrange for DOT to continue if the client is transferred to another institution.

DOT is best with once-daily therapies, but that is often not possible and a modified DOT plan should be considered. To accommodate M-DOT, staff must develop a system to maintain contact with clients outside of the clinic via beepers and so forth to issue reminders to take medications. It is also necessary to coordinate with pharmacists to pack the doses for self-administration. The staff also monitor adherence and attend to clients' psychosocial needs, including housing, legal, and entitlement issues.

DOT is an effective intervention for drug users. Referrals to Dr. McCance-Katz's study included individuals known to be nonadherent in past HIV treatment modalities. After 8 weeks of M-DOT, 80% had undetectable viral loads.

Finally, Dr. McCance-Katz urged treating the entire patient and to promote other positive life changes to include:

- treatment for other substance disorders
- treatment for psychiatric disorders
- fulfillment of psychosocial needs
- positive reinforcement to encourage the patient to continue adherence and make other positive life changes.

Amy Rock Wohl, PhD, of the Los Angeles Department of Health

Dr. Rock Wohldiscussed a CDC-funded evaluation of DAART in a randomized intervention trial. The study is designed as a randomized intervention trial in which 300 HIV-infected patients are being recruited from two large public HIV clinics in Los Angeles. The project is about to be launched; no data are yet available.

The patients will be randomized into one of three arms of care:

- a DAART program
- intensive case management program with enhanced adherence support
- standard of care, which largely consists of receiving adherence counseling from their health care providers and pharmacists.

The major aims of the study are to compare the following among the three arms of the study:

- viral load and immunologic responses
- rates of opportunistic infections and death
- development of resistance
- levels of adherence
- cost and feasibility
- health care utilization costs.

The two large HIV clinics from which the participants will be enrolled report that their clients are approximately 50% Latino and 24% African American. Eighty percent are male. Forty percent fall into the men having sex with men (MSM) risk group, 12% in the IDU risk group, and 7% in the heterosexual exposure risk group. This is a fairly disenfranchised

population, with incomes less than \$10,000 per year and most receiving public assistance. Fifty percent have no insurance and 25% are covered through MediCal.

To be included in the study, patients must not have been exposed to more than one HAART regimen that caused a decline in viral load to less than 400 copies. HAART is defined as any of the following:

- any regimen of three or more drugs that includes a protease inhibitor
- any regimen of three or more drugs that includes an NNRTI
- a three-NRTI regimen that includes abacavir.

To focus on a population that is either HAART-naïve or just experiencing first failure, patients must have either (1) begun a new HAART regimen within the past 6 months; or (2) changed at least two drugs in an existing HAART regimen because of clinical, immunologic, or virologic failure.

In addition, patients must be on a twice-daily HAART regimen and must live or work in the immediate service area so that community workers can make contact.

The DAART program was modeled on successful health department model of TB-DOT. Three bilingual community workers will pick up the clients' prepackaged daily HAART doses from a private pharmacy, go to meet with the client and directly observe the ingestion of one of two daily doses of HAART. In addition, the community worker gives the patient one prepackaged dose for self-administration in the evening. During the visit, the community worker will pick up the empty dosing package and ask the client if dose was ingested. The community worker will also review a checklist of symptoms and side effects, and note any changes in health habits or psychosocial status.

DAART will occur 5 days per week over a 6-month period. On Fridays and before holidays, the community worker will give doses for those days. Patients will receive a 3-day supply to keep at home in case they do not meet with their community worker on a given day.

After 6 months in the DAART study arm, the patients will be transferred to the intensive adherence case management program for 6 months. Any client who refuses to follow the DAART plan will be reevaluated. An exit survey instrument will be used to ascertain reasons for discontinuing DAART. They will be collecting data on adherence, laboratory and clinical data (including viral resistance testing), acceptability of interventions, costs of interventions, and costs of health care utilization. CD4+ cell counts, viral load, and drug resistance data will be

compared for participants in each of the three study arms after 6, 12, 18, and 24 months of enrollment to evaluate the short-term and long-term responses to the interventions.

Dian Sharma, PhD, of the Tacoma Department of Health

Dr. Sharma reported on an innovative model, which arose from a public-private partnership between the Tacoma-Pierce County Health Department and Infections Ltd. In this blue-collar county of the Pacific Northwest, there is a fair amount of industry, some port facilities, three large military facilities, and Mount Rainier National Park. The community is largely white (78%) and about half male. Incidence rates of HIV are substantially higher among people of color than among whites and about twice as high in males as in females. The major HIV risk group is MSM (33%), followed by IDU (29%), MSM/IDU (10%), and sexual contact with an HIV-positive individual (14%).

The county has implemented a rather “aggressive” community disease model, according to Dr. Sharma. The local board of health, in 1997, elected to transfer all direct services to the private sector, leaving the health department responsible for the core functions of assessment, policy, development, and quality assurance. In the network are public health nurses who spend their days conferring with doctors and other service providers to convey the public health message and report communicable diseases.

Subsequent to the clinic transition, the department of health evaluated all services that had been provided previously by the county. One of these services was tuberculosis care. As a result of the privatization of TB treatment, direct costs (e.g., personnel, supplies, physician and pharmacy contracts) declined by 29%, and personnel costs declined by 50%. Dr. Sharma recommended that those who struggle with finances should consider implementing this model, and she offered to provide guidance to any jurisdictions that wish to identify barriers and opportunities presented by this model.

At this point, Lawrence Schwartz, MD, of Infections Limited took over to describe an innovative model for home-based TB-DOT. Infections Limited is a comprehensive infectious disease practice involving seven practitioners.

The DOT model is based on telemedicine and relies upon videophone technology. To be eligible for this program, patients must first demonstrate 4 weeks of 90% adherence with standard DOT administered by health department personnel or community workers. Once the

patient is familiar with the concept of DOT and agrees to have the technology installed in his or her home, the unit is brought into the home. The patient must be capable of keeping their videophone appointments, must be able to communicate with the provider, and must have a telephone line near the television set.

They obtained six set-top videophone units at a cost of \$200 each. Smaller units with newer technology have integrated telephone/LCD displays but the cost is higher—about \$300 to \$500 up to \$1,500 per unit. As broad band and better infrastructure become available, the cost will probably decrease significantly.

On average, a videophone interaction with a health worker takes about 3 to 5 minutes, compared to an hour for driving to remote areas of the county to administer DOT. In fact, 3 hours would be required to make the round trip to remote parts of the county. Another benefit of this system is that the community workers can work from their homes.

Dr. Schwartz reported that with 304 treatment doses, they have had 95% adherence and saved 268 hours of personnel time and 8,830 miles of travel, netting savings of \$11,000. Other benefits included flexibility for the patients and staff, convenience, brief daily time commitment, less intrusiveness than having a community worker visit the home, and cost-effectiveness.

There are some limitations, too. The technology is still developing, significant start-up costs are involved, units may be lost or damaged, and patients must be committed to the DOT program. On some occasions, the patient was not home at the designated time, and 3% to 4% of the time a connection could not be established.

Dr. Schwartz presented a video that demonstrated how the system works; the video and audio feed were certainly of adequate quality to verify that the pills are being taken. Patients are seen monthly in the clinic, and community workers can be dispatched to the patients' homes if necessary. Dr. Schwartz urged the meeting participants to consider videophone interventions for HIV-DOT.

Defining DOT: background for breakout sessions

Valerie Stone, MD – Brown University

Valerie Stone, MD, of Brown University and David Cohn, MD, of the Colorado Department of Health raised provocative questions about the ethics behind the design and implementation of DOT for treatment of HIV. These questions provided a backdrop for the

discussions in the breakout groups. Based on what we have heard today about 13 different programs, we can see how some of these issues play out in the real world.

What are the goals of DOT? According to Dr. Stone, it is important to be explicit about goals and not to make assumptions. Is the goal of DOT to benefit individual patients or to benefit the public health? These differing goals may well result in different programmatic structures. We must also remain mindful about the limits of the TB-DOT analogy. Obviously, the two diseases are spread in different ways, and the implications of not treating HIV are very different from the public health implications for untreated TB. Because of these differences, it is easier to justify incarceration for those who do not comply with their TB treatment regimens.

Who will benefit from DOT? Who are the most likely candidates for DOT programs and why? None of the programs described today mandated or offered DOT to all program participants. Dr. Stone suggested that the breakout sessions consider several populations who may benefit from DOT:

- those who are persistently nonadherent with their therapies
- active injection drug users
- active alcohol abusers
- homeless and marginally housed
- depressed patients
- those who are ART-naïve (or, perhaps, those who are ART-experienced).

Is there a role for involuntary DOT? The community of HIV-positive individuals and the public health have benefited greatly from the voluntary nature of diagnostic and treatment programs. Will that foundation of success be compromised if enrollment in DOT is involuntary at least for certain individuals? We must assure communities that have concerns regarding conspiracies, stigma, and marginalization. For voluntary DOT, we must discover how to motivate patients to enroll and stick with the program. What incentives should be considered and how much do incentives add to program costs? What are the ethical considerations in the use of incentives in DOT programs? How might they affect patients' decisions to enroll, to start treatment, discontinue, or change treatment? Might people, especially in impoverished areas, take potentially toxic medications just to receive the incentives? Is this acceptable?

Is it ever appropriate for DOT to be mandatory? Is it ever appropriate for DOT to be a requirement in order for certain people to receive HAART? Who should be involved with these decisions to ensure that they are made in a fair way without discrimination or reliance upon

preconceived notions? Perhaps there is a role for local, state, or federal policy to govern how these decisions are made.

Other considerations. Some ethical implications center around confidentiality issues. How can programs be structured to maintain patient confidentiality in DOT? We must also consider how DOT may affect patients' treatment options in terms of specific therapies and regimens. Clearly, we must ensure that regimens chosen for DOT are efficacious, durable, and tolerable. We may need more data to show that HAART regimens chosen for use in DOT programs are as good—or better—than other regimens.

Other considerations for DOT programs are

- how to incorporate needed structure while keeping the programs flexible and responsive enough to minimize the intrusiveness and scheduling burden on patients
- how to help patients with the heavy pill burden involved with once-daily regimens
- how to maintain cultural sensitivity and competence.

Can DOT respect individual and cultural differences? Programs must be sensitive to the needs of all the patients it is serving. Programs must be respectful of the individual and differences, including gender differences; responsive to patient needs, expectations, confidentiality, and lifestyles; and responsive to patient change and growth in terms of tapering off DOT.

Can the cost of DOT be justified? Cost, of course, is another important consideration for DOT programs. It seems that most patients do not need DOT, but for whom and in which settings will DOT be cost-effective? When does benefit outweigh the high cost of DOT? When are incentives appropriate and cost effective?

A major budgetary consideration is staffing of DOT programs. Should programs employ nurses or community workers? What qualifications and training do the staff need? How should the link with prescribing practitioner be operationalized and maintained so that we do not cause a separate system of care, or cause the patient to stop seeing their primary care provider?

Which settings are appropriate for DOT? We have heard today about several different settings for DOT programs—methadone programs, needle exchange sites, clients' homes. How can settings be modified to make DOT feasible and acceptable? We have already heard about how handing patients their HIV medications at the methadone window is just not accepted because of the loss of confidentiality and because it may not be possible to gulp down so many

pills so quickly. We can also consider other venues, such as HIV clinics or AIDS service organizations where providers are not already located.

How can DOT be linked to other services? Which service linkages should be high priorities and why?

Need for flexibility. Should there be a variety of DOT program structures, and, if so, what should these be based upon—different patient populations, different programmatic goals, different settings, cost considerations, degree of direct observation (DOT versus partial DOT versus modified DOT)?

Dr. Stone, speaking from her experience as an adherence researcher, stated that the ultimate goal with DOT is to help people adhere to their therapies over the long run. How should DOT programs build in flexibility so that patients can change regimens based on responses, tolerance, preference, or new data? How can programs educate patients about adherence to foster eventual independence from DOT? What technologies (e.g., beepers, pill containers, MEMS caps) can we use to bolster patient independence? Can DOT enhance treatment adherence for other conditions such as mental illness and drug abuse?

How long should we rely upon DOT for a given patient? We have all talked about a role for short-term DOT, but can a given program support a variety of DOT terms and accommodate changing patient needs? How can we assess a patient's readiness to come off DOT and make the transition to autonomous treatment?

Outcomes for assessing DOT programs. The list of applicable outcomes may include viral load, CD4+ cell counts, hospital admissions, opportunistic infections, and status of comorbidities such as substance abuse and mental illness. Patient-centered outcomes could include satisfaction with care, trust, attitudes toward antiretroviral therapies and HIV, knowledge about treatment, risk behaviors, and patient feelings of self-efficacy. All of these are critical if patients are ultimately to be tapered off DOT. If we examine the impact of our programs, which are often multifaceted, how can we isolate the DOT piece, to determine its contribution to observed outcomes?

In summary, numerous intersecting ethical and practical issues affect the design and implementation of DOT programs for HIV treatment. Explicit decisions about programmatic goals will help in program design and evaluation plans. We must take care to maximize respect

of individual patients, including their cultures, lifestyles, and values while designing programs that will have the intended outcomes.

David Cohn, MD, of the Denver Department of Health and the University of Colorado Health Sciences Center

Dr. Cohn presented his thoughts on ways to define DOT. His comments helped to set the stage for the break-out groups. First, he reviewed and proposed some nomenclature:

- DOT—all doses are observed
- DAT (directly administered therapy)—the same as DOT, although others have defined as some but not all doses are observed
- P-DOT (partially directly observed therapy) or M-DOT (modified directly observed therapy)—some but not all doses are observed
- DAART (directly administered antiretroviral therapy)—a new term that seems preferred by CDC.

Dr. Cohn reminded us to keep in mind the difference between effectiveness—the ultimate outcome of all who are involved—and efficacy, which in epidemiologic terms, refers to the outcome as measured by the selected primary endpoint in all who actually take the prescribed regimen. Effectiveness looks at the entire population in the study, whether they took the regimen or not. With P-DOT, effectiveness is potentially compromised by not observing every dose, but the feasibility is likely enhanced by using a program that does not demand that each dose be watched by a program observer. It is likely that the trend will be toward what might be more feasible than what is maximally effective.

Pill counts, MEMS caps, and pharmacy records can evaluate adherence, as well by as clinical objective parameters such as viral load and CD4+ cell counts. All of these are short-term objectives. But, can we settle for short-term effectiveness? We need to look beyond 12 weeks to 48 weeks and beyond. Future studies should include longer-term objectives to look at outcomes after the program has stopped, analogous to an intention-to-treat analysis in a large clinical trial. Is this a reasonable objective for randomized or so-called operational research?

One of the big issues is how long the patient should continue DOT—weeks, months, years, or a lifetime. Lifetime is probably not a realistic option. This decision will be largely resource-driven, but some parameters will likely indicate when and how to stop DOT, among them:

- patient choice

- provider choice
- ongoing patient-provider discussion
- pre-set schedule based on research
- “success” milestones.

In the end, the use of “success” milestones is likely to be the most effective component of this decision. This approach will allow more flexibility than a pre-set schedule for tapering. The patient and provider can then enter the realm of tapering with an option to restart DOT if necessary. This scheme will be difficult to describe from a research perspective, as patients start, stop, taper, or restart DOT. Nevertheless, this should be a topic considered by the breakout groups.

Who should observe the patients taking their medication? We have heard many suggestions based on the 13 programs already presented today, among them health care providers, peer counselors, case managers, social workers, outreach workers, and community members. Two other possibilities are family members and business establishments. Certainly we can look to the model of the CDC-sponsored AIDS prevention demonstration projects, when we were first learned how to do community outreach and we were attempting to change community norms. For those projects, we engaged often-used business establishments as places for interacting with persons at risk. Costs, practical issues, and the nature of the community setting and client base largely drive this decision.

Dr. Cohn also discussed the ramifications of mandatory versus voluntary programs. It is intuitive that the TB model of mandatory programs ensures maximum effectiveness, but involves significant ethical and legal issues. He also brought up the issue of the negative connotation of the word *mandatory* and suggested substituting the word *routine*. Emphasize that DOT is a *service*, not a *mandated intervention*. Voluntary programs preserve patient autonomy, but we must consider this selection factor: Are the patients potentially at greatest risk for nonadherence the most likely ones to decline DOT? This question should be addressed in studies.

Shall we go to the patient or shall the patient come to us? A delivery system for bringing drugs to the patient offers the greatest flexibility but does require an outreach network. If patients go to centers to receive their medications, there is an economy of scale because of the centralization of services, but the centers must have the necessary infrastructure. Toxicity

management can likely be handled most effectively in a clinic setting rather than in an outreach setting.

We have heard many pros and cons about offering incentives. Emerging literature shows that incentives are effective in HIV intervention programs, and a long history of successful TB programs shows that they work. Yes, they are effective, and programs like that at Montefiore give us a wealth of options to consider. Incentives do involve additional costs, but may well offer considerable benefits. Although the potential for fraud exists with cash and checks, the presenters today have discussed several possible alternatives, including certificates and vouchers for food, transportation, and merchandise.

Perhaps the most challenging question of all, according to Dr. Cohn, is this: Who is going to pay for all this? Federal, state, or local HIV-specific funds are logical sources of funds. Third-party payers are a potential funding source if a legislator or insurance company can be convinced that DOT programs are cost-effective. Demonstration projects, foundations, and donations may also be sources.

How can DOT programs be linked to other services? Some successful models have linked to clinics, hospitals, social services, storefront facilities, needle-exchange programs, methadone clinics, and pharmacies. Dr. Cohn related a personal insight, stating that the most significant improvement that his group has done to enhance patient care in the HIV/AIDS clinic was using Ryan White funds to establish an AIDS-specific pharmacy adjacent to the clinic. This has provided both a user-friendly facility for patients and a linked computer-based system for closely monitoring medication refills and indirectly, adherence. Provision of the drugs is not a small issue.

What is the best way to determine a treatment regimen for a patient? This decision should rest with the provider and the patient based on a pharmacokinetic profile, toxicity profile, therapy regimen, and cost. Ultimately the question is whether the patient can tolerate a given regimen, and tolerability of drugs will be a rapidly moving target as new drugs and regimens are developed and shown to be effective. Programs must establish entry and eligibility criteria for DOT, evaluate resources and staffing, and develop the requisite infrastructure. Eligibility also hinges on other factors, including community demographics and the patients' psychiatric and substance use histories and their proximity to the clinic or storefront.

What are the needs of special populations that will most likely be targeted for DOT?

HIV and DOT in a large urban jail - James McAuley MD, MPH, Cermak Health Services of Cook County

Dr. McAuley opened with a few statistics about the populations of U.S. prisons and jails:

- 6.3 million (3.1% of U.S. adults) are on parole, probation, or incarcerated.
- 2 million Americans were behind bars (> 600,000 in jails) at midyear 2000.
- 668 per 100,000 Americans are incarcerated, 5 to 10 times the rate of Europe.
- Most are in for drug use.
- One in 12 black men aged 25–29 is behind bars.
- Corrections is a “growth industry.”

Jails are mostly run by county governments and have very fluid populations because they are intended just for pretrial incarceration or sentences of less than a year. The state or federal government usually runs prisons. Approximately one-third of incarcerated individuals are in jails.

Women represent approximately 15% of the jailed population. One-third of inmates report some physical or mental disability. Fifty-four percent of inmates have a high-school diploma or its equivalent, but 36% were not employed during the month before their arrest. The majority of jail inmates are nonwhite minorities, generally populations that were marginalized from health care prior to incarceration.

In fact, jail may be the primary source of health care for many detainees. Prisoners have a constitutional right to health care, unlike any other population. Lawsuits by inmates and employees have been the primary determinants of what is considered an appropriate level of health care. Consequently, correctional health care has become an emerging discipline.

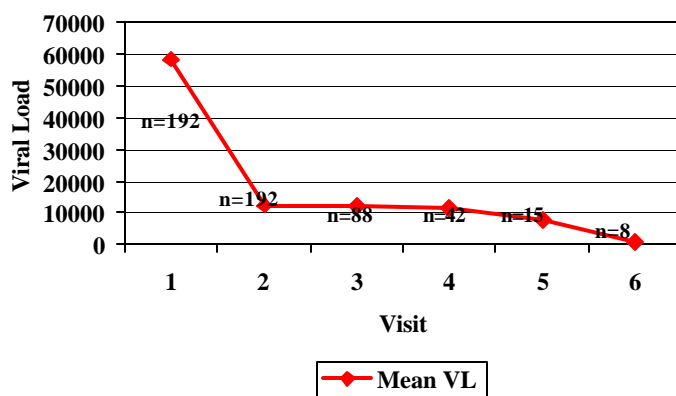
The imprisoned population is at high risk for many health problems. Therefore, jail-based interventions can have a great public health impact. At Cook County Jail, 2.3% of new admissions in 2000 were positive for syphilis, about 35% of all cases reported in Chicago. Mental health problems are also significant among jail inmates. Between 6% and 15% have axis I diagnoses, and 25% report having been treated for mental or emotional problems. In addition, only 2.3% report being under a physician’s care, but 26% report taking prescription medications.

Cermak Health Services is one of the largest jail-health systems in the United States. The annual budget is about \$38 million, and it employs about 540 people. The mean length of stay is 46 days, but the median is 13 days—a revolving door, in essence. The complex occupies a 100-acre site on the southwest side of Chicago.

The HIV counseling and testing service is voluntary. Of those volunteering for such testing, 4.8% are positive. In 1999, they conducted a blinded serosurvey using 2,500 sera from syphilis screening tests (RPR), of which about half were from women. These sera showed a prevalence rate of 2.57% HIV seropositivity in the incoming jail population (women overrepresented). The year 2000 saw more than 700 individuals with HIV diagnosed; these people were then engaged them in care.

Once a person is identified as being HIV-positive, the health care staff tries to get therapy started as soon as possible, usually within 24 to 72 hours. DOT is universal up to two times per day. If a thrice-daily regimen has been prescribed, the inmate must self-medicate for one of the doses. Dr. McAuley presented data on declines in viral loads during jail stays (figure 13).

Figure 13. Viral loads in HIV - positive individuals incarcerated in the Cook County Jail during 2000 (N = 192). Source: Altice F. Cermak Health Services, 2001.



Because the jail stays are brief, after-discharge planning starts right away. With HRSA/CDC cooperative agreements, they have been able to have the same team of physicians and physician assistants provide care both in the jail and in the community at the core center. Because the inmates are usually released without any notice, each inmate is provided a 2-week supply of medication with the understanding that can be refilled anytime at the CORE center, the

HIV center at Cook County Hospital. Much emphasis is placed on the transition program for weaning inmates off DOT because they will be unlikely to receive their medication via DOT in the community. The next phase of data collection will address what happens in terms of viral load after they leave the jail; these data are being collected now.

How do inmates make the transition to self-administration after DOT? Currently about 10% of the HIV-positive jail inmates self-medicate now. Inmates are not allowed to transition off DOT if they are on psychotropic drugs (about 1,000 inmates per day), taking TB medications, or if they have a history of “cheeking” their medications. To enter the transition phase, inmates must state that they are ready to do so, have 2 weeks’ experience in the system, must demonstrate an understanding of their HIV medicines, and submit to weekly checks by a registered nurse.

Do inmates experience stigma if they receive HIV-DOT? Most detainees do not seem to care. Although the inmates have not been formally surveyed, the staff have indicated that because so many medications are given by DOT (approximately 15% of the jail population), there is little stigma associated with the process. First-timers appear to be the ones with the most problem with the system. When problems are reported, the inmates often report that the panel officers are the biggest part of the problem with stigmatization.

After release, they may go to the CORE center where the same providers are available to provide drop-in care. Currently approximately 15 recent detainees appear each week for care (700 annually). Once they have made a connection to the CORE center, the staff try to transition them to other providers so that the CORE center does not become overwhelmed.

This program faces an array of challenges:

- Issues sometimes arise because of different priorities: security versus health care.
- Resources are scant; the center is currently funded as a HRSA demonstration project, but it is not eligible for Ryan White funding, and the public is generally disinterested in incarcerated populations.
- Helping inmates’ transition to care in the community is an immense challenge, especially because little, if any, notice is given about their release back into the community.

Views of an advocate for prisoners with HIV - *Judy Greenspan, California Prison Focus*

Ms. Greenspan noted that two components were lacking during this meeting: more focus on the ethics of DOT and the voices of those who have been affected by DOT firsthand. Her presentation helped remedy those shortcomings. Ms. Greenspan has worked for some years with

California Prison Focus as an advocate for prisoners who are HIV-infected. California Prison Focus is an all-volunteer organization. The members visit and advocate for 100 or so prisoners with HIV, hepatitis C, or both in the California State prison system.

The advocates visit approximately 60 male prisoners who are housed at the Corcoran State Prison and about 40 women prisoners at the Central California Women's Facility. These two facilities seem to provide the most inconsistent care in the California prison system.

In October of 2000, hearings were held inside the women's prisons about the quality of health care and conditions of confinement. Ms. Greenspan chaired a panel of three incarcerated women who co-infected with HIV and HCV. Some of the most moving testimony was about DOT. Consider the words of Beverly Henry, a self-identified woman prisoner living with HIV and hepatitis C, who testified before the committee:

"I also have a problem with confidentiality and the med line.... For the women that have to take meds, these lines last a long time. They have to stand in extreme heat. They stand in severe cold weather just to get their cocktail, which in my personal opinion,...could be administered in their rooms. These are not hot meds. This is not Valium, this is not Vicodin, these are antivirals to take for HIV"....Why does everybody have to know? And, you try and let them know that, well, it's supposed to be confidential, but what's confidential about standing in line and picking up a packet and nobody else is doing it?"

Judy Ricci, another self-identified woman prisoner coinfecting with HIV and hepatitis C who testified shed some light on the origins of DOT in California prisons:

"My other real big problem is that fact that HIV meds are given in daily packets. In 1998, they discontinued the practice of giving HIV meds in a 30-day supply in favor of DOT therapy. This they blame on the *Shumate* lawsuit. DOT is...directly observed therapy. Directly observed therapy meant that we went from a 30-day supply to going to them three times a day....Now we go to the med line every day for three little packets of medication. I want to tell you that this medication is noninjectable. It's not a narcotic. It's not psychotropic. I can't sell it to anybody who wants it, you know. This is the only medication given in a small packet like that. The *Shumate* lawsuit agreement says—the only thing it says about pill lines is that policy shall be provided to ensure the confidentiality of people taking medication, but you just put a flag on me, number one. The second thing is that the *Shumate* lawsuit...required that confidentiality be maintained at the window, so they painted a 15-foot line around it. They also put a little plastic enclosure over the med line so that while we're standing there we won't get wet and we won't get burned."

Ms. Greenspan said that prisons are the testing grounds for projects that are subsequently imported into the community. She hopes that DOT as it exists in prisons today will not be the DOT brought into the community. As we become proponents for DOT, as medicating becomes simpler, we must realize that it will not always be implemented with the safeguards we envision.

In California, the system went from weekly and monthly packets of medicines for self-medication to DOT. They just posted a sign in the clinic saying that as of December 15th, monthly packets would no longer be available for self-administration, that all those requiring HIV medications would have to stand in the pill line at least once a day. There was no attempt to explain DOT or educate the inmates about it. Everyone had to go to DOT.

This phenomenon compounded the women's feelings that they were being punished for having HIV. At the women's prison, the med line was outdoors, and some women had to stand on line three times per day. Some women (about 25%) were too ill or too embarrassed to stand on line. The situation was not as traumatic for the men because they were usually in self-contained HIV units. But, the women were incensed. They felt it was a coercive, humiliating way to care for those with HIV. If they were too ill to stand in the medication line, they did not receive their medications. We must ensure that such is not the case for other marginalized populations outside the prison walls.

Some changes have been made. Women can now receive one dose by DOT and carry one or two doses back to their cells for self-administration, necessitating only one trip to the med line each day.

We must learn from the errors committed during the institution of DOT in prisons. Ms. Greenspan offered the some guidelines for promoting use of DOT in prisons. These guidelines will also translate to DOT in the community.

1. Keep DOT voluntary.
2. Take strong measures to avoid breaching patient confidentiality.
3. Educate the patients before starting DOT programs.
4. Establish linkage to peer educators.
5. Get consent for the program.
6. Conduct resistance testing.
7. Provide support services to explain the regimen and set up a place where people can discuss and deal with side effects.
8. There must be follow-up and assistance to help prisoners make the transition to life back in the community.

In closing, Ms. Greenspan invited the meeting participants to become involved with prisoner-patients and urged them to avoid following the prison model with its reliance on coercion and lack of measures to preserve patient confidentiality.

DOT In the HIV+ Homeless - David Bangsberg, MD,MPH, University of California at San Francisco

Dr. Bangsberg's presentation covered three topics. First, he asked: Are the homeless a special population when it comes to adherence? His answer is no. Then, he addressed the reasons for instituting DOT: lengthening duration of treatment, improving adherence, reducing viral load, avoiding resistance, delaying AIDS progression and death. Finally, he raised the questions of how to select adherence programs and how to select patients to receive DOT.

Comment: Might keep it general after the suggestion that the homeless are not necessarily special adherence population

The REACH cohort - Dr. Bangsberg drew his information from the REACH Cohort (Research in Access to Care in the Homeless) of HIV-positive, urban-poor people, many of whom are homeless. This cohort was identified through population-based sampling of free food lines, low-income hotels, and shelter facilities in San Francisco. To date, 330 people have been enrolled into the cohort to be followed for 2.5 years on average. Participants receive a \$10 incentive for each visit. In this population, the seropositivity rate is 9%.

Adherence is gauged by three measures:

- 3-day self-report
- MEMS cap
- unannounced pill counts at the participant's usual place of residence.

The third measure of adherence is unique to this study. What the investigators do is go out once a month on random days and find a participant. They will gather up all the participants' medications, count their pills, and record their refills. By performing these counts unannounced on random days, it makes it less likely that pill dumping will occur. What they found was very close agreement between MEMS cap openings and pill counts (1).

Adherence to treatment among the homeless - Are the homeless a special population with respect to adherence? The average adherence to ART in this population was about 67%, about 5% to 10% less than a more stable population. There is much more overlap than difference in adherence between the homeless and other populations. More than a third of this population

demonstrated better than 90% adherence. Therefore, this population seems like most other groups in regards to treatment adherence.

Next, Dr. Bangsberg discussed the relationship between level of adherence and early discontinuation of therapy. Everyone who discontinued within 6 months started with less than 80% adherence, whereas those who have better than 80% adherence tended to stick with the program for a long time.

Assessing adherence. Another issue is how to assess adherence in clinical practice. There is a consistent body of literature in both HIV and non-HIV medicine indicating that health care providers are able to discriminate between patients' with good and poor adherence no better than random. Consistent with this literature, Dr. Bangsberg presented data from the REACH study indicating that providers caring for HIV+ homeless patients consistently overestimate adherence; most providers think their patients are taking more than 80% of their medications. Conversely, providers often do not recognize patients having difficulty taking their medicine(2).

While providers have difficulty estimating adherence, individual patients can report adherence precisely using a three-day structured report. This is true even for patients who are addicted, mentally ill and/or homeless. Tools like these could prove useful for therapeutic monitoring and help identify patients who are good candidates for adherence interventions. (2).

Computer-assisted self-interviewing (CASI) may also prove to be a beneficial tool for determining patients' understanding of medication regimens and monitoring their adherence in clinical practice. Another benefit of this system is that the computer can display a picture of the medication, not just the name of the medication. CASI has been used in sexual risk-behavior research in which it proved more effective at eliciting information about risk behaviors than face-to-face interviews, and thus identify adherence or other presumably difficult-to-report behaviors better than patient interview. Early studies suggest that CASI adherence tools are closely associated with viral suppression and are feasible in clinical practice(3).

Correlating adherence with the clinical picture. Dr. Bangsberg then described an analysis of MEMS cap openings, pill counts, and self-reports versus concurrent viral load in 42 individuals. When plotted, all three measures of adherence generated lines with the same slope. As adherence improves, the viral load decreases. Decreasing adherence by even 10% will increase the viral load by 0.3 log, roughly doubling the viral load. Conversely, improving adherence even a little may yield meaningful viral load reductions. Additionally, these measures

of adherence explain between 36% and 67% of the variation in viral load among individuals. This is probably the number-one predictor of the differences in viral load among individuals (4).

One public health rationale for using DOT is avoiding drug resistance. In the TB literature, it is well-documented that nonadherence leads to microbial drug resistance. But, the empirical data for HIV are actually quite scant. By examining pill-count adherence versus viral load, genotyping demonstrates that, for the most part, PI-resistance mutations are occurring in those who were between 60% and 90% adherent over the course of a year. People who were less than 50% adherent had only wild-type viruses with respect to PI resistance. These data seem to indicate that increasing adherence actually increases PI resistance. Nevertheless, DOT and other adherence programs can certainly be justified in light of their viral load suppressive effects because viral loads clearly correlate with clinical outcomes. These results would need to be confirmed by a prospective study, however. John Walsh presented similar data at ICAAC, which demonstrated that the number of drug resistance mutations increased as adherence improved (5).

Dr. Bangsberg and colleagues also looked at adherence and progression to AIDS in 72 individuals stratified by adherence levels. They found that better adherence correlated with far lower rates of progression to AIDS during the 30-month period after entry into study (6). Nevertheless, if it is necessary for people to take 98% of their medications to live longer, the hospitals still would not be empty and the death rate would not be down. Viral load is not the ultimate outcome. There is probably much more going on with the biology of adherence than just viral load suppression. Much of our discussion has centered on driving down viral load, which is probably an important part of the story but not the whole story.

Selecting individuals for adherence interventions - Who needs adherence support and who does not? We must target adherence interventions toward those who are having trouble with adherence. Some parameters may help determine who needs help in the form of DOT: level of adherence, motivational readiness, and stage of HIV disease. If people are already taking 90% of their medications, they may do worse if they are interfered with. Someone with high motivational readiness may be able to improve a great deal with just a little bit of help; if this readiness is lacking, if they are not ready to change, they may need a more intensive intervention and may be more attractive DOT candidates (7).

Another factor for consideration is stage of disease. Someone with a critically low CD4+ cell count needs to have something dramatic happen now. Others may be able to succeed with a less-intensive intervention, such as a case-management approach.

What type of adherence support do people need? Although our focus has been on DOT, there are other strategies, including adherence case management. The limitation is that these other approaches do not change adherence very much, maybe 10% or 15%. Designing exit strategies to extend durability of adherence interventions an outstanding question for both DOT and adherence case management strategies. We need to come up with a rational basis for determining which intervention strategy is most appropriate for individual patients. These strategies should be based on medical urgency defined by stage of disease and carefully assessed adherence behavior rather than membership in a group such as ethnicity, housing, or drug use characteristics. .

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Addressing the Needs of IV-Drug Users - Elinor McCance-Katz, MD, PhD, of the Albert Einstein College of Medicine

Dr. McCance-Katz discussed directly observed HAART in methadone-maintained patients with HIV disease. Injection drug use is a huge problem in terms of HIV disease and HIV transmission; it accounts for 30% of HIV cases in the United States and more than 50% of HIV cases in northeast urban areas. Approximately 25% of individuals in methadone maintenance

programs are HIV-infected. And, injection drug use is often cited as a cofactor in heterosexual and perinatal transmission.

Complicating this picture is the fact that opiate users are 50% less likely to adhere to their antiretroviral regimens. Furthermore, HAART can interfere with opiate substitution therapy because many antiretroviral agents are metabolized by CYP 450 system. This is also true of opioids. An agent that is an inducer of CYP-450 may cause opiate withdrawal. CYP-450 inhibitors can cause toxicity, which can mimic opiate withdrawal, or they can cause frank opiate toxicity, which may be life-threatening.

However, opiate dependence therapy also facilitates HAART by stabilizing chaotic lifestyles of drug users. Once opiate users are stabilized, their adherence to therapy is comparable to those who do not use drugs. Therefore, DOT may enhance adherence in those who are seeking opiate dependence therapy.

The goals of the modified DOT (M-DOT) study described by Dr. McCance-Katz were:

- to determine whether once-daily HAART administered with methadone is effective for HIV disease;
- to determine whether DOT will reduce illicit substance abuse
- to define drug interactions of importance in the methadone-maintained population.

The initial DOT regimen investigated consisted of efavirenz, ddI, and 3TC. 3TC was administered according to the package insert in a twice-daily regimen. One dose was given in the clinic with methadone, and patients received one take-home dose of 3TC.

One unique facet of this study was the collection of pharmacokinetics (PK) data on patients receiving this regimen. To determine drug interactions, all patients had methadone PKs determined before starting HAART and repeated PK studies of methadone and antiretrovirals after HAART initiation. Second PK studies showed significant decline in methadone concentrations and correlated with an increase in methadone dosage; after the dosage adjustment, PK studies were repeated. Patients were closely watched for opioid withdrawal symptoms and closely managed if such adverse events occurred. Study physicians were available 24 hours per day.

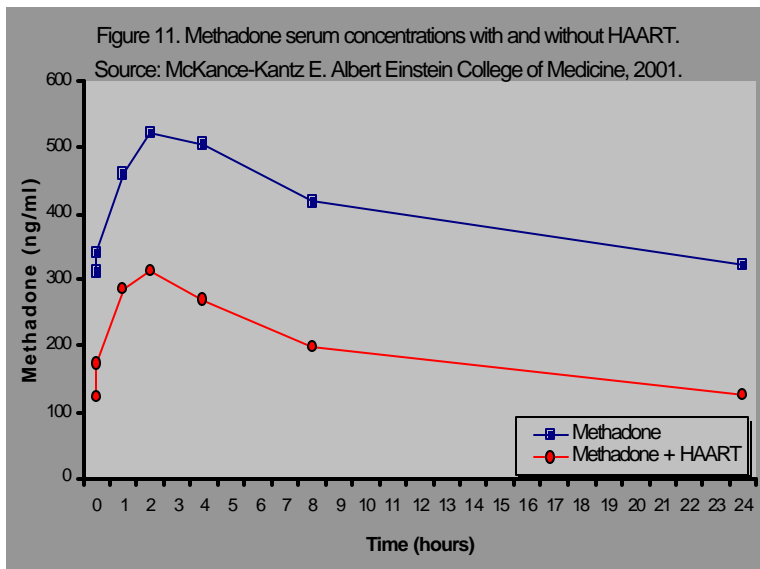
All patients had weekly research clinic visits for 24 weeks. Treatment adherence was monitored three ways: by urine fluorescence, by subject query, and use of a Health Watch to remind them to take their take-home dose. The take-home dose of 3TC was encapsulated with

riboflavin, which fluoresces in urine after the drug is ingested. Other tests performed during the weekly research clinic visits included urine toxicology, viral load, CD4+ cell counts, and opiate withdrawal assessments.

To date, five patients are enrolled. The average age of the study population is 37.5 years. Forty percent are women. Four are Hispanic; one is African American. Sixty percent meet DSM IV criteria for cocaine use disorders, and 40% meet criteria for alcohol use disorders. All have a history of injected drug use.

Dr. McCance-Katz presented a graph of the PK curves for the first five subjects in the study (figure 11). For most people, a trough level of 200 to 400 ng/mL of methadone is therapeutic. When they started on HAART, methadone concentrations rapidly dropped and patients suffered withdrawal symptoms. Without HAART, the average trough is 312 ng/mL; with HAART, the trough drops to 123 ng/mL.

In most clinics, it would not be possible to run 24-hour PK studies, but it should be

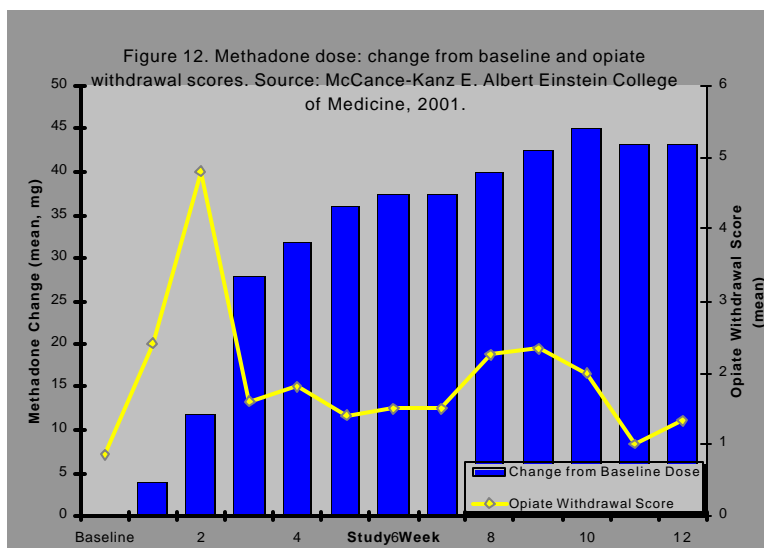


possible to run at least trough levels of methadone. She showed another way to look at these data, which indicates how these patients were treated (figure 12). The yellow line corresponds to the objective methadone-opiate withdrawal scale, a measure used during opiate detoxification. If the score is more than 3, medication is indicated to alleviate withdrawal symptoms. At baseline,

the mean opiate withdrawal score was 1, but by week 2, the score had climbed to 5, which represents significant withdrawal. In response, they increased methadone dosage and restabilized the patients. Dr. McCance-Katz emphasized how important it is to tell patients what to expect with HAART, to encourage them, and to assure the patients that they will get all the help they need to get through this difficult time.

The baseline dosage of methadone was 88 mg per day. To restabilize these patients after initiation of HAART, the mean methadone dosage had to be boosted to 128 mg, an increase of 45%. It took, on average, 5 weeks to reach a stable methadone dose.

The baseline viral load was 123,064, but within 4 weeks, 60% of patients had



undetectable viral loads, and at 8 weeks, 80% had undetectable levels. Baseline CD4+ cell count was 207, but it more than doubled in 8 weeks.

In conclusion, DOT in methadone-maintained individuals is a promising intervention that can increase adherence to HAART and enhance HIV and drug use outcomes. Furthermore, efavirenz is likely to reduce plasma concentrations, but individual clinical assessment is necessary to maintain proper methadone dosing.

Dr. McCance-Katz noted that they would be initiating studies of dual-PI and other regimens. We must create a connection between methadone programs and HIV care. Integration

of primary care with methadone maintenance and having an addiction psychiatrist or other professionals who are interested in addiction medicine on staff is necessary to ensure success of such programs.

During the discussion following the presentation, one meeting participant stated that some patients are unwilling to take efavirenz because increasing methadone is a sign of failure. They may have very rigid ideas about what their dosage should be. Dr. McCance-Katz reiterated that they had to spend a great deal of time with clients to explain that, in fact, the methadone dosage was not truly increasing. Clinicians must also consider that if ART is discontinued that patients will quickly be at a toxic methadone dosage. Skilled professionals are needed to monitor methadone dosage and assure patients that they are not failing their addiction treatment even if their methadone dosage increases with HAART and to assist with a methadone taper and restabilization should the patient no longer require an antiretroviral medication that induces methadone metabolism.

Reports from the Breakout Groups

The workshop participants broke into five discussion groups to consider a series of questions related to practical, ethical, and legal issues surrounding directly observed therapy (DOT). The varied responses and topical overlap reflected the complexities of DOT. The following synthesis highlights the recommendations, concerns, and philosophies concerning DOT as presented to the plenary session.

How do we define what a DOT program is? Does every dose need to be observed?

All the groups called for a standard nomenclature to help structure research and gather comparable data. Most participants agreed that:

- The term *directly observed therapy* should mean that all doses are observed.
- Other programs, in which some doses are observed, should be called *percent DOT* (e.g., 50% DOT) to indicate the proportion of observed doses, or perhaps *modified DOT (MDOT)*, *partially observed DOT (P-DOT)*, or, the term preferred by CDC for its programs, *directly administered antiretroviral therapy (DAART)*.

One breakout group said that the question of whether every dose needs to be observed turns on the rationale behind DOT.

- If the rationale for the program is to address the public health threat posed by viral resistance, then 100% observation is a must.
- If the rationale is that DOT is for the patient's well being, some sense of paternalism, or the reduction of societal costs (as is true for the asthma case management model), then 100% observation may be ideal but is probably unrealistic.

Several groups noted that the DOT programs for HIV and for tuberculosis are more different than they are alike.

- With tuberculosis, there are no choices. To protect public health, the patient receives DOT for a finite period, he or she becomes free of the disease, and DOT is discontinued. Not so with HIV treatment, which is a lifetime prospect. With HIV DOT, we may not need or be able to monitor every dose every day.

- There are also considerable differences in treatment regimen. With HIV, we must consider toxicity profiles, individual treatment decisions, and the different populations who are affected by this virus. Therefore, it is almost a certainty that classical DOT will not be feasible in HIV treatment, and, as a reflection of this reality, it may be more accurate to use terms like DAART, MDOT, or P-DOT.

Above all, HIV DOT programs must be flexible. One size does not fit all. We need multiple programs in multiple settings for multiple populations, e.g., prisons, residential facilities, methadone clinics, storefronts. Therefore:

- operational research is critical to assess how DOT can fit into this spectrum of needs.
- DOT should be accessible in central facilities and through home-based services.
- An array of treatment regimens should be made available.
- Even greater flexibility will be available and needed if structured treatment interruptions and QD (once daily) regimens are shown to be safe and effective.
- In keeping with this need for flexibility, it will be necessary to rely upon community workers and other nonprofessional staff. Only if DOT is flexible and responsive to people's needs will it be viewed as a benefit and valued as such.

What are the parameters for determining who is and who is not an appropriate candidate for DOT programs?

The consensus view was that there is no way to predict who will be adherent to therapy. Rather, many participants believed that DOT should be offered as a treatment option to everyone who meets the criteria for commencing antiretroviral therapy. Others stated that determining who is a candidate for DOT depends upon the rationale behind the treatment—whether the treatment is for the public health or if it to be a patient benefit. And, of course, the embarking on DOT depends on a decision made jointly by the patient and the care provider. Many participants believe that each person about to commence antiretroviral therapy should receive DOT for 2 weeks or more to mold their medication-taking behavior.

Mandatory DOT could be a way to deal with patients who have failed multiple treatments because of nonadherence to therapy. It could represent “one last good regimen” for patients who have experienced treatment failure. Some participants suggested that it could be more

aggressively offered if indicated by viral load, immunologic markers, occurrence of opportunistic infections, or progression to late-stage disease.

When designing a DOT program, how can the parameters of program design, including such issues as choice of regimen, where the DOT is offered, and the integration of DOT into other services, be done in a way that best meets the needs of people with HIV?

- We must always offer the best treatment possible. One concern expressed by the meeting participants is that DOT may be driving treatment choices; that people are fixated on using QD regimens to fit into DOT programs, although DOT regimens have not been proven efficacious. DOT should fit into structure of treatments that have been proven effective on the basis of data on outcomes.
- DOT should be offered anywhere and everywhere that is appropriate for the local population. The three components of DOT—structure, support, and pill taking—should be tailored to the individual and integrated into existing programs but not absorbed by them. It should be a part of a complete program of wraparound services, including substance abuse treatment, psychiatric treatment, transportation, and case management.
- Coordination of the DOT team and the medical team is critical and should be memorialized through case conferences.
- Above all, DOT should be seen as a value-added service that is offered to patients as just one item on the “adherence program” menu.

How long should a DOT program last? How can these programs be designed to help participants adhere to their treatment regimens even after the program ends?

- DOT should be considered a therapeutic intervention. Taking this view will help us design and implement DOT programs.
- The consent form should state up front what the availability of DOT will be after the cessation of the trial.

Tapering programs must be tailored to the individual:

- Some participants believed that DOT should be available as long as patients want it. To taper patients off DOT, we need long-term follow-up procedures to monitor viral load, CD4+ cell counts, and opportunistic infections to ensure that patients can again access the support of a DOT or some other type of intervention if they need to.
- Another group suggested using DOT for all patients for 2 weeks, followed by a tapering-off period that could be adjusted according to how they were doing. For example, some trials involve 6 months DOT, followed by a slow tapering off with 6 months of adherence case management. To address public health concerns, some patients may need lifetime DOT.
- One group suggested that a buddy system might provide needed support; patients may be able to rely upon family and friends to reinforce their medications.

What methods of DOT program evaluation will be most useful to patients and practitioners?

To evaluate DOT, we need standard measures—validated questionnaires and consistent measurements—much like those used for clinical trials. We should collect data on the following outcomes:

- Patient acceptance of and satisfaction with DOT
- Confidentiality maintenance
- Quality of life
- Virologic parameters (viral load, resistance, duration of undetectable viral load status)
- Immunologic changes (CD4+ cell counts)
- Patient understanding of HIV disease and its treatment
- Number of hospitalizations
- Costs
- Use of ancillary services
- Time-to-failure
- Ongoing risk behaviors
- Sustainability of the intervention.

We must learn if DOT is a durable intervention. To do that, we need data from studies longer than 12 weeks to see if DOT is safe, convenient, and efficacious. We also need data to see who stays with DOT, who leaves DOT, and why.

- We need to develop consensus around the rationale for HIV DOT—whether it is to protect public health or to provide individual benefits.
- We need more operational research to learn what works and does not work in diverse communities before embarking on DOT in wholesale fashion.

- The time is now for funding demonstration projects but only with the caveat that assessments be conducted to determine whether primary goals are being met.
- We must take every precaution to ensure that we do not drive the population underground—confidentiality must be maintained.
- In keeping with the history of success in voluntary HIV diagnosis and treatment, HIV DOT, at least for the most part, should be voluntary.

On the other hand, the groups were optimistic that DOT can fill significant gaps in patient care:

- DOT can be a useful option in a portfolio of adherence programs. It should be offered to anyone who meets the criteria for antiretroviral treatment and wants the support that a DOT intervention provides.
- Whatever program of DOT or its variations is instituted, it can and should be tailored to individuals, flexible, and integrated with other services.
- Effective DOT programs will make clear to the patient that DOT will be available as long as necessary and effective, that support will be available to help him or her taper to independence, that he or she can return to DOT if needed.
- Skill-building education in the context of a DOT program can reinforce the necessity of taking medications and instill a habit of taking medications regularly.
- DOT offers many possible benefits for public health, including the potential for reduced viral resistance, reduced HIV transmission, an increased number of people in care for HIV, and decreased morbidity and mortality.
- A “safety net” can help the patient taper toward independence by monitoring adherence and allowing the patient to re-enroll quickly in the DOT program if more intensive support is needed.

Workshop Agenda

Examining the Risks and Benefits of Directly-Observed Therapy for Treatment of HIV Disease

*April 16 – 17, 2001
Westin Fairfax Hotel
2100 Massachusetts Ave., Washington, DC*

Day One: 12:30 pm – 5:30 pm

12:00 – 12:30: **Registration**

12:30 – 1:00: **Introductions**

- *Laura Cheever, M.D. – Health Resources Services Administration*
- *David Barr – Forum for Collaborative HIV Research*

1:00 – 2:00: **Session 1: Creating a context - Why is DOT now an important topic for discussion in HIV treatment?**

- *Richard Moore, M.D. – Johns Hopkins Medical Center*

2:00 – 3:45: **Session Two: What can we learn about the use of DOT in other diseases that will assist in HIV-related DOT research and program implementation efforts?**

- *John Sbarbaro, M.D., M.P.H. – Univ of Colorado*
- *Kenneth Castro, M.D. – Centers for Disease Control*
- *Ron Bayer, Ph.D – Columbia University*

3:45 – 4:00: **Break**

4:00 – 5:00: **Session Three: Once a day dosing - Where are we?**

- *Alice Pau, Pharm.D. – NIH Clinical Center Pharmacy Dept.*

5:00 – 5:30: **Session Four: Evaluation of DOT**

- *Tim Flanigan, M.D. – Brown University*

5:30 – 6:30 **Reception**

Day Two: 8:30 am – 4:30 pm

8:00 – 8:30: **Breakfast**

8:30 – 11:30: **Session Five: Current HIVDOT efforts – short presentations describing current DOT programs in a variety of settings.**

- *Frederick Altice, M.D. – Yale University*
- *Josh Bamberger, M.D., M.P.H. – San Francisco Dept. of Public Health*
- *Daniel Barth Jones, M.P.H., Ph.D. – Wayne State University*
- *Maryrose De Fino, R.N. – Montefiore Medical Center*
- *Shannon Hader, M.D., M.P.H. – Centers for Disease Control*
- *Brian Harrigan/Kathy Vela – Univ. of British Columbia*
- *Christina Hill Zabala, Pharm.D. – Glaxo Smith Kline*
- *Andrew Kaplan, MD – University of North Carolina at Chapel Hill*
- *Greg Lucas, M.D. – Johns Hopkins Medical Center*
- *Kathy McCallum, R.N., ACRN – AIDS Services of Dallas*
- *Elinor McCance-Katz, M.D., Ph.D. – Albert Einstein Coll. of Medicine*
- *Amy Rock Wohl, Ph.D. – Los Angeles Dept. of Health*
- *Dian Sharma, Ph.D. – Tacoma Dept. of Health*

11:30 – 12:00: **Session Five: Defining DOT –**

- **What factors need to be considered in creating DOT programs?**
- **What are the ethical considerations in designing DOT in HIV?**
- **What are the practical considerations in utilizing DOT in HIV?**
 - *Valerie Stone, M.D. – Brown University*
 - *David Cohn, M.D. – Colorado Dept. of Health*

12:00 – 2:00: **Break out groups** (working lunch)

2:00 – 2:30: **Report back from breakout groups**

2:30 – 4:00: **Session Six: What are the needs of special populations that will most likely be targeted for DOT?**

- *Jim McAuley, M.D. – Rush Medical Center, Cermak Health*
- *Judy Greenspan – California Prison Focus*
- *David Bangsberg, M.D. – Univ. of California at San Francisco*
- *Elinor McCance-Katz, M.D., Ph.D. – Albert Einstein College of Medicine*

4:00 – 4:30: **Next steps**

4:30: **Adjourn**

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