Developing an Agenda for Patient Outcomes Research in HIV Disease

Since their introduction in 1996, new therapies for HIV disease have had a remarkable impact in reducing AIDS-related morbidity and mortality in the United States. However, to realize their potential, health care providers and patients need accurate and current information about these new therapies. In June 1998, the Forum held a workshop to examine HIV practice guideline dissemination and implementation. The result was a report that includes a series of recommendations to better disseminate HIV treatment information to providers and patients by government, industry, health care delivery, and community.

We then turned our attention to the need to measure both the implementation of HIV treatment guidelines and the effects of such implementation on patient outcomes and health care delivery. First, the Forum published *The Potential of Patient Outcomes Research in HIV Disease: A Review of Background Research*, which provided a summary of the methodology, scope, and principles of patient outcomes research. That document serves as a companion to this report.

In September 1999, the Forum convened a workshop on patient outcomes research and HIV disease. The workshop was attended by leading researchers, health care providers, government officials, patient advocates, and pharmaceutical and managed care industry representatives. The workshop was prompted, in part, by a growing awareness among researchers that outcomes, or effectiveness, research represents a potentially fruitful area of inquiry in HIV disease. Outcomes research, a relatively new area of scientific investigation, seeks to learn about the long-term effectiveness of specific treatments and procedures, for individual patients and for society-at-large. Of growing interest generally, because of the increased requirement for medical decision-making to be based upon patient and economic outcomes, outcomes research is of specific interest in chronic conditions like HIV disease. This report provides both summaries of the workshop presentations and the research agenda developed by the workshop participants.

Several people assisted in the development of this project. Derek Hodel was the Project Coordinator for the Forum. Susan Brobst and Winfield Swanson drafted the summaries from the workshop and planning meeting. Bruce Agins, Ruth Finkelstein, Julia Hidalgo, John Ludden, and Leona Markson provided invaluable advice and guidance. Helen Schietinger wrote the background paper described above. Helen Nuamah, the Forum’s Administrative Director and assisted in the workshop logistics. Nirav Patel and Nimish Patel also provided administrative support. William Gist provided the logistical and administrative support for this and all other Forum projects from 1997 through December 1999. The Forum wants to thank William for his time, energy, intelligence, patience, and good humor.

The Forum for Collaborative HIV Research, a project of the Center for Health Services Research and Policy at the George Washington University School of Public Health and Health Services, catalyzes discussion about emerging issues in HIV clinical research and the transfer of results into care. For more information about the Forum and for copies of all Forum publications, please visit our web site at www.gwumc.edu/chpr (click on HIV Research).

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The goal of this meeting was to develop research questions to determine to what extent the HIV Clinical Practice Guidelines have been understood and adopted, implemented, and the degree to which they are effective.

EXECUTIVE SUMMARY

In September, 1999, the Forum for Collaborative HIV Research (FCHR) convened a workshop on patient outcomes research and HIV disease, part of its continuing examination of the dissemination and implementation of HIV clinical practice guidelines. A 22-person planning committee had met over the course of nine months to review the field and to develop the agenda for the meeting. The workshop was attended by 83 leading researchers, health care providers, state and local government officials, federal research sponsors, patient advocates, and representatives from the pharmaceutical and managed care industries. The primary goal of the workshop was to begin the development of an agenda for patient outcomes research in HIV disease.

The workshop was prompted, in part, by a growing awareness among researchers that outcomes, or effectiveness, research represents a potentially fruitful area of inquiry in HIV disease. Outcomes research, a relatively new area of scientific investigation, seeks to learn about the long-term effectiveness of specific treatments and procedures, for individual patients and for society-at-large. Of growing interest generally, because of the increased requirement for medical decision-making to be based upon patient and economic outcomes, outcomes research is of specific interest in chronic conditions like HIV disease.

On the morning of the first day of the workshop, to provide background for workshop participants, a series of experts in various aspects of outcomes research discussed their experiences in chronic diseases other than HIV. That afternoon, workshop participants had the opportunity to hear from experts conducting HIV-related research.

On the second day of the workshop, participants were divided into workgroups and asked to develop research questions to evaluate the extent to which the HIV clinical practice guidelines were: 1) understood and adopted, 2) implemented, and 3) effective. Further, they were instructed to consider various stakeholder groups, including:
Payors: ERISA self-insured plans, Medicaid/Medicare, managed care plans;
Providers: staff HMOs, government healthcare provider (e.g., VA), doctors/healthcare workers (physicians, physician assistants, nurses, nurse practitioners);
Social Service Providers: (case managers, educators); and
Patients.

The results of the workgroup sessions have been summarized in this report as the first step towards building a comprehensive outcomes research agenda for HIV disease. It should be understood that the workgroups had limited time to discuss a broad range of issues. The questions listed herein should be seen as a starting point for further discussion. The groups were able to develop a comprehensive list of questions, all which ultimately need to be addressed if we are to better understand the effects of new HIV treatment modalities. What the groups were not able to do was: (1) prioritize the questions, (2) discuss in depth the methodology needed to answer the questions, or (3) discuss the roles of government, academia, industry, and the health care infrastructure in implementing the research agenda. These are issues that the Forum will tackle in the coming year. It is our hope that the questions developed at the workshop will inform the on-going work of researchers, funders, and providers in HIV care.

The work group deliberations revealed the depth of the challenges posed by developing an HIV-related outcomes research agenda. As with other areas of scientific research, outcomes researchers must take into account that HIV disease, while a newly emergent epidemic, has provoked a health crisis now fully intertwined with a range of other social and medical problems. Perhaps more so than other chronic diseases, HIV disease has been said to characterize the best and worst of our healthcare delivery system, a reality that outcomes research will no doubt continue to foreground.

Outcomes Research

Outcomes research seeks to expand upon studies of clinical efficacy, which typically measure the biological effects of an intervention under ideal circumstances. Outcomes research, on the other hand, is concerned with effectiveness, or the impact of the intervention on the overall health of the patient under real-world circumstances. (For the purpose of this meeting, workshop participants were asked to assume that recommendations in the HIV clinical practice guidelines were efficacious.) While the scope of most clinical efficacy studies is necessarily narrow – constrained by the need to tightly control experimental variables – the scope of outcomes research
research is broad. For example, while clinical efficacy studies might narrowly frame a research question related to the impact of an intervention on certain biological markers, outcomes research might consider the impact of the intervention on overall patient health, including functioning, quality of life, patient satisfaction, pain control, or symptom relief. As Dr. Eisenberg notes in his talk, the outcomes patients care about are disappointment, disease, disability, and dysfunction.

Ideally, outcomes research data will aid patients and providers in medical decision-making, by providing information about the overall benefits, risks, and costs of treatments. For individual patients, this information could have enormous practical benefit. For example, while considerable data have recently suggested the benefit of combination antiretroviral therapies in terms of improved mortality, additional research might address the questions of when to initiate therapy, when to switch, and how long to continue therapy, while elucidating the long-term effects of treatment. Outcomes research must consider these questions both in terms of individual patients and overall:

• over time – workshop participants viewed certain cancer research, which looks at outcomes at intervals of 2 years, 5 years, and 10 years, as a potential model;

• over populations – which must include relevant subpopulations, including those defined in terms of substance abuse, mental health diagnosis, gender, socioeconomic status, and significant cultural groups;

• over and across various care systems.

In outcomes research, the intervention itself must also be broadly considered. Thus, outcomes research frequently studies patterns of healthcare utilization, designed to explore variations in medical practice. In HIV disease, wide variations in patient care are well documented. In their presentation, for example, Drs. Bozzette and Shapiro note that among the HCSUS cohort, both care and health outcomes differ significantly by race/ethnicity, insurance, socioeconomic status, and geographic region. In some instances, variations in care may be patient-related; in other instances, they may be due to systemic differences. More research will be necessary to understand why such variations exist, and what the impact of such variations on patient outcomes may be.
Outcomes research is also concerned with the impact of the intervention on society as a whole, typically measured in terms of cost, cost-benefit, or cost-effectiveness. As a consequence, outcomes research has important ramifications for health systems and organizations, as well as for public policy. Because of the expense associated with treating HIV disease, variations in cost-effectiveness are of great importance, not only to patients and providers, but also to insurers, healthcare systems, government, and experts developing clinical practice guidelines. Outcomes research has the potential to help health care managers and purchasers improve not only the quality, but the value of care.

Though the discussion of cost-effectiveness often provokes discomfort among patients and providers, under circumstances where rationing resources is inevitable (the constant funding crisis among ADAP programs in many states is one example), Dr. Freedberg points out in his talk that using limited resources inefficiently is irrational and probably unethical. Quality-adjusted life years saved is one measure of cost-effectiveness that has been employed to evaluate the cost-effectiveness of a variety of HIV-related interventions.

The HIV Clinical Practice Guidelines

As explored in greater detail in the previously cited background paper, outcomes research ideally informs an evolutionary cycle, the process of which is to develop, disseminate, implement, evaluate, and ultimately revise treatment guidelines. Outcomes research encompasses a multiplicity of scientific methodologies, including meta-analysis of scientific literature, examination of administrative databases, development of health status measures, and a range of observational and experimental study designs.

In HIV disease, the evolution of clinical practice – and thus of clinical practice guidelines -- is young. Current guidelines are based largely upon clinical efficacy studies or expert opinion. Because clinical practice for HIV disease changes so rapidly, most clinical studies on which medical decision making is based are relatively short-term. As a result, the long-term efficacy of many HIV treatments remains unknown. Moreover, especially in light of the complexity of most recent HIV antiretroviral treatment regimens (which involve multiple drug combinations), little is known about the effectiveness – the “real world” impact -- of the new treatments.
In part as a means of informing the constant revision of HIV clinical practice guidelines, the extent to which current guidelines are understood, adopted, and implemented warrants further study. Dr. Greenfield notes that in other chronic diseases, clinical practice among physicians varies substantially, based in part on differences among physicians in knowledge, attitudes, and beliefs. Patients also differ significantly in the degree to which they understand, accept, and ultimately, implement their own care. Particularly as rigid adherence to complex regimens has become more important, these variations may be increasingly significant.

Methodological Issues

More so than with other chronic diseases, the rapidly evolving HIV standard of care presents significant challenges to healthcare systems, challenges that are likely to be relevant for outcomes researchers. Of particular note, as individual clinicians and healthcare systems have struggled to adopt clinical practice guidelines, they have also struggled to ensure consistency and quality-of-care. Quality assurance efforts have prompted the development of measurement tools that may be useful to outcomes researchers. While performance measurement for the purposes of quality assurance is often associated with continuous quality improvement (CQI), Dr. Agins notes that the development of measurement tools has important implications for outcomes researchers, particularly in terms of the study of healthcare utilization.

Performance measurement for the purposes of quality assurance is not the same as performance measurement for the purpose of evaluating guideline implementation, however. While both process and outcome measures will be essential to measuring guideline implementation, outcome measures – whether or not they are specifically included in the guidelines – may ultimately provide more compelling evidence that following the guidelines is worthwhile. Dr. Asch notes that feasibility (e.g. scarcity of endpoints) and cost (especially those associated with sequential interviewing necessary for QOL assessments) may prove to be significant burdens in developing appropriate HIV-related outcome measures. He also notes that risk-adjustment, in particular, poses a substantial challenge to the development of HIV-related outcomes measures, as disease severity differs markedly among patients.

One important consideration in developing indicators will be to determine which aspects of the HIV clinical practice guidelines to measure, as the guidelines are so broad as to encompass
a continuum of HIV care from prevention to salvage-therapy. Dr. Asch notes that the recommendations in current guidelines vary by strength of supporting evidence, link to health outcomes, and potential for quality improvement, and that these and other criteria should guide a decision concerning which recommendations to evaluate. He also notes that the considerable practice flexibility (i.e. multiple possible interventions, equivocal supporting data) provided by the guidelines will complicate the development of performance indicators. Dr. Asch proposed that HIV outcome indicators be selected based upon 1) ease of use; 2) accountability; 3) reliability; and 4) adaptability.

Outcomes research examines the full range of health outcomes, from mortality to patient satisfaction. The development of health status measures is an important aspect of outcomes research. In HIV disease, many such health status measures have been developed and are increasingly implemented in both efficacy and effectiveness studies. Dr. Wu describes health-related quality of life (HRQOL) measures to include physical functioning, role limitations, pain, general health perceptions, psychological well-being, energy, quality of life, social functioning, and cognitive functioning. Specific measures of HRQOL include sexual functioning, sleep, eating, body image, recreation, and symptoms. Related outcomes may be important in medical decision-making, as HRQOL differences may “tip the balance” between choosing one intervention and another.

Importantly, the value of individual health outcomes will be weighted differently by different patients, and by different cultures – ultimately, treatment decisions must be based upon the patient’s views concerning the quality, as well as the quantity, of survival. These differences also underscore the imperative to design and implement HIV-related outcomes research in collaboration with multiple stakeholders, including patient advocates and people living with HIV.

HIV-related outcomes research carries with it the tremendous potential to refine treatment guidelines to better reflect the real-world conditions faced by patients with HIV disease and their clinicians, and to more fully take into account patient preferences. Better information about the appropriateness of treatments for HIV disease would benefit not only patients and clinicians, but health care managers and purchasers as well.
MEETING SUMMARY

The Growing Importance of Patient Outcomes Research in the Management of Chronic Diseases

John Eisenberg, M.D., M.B.A., Agency for Health Care Policy and Research (AHCPR), described the growing importance of patient outcomes research in the management of chronic diseases. For health care managers and purchasers, outcomes research can identify potentially effective strategies to improve the quality and value of care. For clinicians and patients, outcomes research provides evidence about benefits, risks, and results of treatments so they can make more informed decisions. To conduct effective outcomes research, one must anticipate which outcomes issues will be key 5 years from now. The outcomes that patients care about are disappointment, disease, disability, and dysfunction.

Substantial variations in medical practice have been well documented across the United States. These disparities are evident in the HIV Cost and Services Utilization Study (HCSUS) study, where differences in care according to race and other factors were found. Such differences in care will most likely result in different outcomes. Reasons for practice variation range from differences in the availability of health services to not understanding adequately what the outcomes and effectiveness are. To address such discrepancies, AHCPR and sister agencies provided support to develop the HIV Resource Utilization Data Coordinating Center, which will pilot test data transmission from a small number of providers. Such databases are necessary to ask questions about HIV, including what are the practice variations, why do these variations exist, and what impact do these variations have on patient outcomes.

Outcomes definition is difficult for chronic diseases like HIV disease, where end results include quality of life as well as mortality. In many cases, surrogate markers and prognostic instruments are necessary to predict outcomes in chronic diseases. Moreover, outcomes will be weighed differently by different people. For example, a laryngeal cancer study indicated that to maintain their voices, many people would choose radiation instead of surgery, even though this lowered their survival odds. These results suggest that treatment choices should be made on the basis of patients’ attitudes toward the quality as well as the quantity of survival. Guidelines

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should recognize cultural, ethnic, age, and gender differences and individual preferences for different outcomes.

To be helpful in the medical decision-making process, health outcomes measures should go beyond traditional biomedical measures to include measures of how people function and their experiences with care. There is a continuum of effects of health care services on health and well-being, ranging from mortality to patient satisfaction. Health outcomes measures include mortality, physiologic measures, clinical events, symptoms, functional measures, and patients’ experiences with care. Hopefully, these outcome measures will be incorporated in clinical trials and ultimately into clinical practice. Examples of health outcomes measures include:

- One of the best-established measures of health perceptions is the patient’s symptoms as determined through disease-specific inventories. For example, the benign prostatic hyperplasia symptom index is used by the majority of urologists to determine whether treatment is necessary or desired.

- Functional measures can be used to assess how patients rate their health overall (through the SF-36, a general health survey) or to detect changes in a disease due to specific treatment.

- Preference-based outcome measures assess the degree to which a function influences a patient’s life and include the Quality of Well-Being Scale, health utility indexes, and disease-specific preference-based measures. As noted above in the laryngeal cancer study, these preferences vary widely according to the individual.

- Patient satisfaction measures reflect what processes of care patients care about. (Did your doctor communicate with you effectively? Do you understand what your disease is all about? Did you have to wait a long time? Did you have to take a lot of time off from work to receive care?) While it could be argued whether these are process or outcome measures, these questions are important to patients.

There is data showing colinearity between satisfaction measures and other measures of health outcomes. The Consumer Assessment Health Plan Survey (CAHPS), a unique state-of-the-art survey and reporting kit, provides consumers and purchasers detailed information that will help them compare health plans based on the experiences of plan enrollees. CAHPS goes beyond statements of overall satisfaction by measuring and reporting on consumer experience with specific aspects of their own health plans that are the basis of satisfaction. More than 90 million Americans can choose their health plans based on data from the CAHPS survey. Perhaps an HIV-oriented CAHPS could be developed.
The impetus for AHCPR was that the Federal Government should support effectiveness research and practice guidelines through increased funding, coordination, and evaluations. AHCPR considers three different decisionmaking levels for outcomes—clinical decisionmakers, health systems or organizations, and public policy -- meeting participants were urged to consider these as well.

The patient should also be part of the treatment decision, and the importance of communicating health services research to lay people in a succinct matter should not be underestimated. For example, in a clinical trial comparing two therapies for prostate cancer, specific outcomes varied considerably, but patients in both groups had positive feelings about their treatments, probably due to their participation in the treatment decision. Better quality can cost less by giving people information on their likely outcomes and letting them participate in the decision-making process in a shared fashion.

Similarly, clinical decision-makers may consider not only health outcomes, but choice of drug and days of restricted work, as well. The business community notes that it will be easier to promote value-based purchasing if policymakers help them make the business case for quality. Don’t just think of outcomes of clinical interventions, but consider the effect of hospital reorganization on outcomes as well. Examples of research that AHCPR funds to help clinical decision-makers include:

• An AHCPR effectiveness research study measuring mortality and outcomes for HIV patients with and without *Pneumocystis carinii* pneumonia (PCP) prophylaxis demonstrated that those with PCP prophylaxis had no deaths and fewer hospital days.

• An AHCPR/FDA initiative will fund regionally based Centers for Education and Research on Therapeutics (CERTs) to conduct outcomes research on pharmaceuticals. The CERT has two primary missions: (1) Conduct the essential research on drugs and therapies that is not being performed by the pharmaceutical industry; and (2) Establish and communicate to practicing physicians therapeutic guidelines incorporating the most effective, safe, and least expensive therapies.

• The Comprehensive Health Enhancement Support System (CHESS) is being used to evaluate shared decisionmaking and whether the lives of patients can be improved if they use computer systems to obtain information, make difficult decisions, and contact experts and support groups. In one study, HIV-infected persons who used CHESS reported fewer and shorter hospital stays (and a 40 percent decrease in hospital costs) and higher quality of care compared with nonusers.
A study of patient satisfaction with care in dedicated AIDS units compared to general hospital units showed that patient satisfaction was higher in dedicated AIDS units.

Research on outcomes and staffing hours showed that increasing nurse hours per patient day by 30 minutes was associated with improved outcomes that were considered nurse-sensitive.

The translation of research results into practice is also important. There is a disturbing lag in changing practice patterns from research results to clinical practice (average is 10 years). A major theme for AHCPR is translating research into practice and shortening this time span, and there are initiatives funded to do so. Obtaining more evidence for HIV-related topics is essential, so that clinical practice guidelines will make a difference. Currently successful examples of translating research into practice include:

- The National Guideline Clearinghouse (NGC) is a public resource for evidence-based clinical practice guidelines. NGC is sponsored by AHCPR in partnership with the American Medical Association (AMA) and the American Association of Health Plans (AAHP). The NGC is an Internet Web site (www.guideline.gov) intended to make evidence-based clinical practice guidelines and related abstract, summary, and comparison materials widely available to health care professionals.

- There are nine guidelines on the NGC specific for people who have or are at risk of having HIV. There are 52 other guidelines that are relevant for managing HIV-infected patients. The Web site is widely used.

- Much evidence for evidence-based practice guidelines will come from the 12 evidence-based practice centers that AHCPR sponsors. However, there are no evidence reports or technology assessments proposed that are HIV-related.

Outcome measures can be used to determine cost-effectiveness, to evaluate clinical trial outcomes, to educate clinicians about how to practice, to help patients share in decision-making, and to adjust inflation for health care. Dr. Eisenberg asked that meeting participants provide guidance to AHCPR on where research efforts should be focused, to help translate research into practice, and to help the public understand the value of outcomes research.

Discussion centered on the need for a more prescriptive approach to outcomes research. For example, there is a need for models to show how outcomes might differ if guidelines and practice were different in a particular way. Ideally, a randomized controlled trial (RCT) would be conducted to evaluate each of these differences. However, this may not be possible. Non-RCT models are not pursued enough to answer these questions for the “real world.” To be able to conduct better observational research controlling for covariates and bias would be quite
important in the outcomes research field. Ultimately, of course, there needs to be latitude for individual decisionmaking in guidelines to allow for individual differences.

**Diffusion of Innovation: What Do We Know About How Clinical Practice Guidelines Are Implemented in Chronic Diseases?**

Sheldon Greenfield, M.D., New England Medical Center, noted that the implementation of guidelines is inconsistent, and offered several reasons why physicians might not follow guidelines. For example, in many instances, physicians disagree with “experts.” Variations in health services research and multiple interpretations can cause physician confusion about which practice to follow.

In some cases, physicians have alternative strategies that appear to work as well. For example, guidelines for asthma exacerbations suggested an algorithm for patients in distress to follow at home. Citing the difficulty of the algorithm, primary care doctors preferred that patients phone them since they were on call anyway. This difference occurred because those developing the guidelines (pulmonologists) were not usually on call.

Often, guidelines do not apply to patients seen by the physician. Most guidelines come from results from RCTs. In clinical practice, women, the elderly, and those with other medical diseases that affect the way a physician would treat an individual condition are seen. Competing comorbidities have a huge impact on many diseases.

Patients don’t always agree with guidelines treatment either. In some cases, doctors recommended mammograms, but 25% of patients didn’t get mammograms. On the other hand, many patients want treatment that goes beyond guidelines care, for example insisting on x-rays for acute complaints.

In certain instances, physicians are already following the guidelines and may have reached a ceiling. In the case of dementia guidelines, 80% of physicians were already following the guidelines and further improvement was unlikely.

Poor learning strategies affect implementation. There are at least four theories of learning, the elements of which need to be more carefully applied. These elements include social influence, adult learning, diffusion of innovation, and social marketing. There is a need to be
cleverer about the ways to influence physician behavior, borrowing more from social science theories.

Discussion centered on evidence-based versus opinion-based guidelines. The suggestion was made, in implementing guidelines, to check where the evidence is good and promote these guidelines more. The first step is awareness of guidelines. Additionally, the impact of guidelines on the health care system must be considered. Finally, in HIV, most guidelines are opinion-based rather than evidence-based. There are outstanding questions as to whether such guidelines may stifle additional research to provide evidence, or influence research committees and grants committees.

**The Challenges of Evaluating the Implementation of the HIV Clinical Practice Guidelines**

Steven Asch, M.D., The Rand Corporation, reviewed the challenges of evaluating the implementation of the HIV Clinical Practice Guidelines. How do we know that providers and patients are following the Guidelines? What are the methodologic challenges, particularly specific to HIV disease, that must be overcome to accurately measure guideline implementation?

The distinctions between guidelines and quality assurance indicators are often blurred. For example, while guidelines are meant to be comprehensive, aspirational (aim to change provider behavior), and flexible, indicators are meant to be targeted, observational (measure existing behavior), precise, measurable, and operational. Inevitably, a good indicator will misclassify people as having good care who do not and vice versa. As long as the misclassification is reasonably rare and randomly distributed, however, the indicator remains useful.

Both outcome and process measures are useful indicators to evaluate guidelines implementation. Outcomes indicators measure the end result (morbidity/mortality), the effect of the guidelines (whether included in the guidelines or not). Outcomes measures are less accountable than process measures and require more risk adjustment, but are the most meaningful to consumers and provide the most convincing evidence that guidelines are worth following.

Process indicators measure whether patients/providers took the recommended actions mandated by the guidelines. Since these actions are more under patient/provider control than
outcomes indicators, they are more accountable and risk adjustment is less of a problem. Moreover, poor performance on process indicators is easier to link to quality improvement than poor performance on outcomes indicators – i.e., poor performance on process indicators lets you know where to improve.

HIV outcomes indicators include period-specific mortality, quality of life (QOL), opportunistic infection (OI) incidence, surrogate clinical markers (viral load and CD4 count), and patient satisfaction. While risk adjustment is a problem because of large variation in disease severity, viral load and CD4 count are common measures that correlate with disease severity, and can be used as risk adjusters. Feasibility of outcomes indicators is also a problem -- in the era of HAART, reasonably sized studies frequently lack statistical power to detect mortality, which is increasingly rare. Cost may also be a factor, since QOL tests require sequential interviewing and validation, significantly increasing costs over review of administrative data.

HIV process measures include the use of OI prophylaxis. This information is easier to abstract from administrative data and charts than outcomes indicators. In contrast to other diseases, the wide variation in the process of care in HIV and more rapid changes in the accepted standard of care has several consequences for outcomes research:

- Good quality can mean discussing treatment options, which is difficult to measure in charts, medical records, and in interviews. Consideration of patient preference is paramount. HCSUS used a community advisory board, which is one solution.

- There is more geographic variation in the standard of care for HIV than for other conditions.

- The role of investigational trials may constitute good care more in HIV than in other conditions because there are high rates of participation.

- Consensus methods may be less valid than in other conditions, and evidence-based methods should be followed more.

Steps for evaluating HIV guidelines to develop an indicator system include the choice of an area to measure, selection of indicators, and testing of indicators. Criteria for choosing an area to measure include strength of evidence, link to outcomes, and potential for quality improvement. Other issues to consider when choosing an area to measure include:

- Chronic outpatient care is preferable to acute inpatient care because acute inpatient measures are more susceptible to risk adjustment problems.
• Antiretroviral therapy is clearly linked to outcomes, and there is much potential for improvement. This is still a complicated matter because of the rapidly changing and complex standards.

• OI prophylaxis is a great area because it is easy to write clear rules based primarily on easily obtained data such as CD4 counts and pharmacy data. There is also good evidence that it works. Dilated funduscopic examinations for cytomegalovirus (CMV) and other treatment indicators might be a bit more problematic. A problem with OI indicators is that OIs are decreasing rapidly in prevalence and there may be a lack of statistical power in studies.

• Counseling to prevent transmission is important but may be poorly documented. Testing high-risk groups for HIV is better documented, but many patients may choose to leave their usual provider for this service. Monitoring of viral loads and CD4 counts depends on expert opinions on the periodicity.

• Community-targeted, public health prevention activities have some of the largest potential for improving outcomes, but it is difficult to measure the processes in these guidelines. To date, the evidence for effectiveness has been variable with obvious notable exceptions (needle exchange).

In one HIV indicator system, called QA Tool, the distribution of indicators is as follows: ART (3), screening/prevention of OIs (9), counseling/testing for HIV (4), and monitoring (4). The ART indicators were the fewest because it was difficult to write them because of the rapidly changing standards. Criteria for indicator selection useful for HIV include:

• Ease of operationalization. Useful indicators must avoid the trap of being euphonious but vague -- the indicator and the target population must be stated without ambiguity.

• Accountability. A well-written indicator will measure that a patient was offered or referred for the indicated care and well as measuring whether care was received or refused. If a patient is enrolled in a clinical trial, with informed consent one can assume that one was offered standard of care. Given that the standards are rapidly changing, sensitivity testing for different professionals will be necessary in constructing indicators with accountability.

• Reliability. The indicator should provide the same results a high proportion of the time when applied to the same underlying populations. To do that, indicators should be robust to varying documentation practices. This is difficult because organizations vary greatly in their use of HIV identifying administrative codes.

• Adaptability. The indicator should apply to a wide variety of delivery and financing systems, and must include both overuse and underuse measures.

After indicators have been selected they must be tested. One testing challenge is sampling acquisition because of confidentiality issues, fragmented nature of care, and the geographic variability in the prevalence of HIV and OIs. Another is data collection on guidelines
implementation. For example, while medical records are best for clinical detail, they often have missing links and are heterogeneous in terminology. Administrative data are excellent for documenting whether people received services, but lack clinical detail to state what occurred during the visit. (This may be somewhat ameliorated by automating laboratory and pharmacy data.) Patient surveys are useful for general health outcomes but are quite expensive and often lacking in clinical detail. Patients might forget details or are afraid that they will get in trouble if they tell the truth.

One way to get around the inherent tradeoffs in the different data sources is to use different sources for different variables. Sometimes it is best to triangulate data sources to produce the best estimate for a variable of interest. Other times the best approach is to use a more accurate but perhaps more expensive data source to validate the cheaper one.

Existing HIV indicator efforts include those sponsored by: Federal agencies (Centers for Disease Control and Prevention [CDC], Health Resources and Services Administration [HRSA]), state agencies (NY, MD), local agencies (Los Angeles county, San Francisco), private agencies and professional societies (the National Committee for Quality Assurance [NCQA], Foundation for Accountability [FACCT], Infectious Diseases Society of America [IDSA]), health plans (Kaiser), and researchers (HCSUS, Johns Hopkins).

The two main challenges of constructing indicators to measure guidelines implementation are confidentiality issues and rapidly changing standards of care. The challenges can be overcome through a wide range of possible indicators. The best strategies will include blended databases of medical chart, administrative data, and interview data. As a consequence of the rapidly changing standards, it is important to repeatedly measure how well we are doing in the spirit of continuous quality improvement. To do that longitudinal data will be most useful.

**Focus on Current HIV Health Services Research:**

**The Care of HIV-infected Adults in the United States**

Samuel A. Bozzette, M.D., Ph.D., RAND Corporation, described the outcomes of HIV care in the era of HAART as studied in HCSUS.¹ HCSUS is a large collaborative study

consisting of a broad participation of funders, the first nationally representative study of people with HIV/AIDS. HCSUS data are weighted to represent the 231,400 adults who received care in the contiguous United States in January/February 1996. This is notable because protease inhibitor (PI) therapy had recently been approved at the start of the study. Study results from 1996-1999 include:

- At 2-year followup, 92% of the adults who were in care at the beginning of the HAART era were alive.

- At the 6-month visit participants appeared to be receiving reasonable care (90% had a clinic visit in the prior 6 months and 87% had a viral load in the prior 6 months).

- There was extraordinary growth in the use of PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) during the 2-year period to the point where 95% of those whose lowest CD4 count was <50 had a trial with these therapies.

Trends in the components of cost shifted dramatically. At the start of the study hospital costs predominated. As the study progressed, the percentage of cost from hospitalization and clinic visits decreased but the percentage of cost attributed to pharmaceuticals increased substantially. The drugs have substituted for more expensive forms of care, resulting in the total cost of care over the 2-year period decreasing by 20%.

There have been physiologic effects noted. The proportion of people who were in the lowest CD4 cell count category halved by 1998. The proportion of people who were at high risk for immediate mortality decreased dramatically, and those who were at high risk for OIs also decreased. This is probably the basis for the decrease in hospitalization rates.

The distribution of viral load by treatment was mixed. At the end of 1998 only 24% of individuals were suppressed to <50 copies per mL. The distribution of therapies for these individuals was as follows: 3 or more ARVs (61%), 2 ARVs (20%), 1 ARV (3%), and no ARV (13%). Of note, two-thirds of those on 3 or more drugs were very unsuppressed (>20,000 copies per mL). Possible reasons for this lack of suppression include poor adherence, resistance, and poor prescribing patterns.
Variations in the Care of HIV-infected Adults in the United States

Martin F. Shapiro, M.D., Ph.D., RAND Corporation, described important demographic differences in care and changes over time as noted in the HCSUS study. Measures of service utilization included having, in the 6 months prior to the interview, fewer than two ambulatory visits, at least one emergency department visit (no hospitalization), and at least one hospitalization. Measures of medication utilization included having taken: PCP prophylaxis for those individuals with CD4 cell count less than 200; at least one antiretroviral medication; and either PI or NNRTI therapy by a specified time.

Disparities in care were noted and differed by CD4 cell count, age, gender, race/ethnic group, insurance, socioeconomic status, and geographic region. Seventy percent of patients initiated HAART, but by 1998 only 53% were still on HAART. Research is underway to determine to what extent this is due to adherence issues, providers not offering therapy, and resistance. Overall, mortality was 8.5%, with blacks being significantly more likely to die than whites. Other significant findings include:

- Inferior patterns of care were observed for blacks and Latinos compared to whites. (Although there was improvement during the study, at the end of 1998 blacks were less likely to be receiving PIs, and Latinos were not going to the doctor as often.)

- Women had more emergency department (ED) visits and less PCP prophylaxis and PI use compared to men.

- The relationship between age and use of needed care was mixed; subjects 50 years old or older were less likely to use the ED but more likely not to be having PCP prophylaxis.

- There were differences by insurance status in ED use and use of PI/NNRTI therapy, with the uninsured patients and Medicaid patients receiving unfavorable care compared to the privately insured.

- Exposure route was associated with disparities in care. Those having either heterosexual contact or injecting drug use (IDU) as their risk factor received inferior care compared to men who had sex with men.

- Differences in care according to income showed that the highest mortality was seen in those subjects with household incomes of $5,000-10,000, suggesting that those who did not qualify for public programs were at a disadvantage.

- A CD4 cell count under 50 was associated with more use of medications, hospitalization, and ambulatory care.
Changes in physical health scores showed less improvement from baseline among older subjects, similar improvement according to gender, and the greatest improvement among blacks. Injecting drug users had the worst physical health status compared to subjects with other modes of HIV risk exposure, and heterosexuals had the greatest improvement. Not surprisingly, the best physical health was found in subjects with the highest income. The worst physical health status was reported by individuals with Medicaid/Medicare insurance. Those with a CD4 cell count under 50 had the worst health status, and had health status similar to those with low income.

Changes in mental health scores showed older subjects improving more rapidly. Men fared slightly better than women. The best mental health was noted among blacks. IDUs had the lowest reported mental health status, while those with highest income had the best mental health status, and those with private insurance had better mental health than those on Medicare/Medicaid. Mental health did not vary significantly by CD4 cell count.

Data analysis is still ongoing, and the patterns of care are not unexpected. The improvement in the use of therapies has been associated with some improvement in health in the population. Often the disparities were diminishing over time, but this was not universally the case. Current and future HSCUS efforts include multivariate analyses studying the relationship between provider characteristics and outcomes; and assessing the relationship between outcomes and pattern of therapy, accessibility of care, adherence patterns, resistance patterns, use of nonmedical services, and post-genetic predictors of outcomes.

One of the innovative features of HCSUS is the opportunity to combine social and biological variables to try to understand the course of HIV disease. For example, the relationship between patient attitudes toward treatment and outcomes, adherence, and resistance is being explored.

Public use datasets will be forwarded to AHCPR as follows: baseline (7/99), first followup (9/99), second followup (1/00), and records (6/00). The data are being screened to ensure that they meet confidentiality standards. Additional funding was received from AHCPR to continue to study outcomes. Finally, collaborations to pursue additional data collection, both patient interviews and biological assessments, are being sought.

Discussion centered on the effect of sites of care and knowledge and competencies of providers on outcomes, since perhaps sites frequented by minorities provide inferior care. Sites
of care and the knowledge and competencies of providers will be correlated to the ways in which treatments are administered. Quality of care will assessed to determine whether sites where minorities receive care are providing similar quality care. Investigators will examine with patient interviews and surveys whether treatments were offered.

Health-related Quality of Life Measures in HIV

Albert Wu, M.D., M.P.H., Johns Hopkins University, described health-related quality of life (HRQOL) measures in HIV. HRQOL is comprised of aspects of health that are directly experienced by the person including physical functioning, social and role functioning, mental health, and general health perceptions. HRQOL measures can be reliable and valid and are sometimes more reliable than commonly used clinical measurements (e.g., there is much subjectivity and hence random error in chest x-ray interpretation). Moreover, HRQOL measures are related in expected ways to objective sources of information, can predict important future events (clinical outcomes, hospitalization, job loss, death), can be used to detect difference between treatments, and can detect changes over time.

Important dimensions of HRQOL include physical functioning, role limitations, pain, general health perceptions, psychological well-being, energy, QOL, social functioning, and cognitive functioning. Specific measures of HRQOL include sexual functioning, sleep, eating, body image, recreation, and symptoms. Available instruments to measure generic HRQOL include the ACTG-21, the Medical Outcomes Study HIV Health Survey (MOS-HIV), HCSUS measures, and the SF-36 survey. (Current Adult ACTG measures are available at www.fstrf.org.) Disease-specific instruments include the Studies of Ocular Complications of AIDS (SOCA) vision measure for CMV retinitis. Symptoms can be measured with the use of the ACTG symptom distress instrument. Instruments are administered and scored in a variety of ways including self-administration (paper and pencil, computer-assisted means) and interviews in person or by phone. Standardized response choices are generally given and responses are combined to yield scores.

QOL assessment can helpful for choosing therapies. For example, a comparison of ddC versus zidovudine (ZDV) showed that clinical results were similar but ZDV was superior to ddC for QOL (Bozzette et al, JAMA). HRQOL assessments provide a comprehensive look at patient outcomes, integrate both good and bad influences of treatment versus the negative effects of
disease, and can be the most sensitive measure of interventions because they occur immediately. In addition, they are policy relevant, and are important to people.

HRQOL assessments can present numerous challenges, as well. For example, data collection from patients requires methods beyond chart review, may add expense, and requires more expertise. (For example, missing data are often “informative” since those for whom data are missing are often not feeling well.) Finally, these measures are less familiar to physicians, and are susceptible to non-treatment-related factors.

Importantly, HRQOL data can be used in both efficacy and effectiveness research, including clinical applications (e.g. screening tests) and policy applications (e.g. quality assessment and cost-effectiveness analyses).

Discussion was focused on the issue of literacy. It was noted that the cited measures do not incorporate measures of literacy. It is known that as much as 50% of the population does not read well enough to read a medicine label or standard information in a medical setting. For some applications, literacy screening tests could be used in conjunction with HRQOL assessments.

**A Statewide Program to Evaluate the Quality of Care Provided to Persons With HIV-Infection**

Bruce Agins, M.D., M.P.H., New York State AIDS Institute, described New York State’s quality monitoring program as a way of viewing process measures. In viewing performance measurement for purposes of improving quality or for monitoring adherence to guidelines, one is simultaneously attempting to improve the result. The process itself may be a stimulus for improving care.

The NYS quality of care program has been in place for 10 years and has the purpose of promoting the quality of HIV clinical services delivered to people with HIV in New York. The basis for this program is founded in law and in regulation (hospital code, Medicaid provider agreements, contract workplans for the AIDS Institute, and through formal enforcement surveys as necessary), required for Title II grantees in the Ryan White CARE Act (RWCA), and provides for independent peer review to assess quality and appropriateness of care.

The NYS HIV Quality-of-Care Program includes active processes for involving clinicians to collaborate on the development of clinical practice guidelines, to develop algorithms
based on the guidelines, and to translate algorithms into indicators. On-site quality-of-care reviews are conducted through a contractor, while providers participate in the guidelines committee and quality-of-care advisory committee. A formal decision-making process is employed for the development of measures and review criteria, and consultative services are available to aid facilities in the development of their own quality monitoring processes. Quality data are released publicly, and there are plans to include an assessment of quality in HIV special needs plans as they become operative.

Generally, methods of data collection for CQI may include administrative datasets, record review, self-reports, and site reviews. The advantages of administrative datasets include breadth of data, sampling, and uniformity of processes -- difficulties associated with administrative datasets include coding variations, definitions for clinical information and their uniformity, lack of timeliness, and the enormous effort required to clean data tapes.

Medical record review is heavily relied upon -- its advantages include uniformity of processes, standards applied universally, consistency of training of abstractors, and enhanced validity. However, a vigorous inter-rater reliability program is required to ensure uniformity of data collection. The disadvantages are resources needed (expensive process) and confidentiality issues. Fragmentation of care has been addressed by embracing a primary care model. If the primary care HIV provider does not directly provide the care, he/she must be aware of the care received and include it in the medical record.

Self-report has been used in HIVQual, a Title III-supported project designed to promote quality care improvement capacity and capability among Title III grantees. The advantages of self-report are that it is less expensive than other data collection methods, it institutionalizes the culture of quality, it builds provider capability, it gives providers data skill in sampling and validity, and it requires few external resources. The disadvantages of self-report are the lack of reliability, lack of uniformity of statewide data, and the requirement of many internal resources. A formal validation strategy is necessary.

Core performance measures include: HIV staging (CD4 cell count and viral load monitoring every 6 months), use of ART, OI prophylaxis, annual PPD screening, annual pelvic exam, STD screening, and oral health care. Viral load performance is an example of a measure on which providers perform very well. Performance has been consistently high for PCP
prophylaxis, as well, and has increased for pelvic examinations. There has been a drop in PPD screening since there is no longer a heightened sensitivity about tuberculosis. Referrals for dental primary care were abysmal at the beginning of the program, but have improved over the past 2 years.

Several States and Puerto Rico were included in *HIVQual* in early 1999, and the population (n=1804) is typical for Title III clients. *HIVQual* also provides consultation and organizational development to build infrastructure for quality in programs, and to monitor clinical performance using the indicators. Preliminary data on performance rates among the States showed fairly high performance in the use of CD4 cell count and viral load testing and use of HAART. Of the subjects with a viral load >10,000 copies per mL, 350 were on HAART and nearly 100 were on other combination therapy.

While overall in the New York State Quality of Care Program, HAART therapy utilization over time was similar to that observed in the HCSUS study (4% on monotherapy and 10% on no therapy), HAART utilization by risk factor showed little difference according to gender, exposure category, and racial/ethnic group. Differences in the use of HAART therapy exist according to geographic region and facility type, however. For example, HAART therapy is not used as much in Upstate New York as in the metropolitan New York City area.

The benefits of HAART therapy as a process measure are the ease of monitoring whether providers are adhering to guidelines and whether people are receiving care. The pitfalls are the changing definition of HAART, inconsistency of clinical practice, and the inability to capture people not in care. The ultimate challenge is to ask the right questions to link process measures from an observational dataset to outcomes.

**The Cost-Effectiveness of Preventing AIDS-related Opportunistic Infections**

Kenneth A. Freedberg, M.D., Boston University School of Medicine, discussed the cost-effectiveness of preventing AIDS-related OIs, and addressed the question of what the standard of care should be for those with early-stage HIV disease versus those with advanced HIV disease, from the perspective of the patient, individual provider, insurance provider, Medicaid, the USPHS/IDSA OI Guidelines panel, and the DHHS Antiretroviral Guidelines panel.
There is a wide range of costs associated with antiretrovirals and agents for PCP prophylaxis. There variation presents a policy problem, as illustrated in a March 1999 ADAP survey showing that 26 States had waiting lists, had cut medications, or otherwise restricted formularies for their ADAPs. With waiting lists, some patients get no medications while they wait and others get limited medications. There is a dramatic range in the medications covered in ADAP programs, with Nebraska covering 11 drugs to New York covering 218.

Cost analysis is distinguished from cost-benefit analysis and from cost-effectiveness analysis. Cost-effectiveness analysis includes two different outcome measures—cost in dollars and effectiveness in years of life saved (YLS) or quality-adjusted life years (QALYs) saved. If resources are limited, then the outcome of interest is a cost-effectiveness ratio, which is the additional resource use (cost) divided by the additional health benefits. The higher the ratio, the less cost-effective the treatment or intervention.

The Cost-Effectiveness of Preventing AIDS Complications (CEPAC) project, a computer simulation model of HIV disease, compares clinical outcomes, cost, and cost-effectiveness of different strategies. CEPAC includes data from the Multicenter AIDS Cohort Study (MACS), natural history studies, clinical trials, and cost data from the AIDS Cost and Services Utilization Study (ACSUS). CEPAC allows investigators to define CD4 cell counts and viral RNA distributions for groups of patients and to examine different antiretroviral strategies as well as OI prophylaxis.

An analysis of the cost-effectiveness of OI prophylaxis for subjects on HAART showed PCP prophylaxis had a big effect on QALY and was very cost-effective ($6,500 per QALY). Conversely, oral ganciclovir gave a slight survival benefit compared with no prophylaxis but was much less cost-effective, with a cost of over $500,000 per QALY. Using the CEPAC model, the cost-effectiveness of resistance-testing as in the GART study was determined. On the basis of virologic outcomes, resistance testing improved survival and the cost-effectiveness of the $400 test was $18,000 per QALY.

The CEPAC model can also be used to analyze situations in which data are pending. Using adherence interventions presented at the 12 World AIDS Conference in Geneva, for example, an analysis of how cost-effective these interventions are likely to be was conducted.
no one experiences virologic failure and people stay in care on therapy, then it will cost $20,000 per QALY. This is similar to the costs in the HCSUS study.

The issue of cost-effectiveness makes many people uncomfortable and raises the issue of whether limiting treatment is unethical. However, using limited resources inefficiently is irrational and probably unethical. Since resources are limited one must demonstrate the value of clinical interventions, and cost-effectiveness is a tool that can be used with other datasets to try to develop a standard of care.

Panel Discussion

Discussion was focused on the cost-effectiveness of interventions on the basis of increased patient productivity. Such indirect costs are necessary for a complete economic analysis from the United States perspective. From the perspective of an ADAP program or insurance provider, however, there is a need for caution in making such judgments because women and people of color are disproportionately affected by HIV disease and would be considered the “least productive” if they do not have jobs or have low incomes.

It appeared that HCSUS data for mental health and physical change status showed that those with no insurance did better than those with Medicaid/Medicare. However, the data need to be adjusted for disease stage. Those with no insurance were probably in earlier stages of disease. Data from HCSUS indicated that as people get sicker they are more likely to be insured. Often people at the most advanced stages of disease are publicly insured.

It was suggested that blood will have to be drawn more than once over the course of a study to determine whether patients had never become undetectable or whether they had succeeded and now had virologic failure.

It was suggested to study the standard of HIV care received by those in the corrections system. New York State did not include such patients but is encouraging the State correctional system to undertake quality improvement studies. HCSUS did not include incarcerated subjects unless they obtained care outside of prison.

Analysis is underway to determine how self-report correlated with medical record and phone data in HCSUS. While clinical outcomes are important, it is important to link information to prevention messages and systems of care. For example, insurance will cover ART for
newborns but won’t necessarily conduct programs to prevent HIV in the mother. The National Institute of Child Health and Human Development funded an ROI initiative to study risk practices and prevention messages and this can be linked to systems of care. In HCSUS, the questionnaire for the risk and prevention study asks what kinds of prevention messages people received and where. The organizational site survey asks what special risk reduction programs are in place.

**HIV Disease and Patient Outcomes Research: A New Opportunity to Improve Quality of Care?**

Sophia W. Chang, M.D., who became Director, Center for Quality Management in HIV Care, Department of Veterans Affairs on September 27, framed the larger context for what kinds of questions should be answered in this stage of the HIV epidemic given the available tools, technology, and data.

Outcome measurement challenges in HIV include: the rapidly changing technology/standard of care; randomized clinical trials with short timelines (24 to 48 weeks) for outcome measures; costly interventions for the system and individual; and the complexity of the real world. These “real world” factors impact effectiveness as compared to efficacy. While much of the focus to date has documented the effects of treatment on reducing mortality, additional questions to consider are when to initiate therapy, when to switch, how long to continue therapy, and what are the long-term effects of treatment.

Helpful “enablers” of outcomes research in HIV care are the significant clinical impact of interventions; considerable investments by both the public and private sectors; strong consumer involvement in care, policy, and decision-making; a strong research history; as well as a history of rapid translation of basic science innovations into practice and policy.

The pitfalls of outcomes research can be the overemphasis on measures, thereby losing qualitative information and the perspective necessary for understanding the clinical environment for both patient and provider. There should be caveats about what the indicators tell us and how they should be used, so that they do not become disengaged from the process being measured. This “mismatch” is often found when the primary “tool” used to spur change is financial incentives based on outcome measures.
HIV care continuums have a strong emphasis on services that surround and include primary care, and place more attention on “life issues” that impact effectiveness. Measuring effective improvements in HIV care must include these care models, which will be difficult. Interdisciplinary approaches are key in both the research and clinical settings and we must measure the effect of these approaches on outcomes. Learning more about how systems can improve the quality of care is vital, rather than just focusing on the patient/provider relationship. We need to identify opportunities to make a measurable difference in patient quality of life, as well as morbidity/mortality.

Some questions that will help us identify system issues include 1) What is the individual path from identification of disease through care and treatment? (How many programs are people accessing?) 2) Once in care, how do we improve the health of a person with HIV? 3) How do disease management programs (usually specific to a payor) interact with a population over time?

Ideal next steps include gaining a better understanding of the care system (not simply from a payor perspective); accounting for and accommodating comorbid conditions (specifically mental illness and substance use); and improving quality of care from a system perspective.

Methods for Evaluating Treatments to Support Clinical Practice Guidelines and Coverage Policies in Chronic Diseases

David M. Eddy, M.D., Ph.D., Kaiser Permanente Southern California, presented methods for evaluating treatments to support clinical practice guidelines and coverage policies in chronic diseases. Before an organization recommends a guideline or expends resources on a given treatment, it requires good evidence that the treatment is effective and beneficial.

The reasons for why evidence is needed were examined. Clinical or expert judgment to “know” what is right (effective) can’t be counted on, therefore research needs to be conducted. Even where there is evidence, practitioners don’t always do what the evidence shows. There is a wide variation in perceptions and practices and a high rate of inappropriate care (e.g., prescribing contraindicated drugs). Therefore, practitioners’ decisions must be supported through guidelines, coverage policies, and “clinical management.” Medicine is too complex for the unaided human mind. Good research must be conducted and used.
Good evidence demonstrates the effect of the treatment on health outcomes, compares the treatment with an appropriate alternative treatment or no treatment in equal patients, includes designs with appropriate methods, and has results from multiple studies that are reproducible and consistent. The biology of disease and effects of treatment are far more complicated and unpredictable than commonly believed. While biological outcomes are much faster than health outcomes, they are sometimes wrong. In designing research, identify the health outcomes to be improved and measure them. In addition, collect data that might tell the causality or predictability associated with biological outcomes.

The justifications for a comparison group are multiple. For example, much published information includes noncomparative data, such as anecdotes, physicians’ experiences, clinical series, and registries. Noncomparative data are seductive because they are easier to obtain, but they will be compared to something. The quality of these comparisons will depend on whether they address equal patients because health outcomes can be affected by cofactors. Ways to compare equal patients include randomization, “adjacent” controls, matching, historical comparison, and patients serving as their own controls.

In contrast, RCTs may not be necessary when the effect of treatment swamps any conceivable cofactors or when all cofactors are known and can be matched or adjusted for. For example, a patient can serve as his/her own control when the outcome without treatment is deterministic, when the natural course of the disease is inexorable without fluctuation, or when there is no placebo effect. Caution must be exercised, however, in the use of comparisons based on historical comparisons, clinical series, and registries. If one is to use registries, information must be collected in advance on all possible cofactors, using identical definitions.

Good methods include randomized controls, a sufficient sample size to find the desired effect, standardization of the treatment and an alternative, standardization of outcomes, blinding of patients and those assessing outcomes, low crossover, complete followup, and measurement of possible cofactors.

Good evidence is essential. Treatments are serious, have side effects, risks, and costs. Before treatments are used, it is important to know that patients will benefit from them. One can’t count on clinical or expert judgment to get the right answer; this must come from research. If a treatment is covered by insurance or promoted before its effects are known, the ability to
conduct research to learn whether the treatment is effective will be hampered and all current and future uses of the treatment will be blind. If one is to help support clinical practice guidelines and insurance coverage policies, then conduct RCTs.

Discussion centered on the evaluation of health outcomes in asymptomatic HIV-infected people. If most of the health outcomes won’t occur during the period of observation, then a large sample size and a long duration will be necessary to determine the effect of the treatment on those outcomes. In the case of HIV therapy, the treatment causes side effects in both infected and uninfected individuals. Such effects can be studied with registries because they meet the test of the outcome being deterministic.

The need to measure health outcomes versus biological outcomes in HIV was debated. Because of the nature of the HIV epidemic, ART was approved on the basis of 24 weeks of viral load data. Although the impact of the intervention was great in the short-term (HIV mortality has dropped 46% in New York), the long-term impact is unknown. The current position is one where drugs are on the market, guidelines have been issued and continue to change, and there are several unanswered questions about the outcomes of therapy. While there is evidence that lowering viral load correlated with dramatic decreases in mortality in those with late-stage disease, there is uncertainty about when to initiate treatment because, there is little data to show whether treatment is making a difference in early-stage disease because people are asymptomatic.

*Toward Patient Outcomes: New Directions in HIV Research*

**The Development of an HIV Resource Utilization Data Collection Center**

Richard Moore, M.D., Johns Hopkins University, discussed the development of a multisite HIV clinical and resource utilization database. The rationale for this database is the rapidly changing therapeutic milieu. The purpose of this project is 1) to establish a network of providers to transmit clinical and health resources utilization data for aggregate analysis in real time, and 2) to establish the infrastructure of an HIV clinical and resource utilization database and data collection center. This longitudinal cohort study is being funded by AHCPR, HRSA, the Substance Abuse and Mental Health Services Administration (SAMHSA), and the Office of the Assistant Secretary of Planning and Evaluation (OASPE).
The sites selected for the database came from a consortium of HIV/AIDS care providers called the HIV Managed Care Network. Due to fiscal and data collection constraints, 16 sites representing 20,000 HIV-infected patients were chosen to be in the database. As a result, this is not a nationally representative sample of the HIV/AIDS population in the United States. Medicaid is the principal insurer of patients in these sites. There are approximately 3,000 new cases projected annually. A majority of providers receive Ryan White funding.

Resource utilization data are generally electronically available for both acute care and chronic care. In phase I of the study, participating sites were identified, a Central Data Coordinating Center was established, HIV clinical and resource use data availability and needs were identified, and pilot data from January 1, 1998 through June 30, 1998 were collected. A compatible, multisite database is being created, and preliminary data analysis is underway.

During phase II of the project, an expert meeting will be held to specify priority HIV policy-relevant issues. Quality assurance of in-house data from phase I will be conducted. Further development of confidentiality and data access issues will be explored. Data collection from the phase I sites will be expanded.

Additional activities include the development of a provider site sampling frame, expansion of participating HIV provider sites, development and pretesting patient interview schedules, and development of a data querying system.

The Kaiser Permanente National HIV Research Consortium

Michael Allerton, Kaiser Permanente Northern California, discussed qualitative observational studies and experiences in the development of the Kaiser Permanente National HIV Research Consortium. In California, in the absence of an HIV registry in 1986, Kaiser Permanente had to determine anticipated hospital utilization and other medical services. To ensure confidentiality, data was collected on unconnected computer terminals where known HIV-positive patients were registered by medical record number. The medical record number database could access mainframe computers for utilization data, visit records, etc.

While the database was designed for program planning and not for research and quality outcomes research, there was controversy around the model of care, which was a disseminated internal medicine model without subspecialties. The database was used as a quality outcomes
measure to determine how well the model worked across medical centers versus the need for subspecialties.

A means to facilitate collaboration between providers at medical centers and providers within regions was sought. The evaluation process began in 1996 when PIs were introduced, which confounded the analysis. However other factors were important in the development of the research collaborative between Northern and Southern California. There were cultural barriers between the realities of clinical care (whose providers paid for the confidential database) and the demands of academic research (where the data was housed). Such issues included ownership of the data and publishing rights. Clinical care providers desire data to determine whether local trends are generalized. Researchers who have access to the data support the notion but desire involved studies over a long duration. There is also a cultural bias against research because the company’s mission is provision of care. After these hurdles were overcome and a unified database was developed, two studies were published on the decreased costs of laboratory diagnostics after the introduction of PIs and the incidence of cardiovascular events in patients on PIs.

On the basis of the success of the California project, this process was applied to other regions in the Kaiser Permanente system. Eventually an HIV national research consortium was formed. The reasons for success in forming the consortium include funding from non-HIV sources (unused oncology and genetics funds were used) and the intense desire by HIV physicians to find an answer to a research problem rather than to obtain first authorship compared with physicians in other fields.

Clinical-based research in the consortium had to be 1) focused on outcomes and quality measures (not clinical trials), 2) scientifically valid, 3) appropriate for confidentiality and the needs of the organization around confidentiality, and 4) ethical. Consortium research must benefit members of the health plan as well as the community, must reflect the unique capabilities of the organization (standardized computers and technology/methodology, and must provide assurance that there would be an expanded and appropriate relationship with industry (obtain funds from industry while ensuring that relationships are mutually beneficial). Current and planned studies include:
A seropositive lookback study -- all new diagnosed HIV patients for the last year will have a chart review to determine indicator events, sentinel events, or earlier indications of infection for the purposes of developing clinical guidelines for early detection.

The pharmacoeconomics of PI versus non-PI regimens;

The incidence of cardiovascular disease in those on PIs;

Examination of discordant populations (according to CD4 cell count and viral load);

Detection and recognition of acute retroviral syndrome; and

A prevention study as part of the NCQA quality improvement program to determine how often HIV tests are conducted within 6 months of STD diagnoses.

The Glaxo-Wellcome CHORUS Project

Amy Justice, M.D., Ph.D., VA Pittsburgh Healthcare System and the University of Pittsburgh, described the use of observational databases (ODBs) and large, simple RCTs for HIV guidelines evaluation. She began with the observation that guidelines should be careful not to over-reach evidence; variation in care in the absence of evidence is not necessarily bad and may provide evidence on which to base guidelines.

Efficacy and effectiveness research are complementary. Efficacy research is designed to optimize the benefit of a given therapy to show whether or not in the best of circumstances a therapy is effective. Effectiveness research asks whether or not the benefit is realized in realistic circumstances. Effectiveness research is needed in HIV disease because antiviral efficacy has been established with surrogate markers and short term survival. In most cases, long-term effectiveness is unknown in terms of adherence, resistance, side effects, toxicity, and comorbidities. In future research, management of the number, order, and timing of therapies must be optimized; surrogate markers for the future must be evaluated; and the level of evidence upon which the current HIV guidelines are based is primarily expert opinion.

Effectiveness research uses several sources of data including large ODBs and large simple RCTs. Each have weaknesses and strengths. ODBs have uneven quality of data and therefore must be quite large to overcome the substantial noise in the data. However, ODBs can more easily achieve long-term patient outcomes, provide a rich source of variables, and can be used for both multiple hypothesis generation and for initial validation. ODBs can sometimes be
used for final validation when the effect size is very large and when there is confidence that appropriate adjustment for confounders has been accomplished. Because large, simple RCTs test focused hypotheses, they can concentrate on a few variables and ensure that there is quality behind those variables. In order to be successful, large simple RCTs must be very large, follow long-term patient outcomes, and must be highly focused. Because of these restrictions, and the approximate ten-fold greater cost per observation for RCTs over ODBs, large simple RCTs should be reserved for questions that cannot be resolved with ODBs.

The Glaxo-Wellcome Collaborative in HIV Outcomes Research/U.S. (CHORUS) Project is an ODB begun in 1997 involving four community-based clinics funded by Glaxo-Wellcome. CHORUS is a real-time study in which electronic medical records are used, and data are downloaded to a central repository every day for the purposes of studying changing outcomes and changing clinical effectiveness. Post-marketing surveillance is a primary goal.

CHORUS, among the most mature databases available in the post-HAART era, provides several advantages: 1) patient consent has been prospectively obtained; 2) data are standardized and data quality is monitored for critical data elements; 3) there are procedures to review, approve, and prioritize scientific questions; and 4) there is infrastructure for future RCTs, including patients, data management, and outcomes assessment.

Conversely, CHORUS is not currently RCT-ready, and has a number of other limitations: 1) its data elements are somewhat restricted; 2) there is a limited patient population that is largely white males; 3) it is subject to the short-time horizon of industry; 4) there are potential conflicts of interest between marketing and science; 5) the ongoing maintenance of the database requires both time and money; and 6) CHORUS data are not publicly available. (There is, however, a process for submitting proposals for analysis of the data.)

The VA HIV Registry is an ODB begun in 1989 and mandated in 1992 for HIV case identification and tracking. Through links with computerized records within the VA it is possible to study capitation, utilization, and quality assurance. Because data are collected for other purposes, the VA HIV Registry is essentially free. It has a diversified population of minorities (excepting women), comorbid conditions, and older patients; approximately 5% of U.S. AIDS cases are included in this registry. Long-term follow-up is available and assured.
Conversely, the VA HIV Registry also has a number of limitations: 1) data quality is not assured; 2) there is no formal patient consent; 3) only VA-associated care is documented; and 4) women are nearly absent. In conclusion, the VA HIV Registry is a rough ODB limited to aggregated analyses; suited to supplementing targeted studies that can assess data quality; provides resources for hypothesis generation, and serves as an independent source of validation for more rigorous but perhaps not as generalizable data.

VA Net is a proposed RCT network including the VA, Kaiser Permanente, and other independent sites, designed to conduct large-scale, simple trials with limited data collection for the purposes of studying management strategies in HIV care. The VA Net’s strengths are formal patient consent; excellent patient population; experience in large-scale trials in chronic disease and in HIV; a sample size and follow-up needed to study survival; and its ability to inform study design and analysis.

Its weaknesses are that it is costly (but not as costly as traditional RCTs); it is an untested collaboration; it may be difficult to maintain; and there may be substantial crossovers over time. The VA Net is ambitious but important – it is likely the best source of a large-scale, simple RCT network and an excellent source for resolving questions that cannot be resolved by observational data, although further collaborative funding is needed.

In conclusion, observational data are the bedrock of outcomes research and should inform guidelines development and implementation. Large, simple RCTs are needed when the question cannot be resolved by observational data. Substantial long-term funding is required for both.

The HIV Treatment Data Project

Dr. Greenfield (for Sherrie Kaplan, M.D., Ph.D., New England Medical Center) described the HIV Treatment Data Project (TDP), an Internet-based, consumer-driven, ODB sponsored by WebMD and operated through the New England Medical Center. It is a consortium of a nontraditional nature in that it is not dominated by academic medical centers.

The HIV TDP is a longitudinal observational prospective cohort study to consider “N of 1” trial design modifications; use of instrumental variables and optimal, uniform, and consistent observation points; and large numbers and large effects. The TDP won’t compare individual drugs or specific combinations of drugs to each other; won’t compare care of individual
physicians, clinics, or care sites; won’t overcome prejudice against self-reported data; and won’t substitute for good provider-patient interactions.

The limits of the study design include the lack of causal inferences and investigator control over interventions, as well as the great heterogeneity of patients and physicians (both undesirable and desirable). The strengths of the study design are generalizability, the heterogeneity of patients, consideration of multiple health end points, flexibility for adding interventions and end points through a single computer mechanism, its potential to be cheaper, faster, and include larger numbers, and its ability to interdigitate with RCTs. Phase I research questions include:

- Can patients with HIV accurately report treatment regimens, test results, and clinical data?
- Can the database be used to maximize the validity of patient-reported data (i.e., asking the right questions)?
- Which patients prefer computer versus telephone surveys?
- What combinations of regimens are currently in use and how much variation in management by selected patient groups and across practices is present?
- What are the optimal “fixed” intervals between observation points to minimize measurement error and maximize detection of meaningful change?
- How reliable and valid are the HIV QOL, symptom experience, and hospitalization rates?
- How can data be optimally presented to maximize patient/physician accurate interpretation and effective data use? Which users need additional help to interpret data and how?
- How do HIV complications and comorbidities affect clinical management and outcomes?

Study sample size will depend upon the questions asked. In the beginning, survey data will be matched with medical records. Survey measures will include regimen descriptions, regimen adherence, regimen history, questions about CD4 cell counts and viral load, symptom experience, HIV-specific QOL, HIV-specific health distress, clinical stage, comorbidities, satisfaction with interpersonal care, participation in treatment decisions, barriers to care, risk behaviors, and demographics.

In summary, the HIV TDP shares many things with ODBs previously described. It has considerable differences, including being Internet-based and completely dependent on patient
self-report, and data are ultimately to be collected as inexpensively as possible with wide consent.

**Integrating Outcomes Measures in the Ryan White CARE Act Programs**

Faye Malitz, HRSA, HIV/AIDS Bureau, discussed integrating outcomes measures in the RWCA programs. The activities that she described were about program evaluation rather than outcomes research. Consolidation of all RWCA programs into the HIV/AIDS Bureau in 1997 provided an opportunity and continues to provide an opportunity to intensify and refocus evaluation efforts. While the RWCA programs have differing legislative and program requirements, there is still a need for a unified and consistent approach to evaluation across all programs to enable the assessment of the overall impact of the RWCA programs on people living with HIV/AIDS.

Multiple factors serve to emphasize the need for outcomes data. For example, the epidemic is growing among segments of the population that have traditionally lacked access to care. Moreover, the continued movement toward managed care represents opportunities and challenges for meeting the needs of multiple populations. Comprehensive outcomes evaluation is essential in an era where an ever-increasing emphasis is being placed on the relationship between program funding and program outcomes.

The HIV/AIDS Bureau has developed an evaluation approach that provides all RWCA programs with the framework for developing outcome measures and evaluations. This approach proposes evaluations that assess the extent to which programs are enrolling underserved and vulnerable populations, providing quality care that meets or exceeds current standards of care, providing services that remove barriers to primary care, reducing morbidity and mortality, and adapting to changing service and cost in the illness.

Current and planned HIV outcomes evaluation activities for the different RWCA programs include:

- The Outcomes Evaluation Technical Assistance Guide for Primary Care is being published for distribution and was developed primarily for Title I and II programs. It clarifies program expectations regarding outcomes evaluation of services funded under Titles I and II. The guide supports outcomes evaluations of Title I and II grantees by providing them with methods, references, indicators, and outcomes and recommends widely used outcome measures.
• Both Title I and II grantees are required to report on the impact of RWCA funding in terms of outcomes in their FY2000 applications. Grant application guidance provided examples for assessing the impact of RWCA funds.

• Through *HIVQual*, Title III grantees can develop continuous quality improvement activities required by the RWCA. *HIVQual* monitors the quality of HIV clinical care on the dimensions of HIV staging, ART, PCP/MAC prophylaxis, gynecologic care, and PPD screening. Indicators in *HIVQual* are in guidance for Titles I and II.

• Under Title IV there are voluntary outcomes evaluation projects including service delivery typology, perinatal transmission rates, and medical outcomes of children ages 5-12 served by Title IV sites.

  AIDS Education and Training Centers (AETCs) provide training, education, and consultation to providers of care for people living with HIV/AIDS. Applications are being accepted for a national AETC evaluation center. The center will be responsible for developing and implementing a data collection process to document education, training, and consultation provided by the regional centers. The center will also design and implement evaluation studies that focus on measuring program outcomes of AETC activities; coordinate an evaluation committee consisting of representatives from the funded AETC grantees, the evaluation center, and the HIV/AIDS Bureau; and support and provide assistance to AETC grantees in writing evaluation reports and scientific activities.

  The focus of the AETC evaluation will be viewed along a continuum starting with an assessment of provider education and training needs and the extent to which regional AETCs are meeting these needs, followed by an assessment of AETC educational activities, and finally an assessment of the impact of this training on clinical care.

  Through a SPNS-funded cooperative agreement with the Institute for Healthcare Improvement, an initiative to improve care for HIV-infected people will soon be underway. The aims of this collaborative with be to achieve measurable and dramatic improvements in health outcomes, to develop leadership capabilities and infrastructure, to facilitate the continuous improvement in care provided by participating grantees, and to disseminate models of improvement that can be used across all titles of the RWCA. Although primarily Title III grantees, other providers will be included.
There are also several local evaluation studies to incorporate outcome measures into local analyses and initiatives with the CDC to test new methods for measuring outcomes in care and treatment.

**Panel Discussion**

It was noted that speakers focused on people with known HIV infection. Given that roughly half of the HIV-infected people aren’t in care, the question of outreach/intervention for primary prevention and to bring people into care was raised. Potential avenues include:

- There are testing and counseling, outreach to adolescents, and other activities within the RWCA programs.

- A PCP index study cofunded with CDC is examining hospitalizations for PCP and analyzing how these rates compare with known HIV incidence.

- HRSA is discussing ways of coordinating service delivery for HIV prevention with CDC.

- NIH is in the process of funding an HIV prevention trials network directed at the uninfected in target populations.
DEVELOPING A PATIENT OUTCOMES RESEARCH AGENDA

On the second day of the workshop, participants were divided into workgroups and asked to develop research questions to evaluate the extent to which the HIV clinical practice guidelines were: 1) understood and adopted, 2) implemented, and 3) effective. Further, they were instructed to consider various stakeholder groups, including:

- Payors: ERISA self-insured plans, Medicaid/Medicare, managed care plans;
- Providers: staff HMOs, government healthcare provider (e.g., VA), doctors/healthcare workers (physicians, physician assistants, nurses, nurse practitioners);
- Social Service Providers: (case managers, educators); and
- Patients.

Below are the results of the workgroup sessions. It should be understood that the workgroups had limited time to discuss a broad range of issues. The questions below should be seen as a starting point for further discussion. The groups were able to develop a comprehensive list of questions, all which ultimately need to be addressed if we are to better understand the effects of new HIV treatment modalities. What the groups were not able to do was: (1) prioritize the questions, (2) discuss the methodology needed to answer the questions, or (3) discuss the roles of government, academia, industry, and the health care infrastructure in implementing the research agenda. These are issues that the Forum will tackle in the coming year. It is our hope that the questions developed at the workshop will inform the on-going work of researchers, funders, and providers in HIV care.

Adoption: Do the stakeholders understand and accept the Guidelines’ recommendations as valid?

Payors

- Are payors aware of the Guidelines?
- To what extent have they adapted the Guidelines for their own use? If they have ownership, they are more likely to implement the Guidelines.
- How have the payors modified the Guidelines? Do these modifications still convey the Guidelines’ intent?
- How do payors disseminate Guidelines to providers in their system?
- What are the reasons for quick adoption of the Guidelines? For example, the perinatal guidelines were adopted very quickly in the United States. It was acknowledged that some reasons for their adoption and implementation were that they were brief, simple, and about children.
• What are the barriers to adoption of the Guidelines? For example, in managed care organizations (MCOs), the cost of Guidelines care for HIV-infected patients may exceed the capitation, and the MCOs may be reluctant to adopt the Guidelines. Maybe there isn’t enough access to experienced providers to implement the Guidelines.
• How compatible are the Guidelines with the reimbursement strategies or payment structures within Medicaid organizations or other systems?
• What are the political influences that may obstruct adoption of the Guidelines?
• What are the effects of legislation on adoption of the Guidelines?
• To what extent do the Guidelines structure/complexity and frequent updates affect adoption by payors?
• How do the Guidelines fit into the payors’ overall priorities?

Providers

• How do we differentiate between providers (more and less experienced)?
• What is the level of adoption of the Guidelines by experienced providers? Which parts of the Guidelines do they follow and why?
• How do we identify less experienced providers and assess their level of pickup of the Guidelines? What mechanisms (personalized encounters, computerized feedback) can we institute to improve the adoption of the Guidelines by those providers?
• How do confidentiality laws affect the adoption of Guidelines and their willingness to offer services?
• How do providers’ perceptions of adherence to therapy affect adoption of the Guidelines? For example, if a population is thought to be unable to adhere to HAART will it impede the prescription of certain drugs?

Patients

• Some patients believe that the HIV therapies don’t work or aren’t good for them. What are the reasons for these disbeliefs and how can we correct them?
• Are certain feedback mechanisms, such as the availability of information on websites or other written materials targeted to different populations and at different reading levels, helpful?
• What is the role of patient advocates in improving patient adoption of the guidelines?
• What competing demands on patients’ lives and comorbidities affect adherence to ART and how? For example, a patient might believe and understand the Guidelines, but be unable to afford both HIV therapy and medications for depression.

Social service providers

• Social service providers often have more influence on patients than primary care physicians do. How do we improve social service providers’ knowledge concerning the Guidelines?
IMPLEMENTATION: Has the stakeholder put the Guidelines’ recommendations into practice?

Patients

• What are the practical barriers that exist in people’s lives and how do they affect implementation? (For example, childcare or lack of refrigeration for drugs)
• What other factors relate to adherence to therapy?

Providers

• What are the barriers to implementation for providers? For example, the health care system they are working in may not cover many of the recommended drugs in its formulary, tests might not be allowed to be performed as often as recommended, and there might not be a team approach to care.
• What is the process that providers go through with the patient in the decision to initiate ART? The Guidelines provide details on items to be discussed. Is this occurring?
• What are effective feedback mechanisms to providers to improve their implementation of the Guidelines?

Healthcare systems

• In terms of process, there must be population-based mechanisms to evaluate to what extent ART and OI prophylaxis and other elements of HIV care are being offered.
• Compare U.S. HIV guidelines to other developed countries’ guidelines and implementation to determine whether stronger recommendations improve health outcomes.

Effectiveness: What are the patient preferences for outcomes?

• Patient populations to examine include substance abusers, those with mental illness, women, those of different socioeconomic status, and significant cultural groups.
• Which outcomes are most important to patients?
• What differences are there in patient preferences according to race, gender, disease stage, and other patient characteristics? Incorporate the individuality of preferences in outcome measures.
• Develop tools to assess individual preferences to assist in treatment planning and the outcome definition. This will be necessary to evaluate whether the care accomplished these outcomes.
• Examine patient-provider interaction to test the notion that perhaps if patients feel their providers care about them they might be more likely to adhere to treatment. Examine the patient-provider interaction by different populations in terms of treatment initiation.
• Examine the psychosocial and socioeconomic context of people’s lives and how these issues affect treatment. Develop a protocol or form that could be used at the time of ARV initiation by providers to ask questions about the context of people’s lives that might influence patients’ decisionmaking about the treatment and their ability to be adherent. Compare this intervention to no intervention to determine whether this has an effect on adherence, viral suppression, and other health outcomes.
From the providers’ viewpoint, can optimal treatment of patients be provided successfully?

- Break the Guidelines into several components to evaluate effectiveness.
- Is each Guidelines component feasible to implement according to geography, individual needs/abilities, payor systems, and provider capabilities? Guidelines might not be applicable for certain populations or in certain situations.
- What is the cost of each component of care? This is more than the financial cost of conducting tests such as viral loads. What is the cost to bring a patient in to receive treatment? What does it cost to give a person treatment in terms of the stigma of receiving treatment? What are patients willing to endure to receive treatment?
- To address these questions augment administrative databases with provider surveys, patient surveys, and clinical data. Make these databases accessible to learn what is the best way to treatment individual patients.
- Conduct a RCT to compare the effect of delivery systems on patient outcomes. For example, in New York patients are receiving a choice of health plans. Use this to compare whether one provider plan is better than another for different types of patients. From a patient perspective, what are the costs of the plans, how can the Guidelines be implemented differently in different plans, and what are the outcomes?
- Examine the occurrence of the use of monotherapy and other discouraged practices for which there is good evidence, reasons for the persistence of such practices [aren’t aware of the Guidelines, didn’t understand the Guidelines, think they know better than the Guidelines, Guidelines didn’t cover this situation (comorbidities)], and possible interventions targeted to those providers.

What is the relationship between access to care, utilization of care, and outcomes?

- There is need for a HCSUS-type study for 1999 to get a current snapshot of variations in HIV care.
- What are the outcomes for people in nontraditional care (e.g., emergency rooms, STD clinics, ambulatory care settings)?
  - Track disease stage when people enter into care and the reasons why.
  - Where is the point of entry into care (e.g., emergency room, social worker, outreach workers)?
  - Once in care, what is the subsequent referral process for ongoing HIV care?
- What are the barriers to patients receiving care? Given these barriers, how do we get patients into care?
- What is the cost-effectiveness of the Guidelines over the long term to bring these people into care?
  - Financial considerations of treatment
  - Holistic view (If one brings a homeless person into care, their homelessness will also have to be addressed to provide effective treatment.) This view will vary by populations and demography.
- Conduct an RCT comparing outreach interventions to determine which ones work, where, and for whom.
• Use HIV surveillance data, especially as HIV reporting data are embraced by States, as a tool to determine OI rates, etc.

**What is the public health impact of implementation of the Guidelines?**

• What is the impact on HIV transmission?
• What is the cost of care?
• What is the effect on public health versus individual health?

**What are the long-term effects of Guidelines treatment?**

• Focus on the HIV ARV Guidelines rather than on the perinatal transmission guidelines.
• How do you define “long-term” and what the median survival is? It was suggested to use the paradigm available from cancer research, which is to examine health outcomes at 2 years, 5 years, and 10 years.
• All studies in this area need an intend-to-treat modality.

**What measures should be used to study long-term effectiveness?**

• Suggested areas to measure included long-term survival, health-related QOL, QOL measures comparable to other diseases (e.g., SF-36 and SF 12), patient satisfaction with care surveys, objective measures of functional status, morbidity (OIs, treatment-related morbidity, and effects of other comorbid conditions), cost, HIV transmission rates, and productivity.
• Include surrogate markers (they must represent a central piece by which the outcome occurs) such as viral load and CD4 cell count to understand the mechanism of disease, especially over time.
• Clinical measures are effectiveness measures and are closely related to end result, i.e., side effects and preventable effects.
• Measure provider satisfaction.
• Examine whether there are other long-range outcomes related to different stakeholders.
• Integrate these health outcomes measures into AACTG clinical trials for those trials not currently using these measures.

**What are issues to consider in designing studies for HIV patient outcomes?**

• Design studies and measures in conjunction with people living with HIV/AIDS to ensure that the special context of the disease state is taken into account.
• Results of the HIV patient outcomes study need to be comparable to other chronic disease states.
• A suggested study design matrix included examining patient outcomes and the role that medical care as an entity (guidelines in it), systems issues (payors and whole range of providers), adoption, implementation, and patient behaviors have on these outcomes. The study matrix was applied was over time, in different populations, and in different care systems.
• A grid was developed to view outcome measures according to stakeholders over time.
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<tr>
<th>Stakeholder</th>
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<th>Intermediate Term</th>
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Does Guidelines treatment affect survival rates with intent to treat analysis over time?

- Study design issues include the need for a large cohort, long study duration, and a simple study design. For example, conduct a RCT to compare the effect of Guidelines care with and without adherence support. Conduct observational studies.
- The quality of data must be assessed. Data to evaluate include: chart review, patient self-report, pharmacy data (prescriptions and refill rates), and other technology to assess adherence (e.g., MEMS caps and patient drug levels).
- Study the impact of data systems in HIV care practices on Guidelines implementation, treatment effectiveness, and health outcomes. For example, if there aren’t adequate systems to track hepatitis B shots and clinic visits, it will be difficult to adhere to the Guidelines.
- Evaluate administrative data (claims data, payor data) to determine whether the medication was bought or covered.
- There is a need to triangulate the data to confirm data points.
- Barriers to such studies include:
  - the cycle of funding (To conduct a 10-year survival study, a minimum of 12 years of funding is needed),
  - provider and patient buy-in (e.g., belief in surrogate markers),
  - changing Guidelines,
  - treatment failure,
  - socioeconomic variables and other demographic variables and patient characteristics, such as literacy, language, and mental status,
  - patient retention in the original care system, and
  - access to data elements (e.g., lack of access to the CDC HIV Registry).

How does HAART affect QOL over time and in different populations in different systems of care?

- Conduct baseline measures of QOL even if this means using a treatment-naive subset.
- Study QOL frequently to capture fine differences through a study interval every 3 or 6 months. Use internally and externally comparable measures such as the SF-36 and SF-12.
- Control for language, literacy, interviewer bias, administration, cultural bias, time to administer tests, and location.
- Ask process questions such as is the patient satisfied with how the provider follows the guidelines.

Determine patient satisfaction with care over time, in different populations, and in different settings. Questions relate to the patient perception of health care. Measures include:

- Physician/social service provider explanations of what is happening to the patient over time,
- Comprehensiveness of treatment, (e.g. treatment for mental illness or substance abuse and improved access to entitlements)
- Waiting time in physician’s offices and ease of obtaining appointments/test results,
• Questions tailored to satisfaction with HIV-specific care (Do you know enough about your HIV services compared to the larger context of your health?), and
• Population-specific questions and the baseline expectations of those populations.
• Administer these tests every 3-6 months. The barriers to such studies are similar to those in the QOL study. Be cognizant of interviewer bias.
• Assess the effectiveness of patient advocacy and assertiveness training to empower their discussions with providers about treatment decisions to determine its effect on patient adherence and health outcomes.

How are morbidities linked to outcome measures over time in different populations?
• Intermediate outcomes should be studied, such as cognitive function, service utilization (e.g., hospitalizations), clinical morbidities, including HIV-related morbidities; OIs, hepatitis C, treatment-related morbidities, co-morbid condition-related morbidities (adherence to mental health treatments and substance abuse treatments), and functional status.
• Conduct large, simple trials across payor systems to determine rates of OIs, OI prophylaxis practices, mortality, etc. Consider Medicaid/Medicare/VA in particular as large systems that are perhaps underutilized.

Using the same study design matrix, study the effect of the Guidelines on HIV transmission rates.
• Look at trends in the counseling and testing of HIV-infected pregnant women before and after the Institute of Medicine report and in anticipation of potential new CDC guidelines on counseling and testing of pregnant women.

Using the same study design matrix, study the effect of the Guidelines on patient’s productivity. (This will be an important issue for non-government payors.)
• Compare the person’s productivity at baseline to after receipt of care.
• Compare both job-related and non-job-related functionalities. (i.e., consider a person’s ability to work compared to previous jobs they held; compare patients’ ability to care for children before and after receipt of care)
Developing an Agenda for Patient Outcomes Research in HIV Disease

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Catherine Wilfert, MD, Duke University Medical Center
Robert Zackin, ScD, Statistical & Data Analysis Center, Harvard University School of Public Health
APPENDIX C: WORKSHOP AGENDA

Project to Develop a Research Agenda Regarding the Effect of the HIV Standard of Care on Patient Outcomes
Washington West End Marriott Hotel
1221 22nd Street, NW
Washington, DC

Thursday, September 23, 1999

8:30 – 9:00 Continental Breakfast

9:00 – 9:15 Welcome and Introductions (David Barr, director; Derek Hodel, project coordinator; Forum for Collaborative HIV Research)

9:15 – 10:15 The growing importance of patient outcomes research in the management of chronic diseases (John Eisenberg, MD, MBA; Agency for Health Care Policy and Research)

10:15 – 10:45 Diffusion of innovation: what do we know about how clinical practice guidelines are implemented in chronic diseases? (Sheldon Greenfield, MD; New England Medical Center)

10:45 – 11:00 Break

11:00 – 11:30 The challenges of evaluating the implementation of the HIV Clinical Practice Guidelines (Steven Asch, MD; The Rand Corporation)

11:30 – 1:00 Focus on current HIV health services research
  • Variations in the Care of HIV-infected Adults in the United States (Martin F. Shapiro, MD, PhD; Rand Corporation)
  • The care of HIV-infected adults in the United States (Samuel A. Bozzette, MD, PhD; Rand Corporation)
  • Health-related Quality of Life Measures in HIV (Albert Wu, MD, MPH; Johns Hopkins University)
  • A Statewide Program to Evaluate the Quality of Care Provided to Persons With HIV-Infection (Bruce Agins, MD, MPH; New York State AIDS Institute)
  • Cost-Effectiveness Issues in HIV Care (Kenneth A. Freedberg, MD; Boston University School of Medicine)

1:00 – 2:00 Lunch
2:00 – 2:30 HIV disease and patient outcomes research: a new opportunity to improve quality of care? (Sophia W. Chang, MD, MPH)

2:30 – 3:30 Methods for evaluating treatments to support clinical practice guidelines and coverage policies in chronic diseases (David M. Eddy, MD, PhD; Kaiser Permanente Southern California)

3:30 – 3:45 Break

3:45 – 5:00 Toward patient outcomes: new directions in HIV research
• The Development of an HIV Resource Utilization Data Collection Center (Richard Moore, MD; Johns Hopkins University)
• The Kaiser Permanente National HIV Research Consortium (Michael Allerton, Kaiser Permanente Northern California)
• The Glaxo-Wellcome CHORUS Project (Amy Justice, MD, PhD; VA Pittsburgh Healthcare System)
• The HIV Treatment Data Project (Sherrie Kaplan, MD, PhD; New England Medical Center)
• Integrating Outcomes Measures in the Ryan White CARE Act Program (Faye Malitz, MS; HIV/AIDS Bureau, Health Resources Services Administration)

5:00 – 5:30 Wrap-up discussion and adjourn

5:30 – 6:30 Reception

Friday, September 24, 1999

8:30 – 9:00 Continental breakfast

9:00 – 9:30 Charge to Workgroups

9:30 – 1:30 Workgroup session (with working lunch 12:00 – 1:00pm)

1:30 – 3:00 Reports from the Workgroups/Close

Workshop participants have been assigned to one of four workgroups, each representing a broad category of research questions -- participants are assigned in such a way to ensure a diverse mix in every workgroup. Workgroups, each of which will have a facilitator and rapporteur, are as follows:
WORKGROUPS:

- DISSEMINATION. Hypothesis: The stakeholder is aware of and has access to the Guidelines.
- ADOPTION. Hypothesis: The stakeholder understands and accepts the Guidelines' recommendations as valid.
- IMPLEMENTATION. Hypothesis: The stakeholder has put the Guidelines' recommendations into practice.
- EFFECTIVENESS. Hypothesis: The Guidelines' recommendations, when applied, are effective.

Each workgroup will be asked to consider a hypothesis concerning the HIV Clinical Practice Guidelines (the “standard of care”), and to develop research questions to test the hypothesis for different stakeholders, including:

- PAYORS (Company ERISA self-insured plans, HCFA/Medicaid-Medicare managed care, managed care plans)
- PROVIDERS (staff HMO’s, government healthcare provider [e.g., VA], physicians)
- SOCIAL SERVICE PROVIDERS (case managers, educators); and,
- PATIENTS

In developing research questions, workgroups will be asked to consider methodology (e.g., sample size and stratification; process and outcome measures; research questions) and context (e.g., what is the value of answering the question? what are the barriers?).

- SPECIFY VALUES: What is the value of determining the answer?
- DESCRIBE POPULATION: How can stakeholder group be stratified? (geography, payor, socio-economics, public/private)
- DEFINE RESEARCH QUESTIONS: Which elements of the standard of care can be evaluated? (prioritize)
- DETERMINE METHODS: How? What does “evidence” of implementation look like? (process measures, outcomes measures)
- IDENTIFY CHALLENGES: define barriers to outcome evaluation

NOTE: For the purpose of today’s exercise, workgroup participants should assume that the recommendations made in the Clinical Practice Guidelines have been validated, at least in the context of a controlled clinical setting. The challenge today is to determine to what extent the guidelines have been implemented, and the degree to which they are effective (i.e., efficacious in a practice setting)
## APPENDIX D: WORKSHOP PARTICIPANT LIST

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution/Department</th>
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<tbody>
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<td>NYS AIDS Institute</td>
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<td>Steve Asch, M.D.</td>
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