FCHR Project on Metabolic Abnormalities in HIV Disease and Treatment

The Need for an Interim Case Definition and a Study to Examine Prevalence

The Forum for Collaborative HIV Research, (FCHR) situated within the Center for Health Policy Research (CHPR) at The George Washington University Medical Center, is an independent public-private partnership composed of representatives from multiple interests in the HIV clinical research arena. The FCHR facilitates ongoing discussion and collaboration between appropriate stakeholders on the development and implementation of new clinical studies in HIV and on the transfer of the results of research into clinical practice. The main purpose of the FCHR is to enhance collaboration between interested groups in order to address the critical unanswered questions regarding the optimal medical management of HIV disease. By encouraging coordination among public and private HIV/AIDS clinical research efforts, the FCHR hopes to integrate these efforts into HIV/AIDS medical care settings. Therefore, studies performed by these various research entities, separately or in cooperation, can begin faster; duplication of efforts can be reduced; patient enrollment and retention can be further facilitated; and costs of getting answers to the critical questions can be shared. At present, the FCHR is staffed by three persons and consists of over one hundred members, representing all facets of the field. These include pharmaceutical companies; public and private third-party payors; health care delivery system groups; government agencies; clinical research centers; and patient advocacy groups.

For further information about the Forum for Collaborative HIV Research and its projects, please call William Gist at 202-530-2334 or visit our Web site at: www.gwumc.edu/chpr and click on HIV Research.

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INTRODUCTION

On October 26, 1998, the Forum for Collaborative HIV Research (FCHR) sponsored a meeting in Chicago to discuss metabolic abnormalities in people with HIV disease. The meeting focused on the need for a case definition for these problems, and the need for and design and implementation of a cross-sectional prevalence study. This report provides a summary of that discussion. It is our hope that this report will inform further developments in research and efforts to define these emerging and potentially life-threatening problems.

BACKGROUND

The FCHR Meeting on Metabolic Abnormalities in HIV Disease and Treatment arose because of reports of metabolic changes and unusual symptoms that were occurring in people with HIV. Anecdotal reports showed these changes were occurring in people who were otherwise experiencing an excellent response to antiretroviral therapy, as well as, to a much lesser degree, in those who were not on antiretroviral therapy or not on a protease inhibitor-containing regimen.

In response to these reports, the FCHR held a meeting in September 1997 to discuss metabolic consequences of HIV disease and treatment. This was the first organized discussion to identify the problem and raised questions for further consideration. Two of the central pieces of research needed were identified as 1) characterization of these metabolic effects to determine the best means for their identification and assessment and to clarify the causes, progression, and treatment of these metabolic disorders, and 2) determination of the prevalence of these symptoms overall.

Interest in this area grew, and studies were presented at the XII World AIDS Conference in Geneva and at the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Diego. The FCHR prepared a report that summarized the September 1997 meeting and presented an overview of reported research into the metabolic consequences of HIV disease and therapies through September 1998 [1].

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[1] The FCHR report is available through its website: www.gwumc.edu/chpr, then click on HIV Research.

MEETING ATTENDEES

Beverly Alston - NIAID
Dawn Averitt – WORLD
David Barr – FCHR
Joan Benson, M.D. – Merck Research Laboratories
Sue Brobst – FCHR
Dawn Carlson, M.D. – Abbott Laboratories
Andrew Carr, M.D. – St. Vincent's Hospital Sydney
Henry Chang, M.D. – Dupont Pharmaceuticals
Ben Cheng – Project Inform
Jenny Columbo, Pharm.D. – Hoffman LaRoche
Lawrence Deyton, M.D. – Dept. of Veteran's Affairs
Michael Dube, M.D. – USC Medical Center
William Duncan, Ph.D. – NIAID
Wafaa El Sadr, M.D. – Harlem Hospital Center
Julian Falutz, M.D. – Montreal General Hospital
March Fenton, R.D. – AIDS Proj. Los Angeles
Judith Fradkin, M.D. – NIDDK
Eric Furfine, Ph.D. – Glaxo Wellcome
Merril Gerston, M.D. – Agouron Pharmaceuticals
David Gilden – Gay Mens' Health Crisis
William Gist – FCHR
Dianne Goodwin, Pharm.D – Glaxo Wellcome
Neil Graham, M.D. – Glaxo Wellcome
Carl Grunfeld, M.D. – S.F. V.A. Medical Center
Rebecca Hoffman, M.D. – Abbott Laboratories
Don Howard – ACT UP Golden Gate
Reginald Jackson – CPCRA CCG
Anthony Japour, M.D. – Abbott Laboratories

Jonathon Kaplan, M.D. – CDC
Cheryl Karol, Ph.D. – Hoffman LaRoche
Connie Kohne, M.D. – Agouron Pharmaceuticals
Barney Koszalka, M.D. – Glaxo Wellcome
Kevin Curtis – Keystone Center
Jules Levin – NATIP
Ronald Lewis, M.D. – Agouron Pharmaceuticals
Kyra Lindemann – Merck & Co.
Douglas Manion, M.D. – DuPont Pharmaceuticals
Kathleen Mulligan, M.D. – Univ. of California/SF
Bob Munk – University of New Mexico
Jeff Murray, Ph.D – Food and Drug Administration
Norma Muuraheinen, M.D. – Serono Laboratories
Judy O'Brien – Keystone Center
Faith Ottery, M.D. – Bio-Technology General
Frank Pallela, M.D. – Northwestern University
Franck Rousseau, M.D. – Triangle Pharmaceuticals
Peter Ruane, M.D.
Steven Schnittman, M.D. – Bristol Myers Squibb
Eve Slater, M.D. – Merck & Co.
William Strain – AIDS Project Los Angeles
Subhasree Raghavan, Ph.D. – Harlem Hospital
Fulvia Veronese, M.D. – NIH Office of AIDS Research
Yenyun Wang, M.D. – Pharmacia & Upjohn
D. Scott Weigle, M.D. – University of Washington
Robert Zackin, Ph.D. – Harvard University

PROS AND CONS OF FOCUSING ON A PREVALENCE STUDY

a.   What do we learn from such a study?

The FCHR Report on Metabolic Consequences of HIV Disease and Treatment cites several studies describing symptoms including: elevated triglyceride and cholesterol levels, irregular glucose metabolism including insulin resistance, abnormal distribution of body fat, truncal obesity, breast enlargement, weight loss, peripheral wasting, and development of "buffalo hump." However, there are difficulties in evaluating the sum of this research. The discrepancies in reported data on prevalence led to the October 26, 1998 FCHR meeting. Much of the research in this area cannot move forward without a better sense of the prevalence and clear definition of the problem. A study to establish prevalence would, by its nature, be complex and require the collaboration of expertise and resources from academia, industry, and government. The mission of the FCHR is to foster such collaboration in HIV research. Therefore, a decision was made to focus the discussion on the need for a prevalence study. Such a study will tell us if and how these disparate symptoms are connected, and will lead the way for further research on the cause, ramifications, and treatments for people with metabolic abnormalities.

b.   The importance of further research

A preliminary review of the literature showed that prevalence of metabolic abnormalities varies in individual reports from 2 percent to 80 percent, and this variance depends in great part on how one defines the symptoms and what measurement techniques are used. The precise spectrum of the syndrome(s), the prevalence, and the possible link to protease inhibitor (PI) therapy remain unclear. Many studies consist of self-report without prospective data, and there are major differences between groups. Some healthcare providers who are observing a very high percentage of metabolic abnormalities have begun to recommend against taking PI therapy. This meeting was an opportunity to discuss what diagnostic evaluations need to be performed so that there can be some standardization across studies and then determine the difference in metabolic abnormalities to that of existing data sets such as the National Health and Nutrition Examination Survey III (NHANES) and CARDIO.

c.   What is to be learned overall from studying the syndrome

The participants achieved a consensus on what the most common clinical manifestations of the syndrome are. In order to conduct treatment trials or to monitor how body composition changes for those on highly active antiretroviral therapy (HAART), the case definition will have to be refined. Current studies will answer some very important questions definitively, such as whether or not the metabolic abnormalities are from the effects of PIs and the long-term information on the nature of the syndrome. In the mean time, the prevalence and risk factors for cardiovascular disease must be obtained more quickly.

Associating fat maldistribution with metabolic abnormalities is unclear at this point. Preliminary analysis suggests that clinical manifestations appear first, followed by fat depletion, and finally a combination of fat depletion and fat accumulation. Further, it appears that lipid abnormalities get progressively worse. It is important to determine whether these manifestations are linked.

There is an urgency to get an answer to the problem both from a clinical and patient point of view. Other questions that have not been addressed include:

1. Will the syndrome stop if therapy is discontinued?
2. If so, how long will it take for the symptoms to disappear? Will they disappear?
3. Will the syndrome persist forever?
4. Are the buffalo hump and body composition changes surrogate markers for a disease or disorder that is more serious?
5. Will the syndrome stop if I switch from a protease inhibitor to another class of antiretroviral therapy?
6. Can symptoms be reversed by diet, exercise, and/or medication?

d.   How might prevalence study lead to that information?

The various components of the syndrome beg the question of what is normal and what is abnormal. One needs to discern the normative distribution of fat accumulation and fat loss or spectrum of lean body cell mass in an HIV-infected population, possibly at different stages of HIV disease. Such a determination might involve using each person as an internal control and looking at changes over time.

An interim case definition can provide a framework for further research. A study that examines the prevalence of the various candidate signs and symptoms may help to better characterize this syndrome and to refine the case definition. Without a good case definition, it is difficult to develop eligibility criteria for clinical trials and harder to monitor end points within subsets of the disorder. A prevalence study would be able to examine a cross-section of patients from different populations, in various stages of disease, and with varying treatment histories. Such a study would provide crucial information about whether and how these signs and symptoms are related to each other— information that is essential in determining the cause or causes of these problems.

e.   Reasons why current information is not enough

Some previous studies have examined only one of the symptoms of the syndrome. Others only compared the development of specific symptoms between different treatment regimens. The lack of standardized clinical and diagnostic criteria prevents comparison between studies. Furthermore many studies included only a small number of patients and can not be extrapolated. There is no large-scale study using standardized diagnostic criteria to determine the prevalence of the metabolic syndromes associated with HIV disease and antiretroviral therapy.

The Surrogate Marker Working Group has a database that includes data from the Adult AIDS Clinical Trials Group (ACTG). However, most of the data currently available on metabolic disorders comes from industry databases that had been re-analyzed following guidelines given by the FDA. Retrospective analyses will provide little pertinent information about morphological characteristics of patients on HAART regimens because data collection was not designed to adequately look for such characteristics. Some individual practices and cohorts have attempted to mine the information from patients' charts and/or from information reported to pharmaceutical companies. Such efforts are not satisfactory to give the overall picture because of the lack of standardized measurements and the absence of normative standards. This increases the sense of urgency to design a study to obtain information that has not been obtainable through retrospective studies.

The several studies examining incidence of metabolic abnormalities (see below) will provide important information, but data will not be available for approximately three years. A cross-sectional prevalence study would provide important data in a relatively short period of time.

f.   Patient concerns about the metabolic abnormalities

Patients have the perception that their antiretroviral therapies are causing the metabolic abnormalities. The changes in body habitus are frightening, disfiguring, and can cause severe discomfort. The development of these signs and symptoms are causing some patients to discontinue their otherwise-effective antiretroviral therapies and causing other patients to decide not to begin treatment. Patients are being treated with human growth hormone and multiple anabolic steroids and are being told by physicians that such treatments may be effective in treating the abnormalities. These treatments are being used without any evidence that these therapies will be effective or with knowledge about how they interact with antiretroviral therapies.

Community activists are frustrated at being told that progress in treating this syndrome can not be made until a prevalence study is done. Although a firmer case definition of the syndrome will be helpful, knowing whether the prevalence is 55% versus 40% is not going to improve the quality of life of those immediately suffering from this syndrome. The importance of making progress in areas other than those that seem to be intellectually interesting was underscored. Community activists wanted to know that investigators are aggressively pursuing both the mechanisms and treatment of the syndrome.   Further, patients want information about how these effects should impact their decisions to start or continue antiretroviral therapy.
The prevalence of fat maldistribution is a key issue. Lipid and glucose metabolic abnormalities occur in non-HIV populations and may be different in the HIV-infected population, but these can be studied much more simply than fat maldistribution. Physiologic abnormalities such as cardiovascular disease (CVD) is of most concern, and whether these were consequences of the fat maldistribution or metabolic abnormalities is of high interest.

There were reports of discussions with local AIDS service organizations (ASOs) which revealed that people who have undetectable viral loads are discontinuing PI therapy. Despite increasing viral loads many of these patients are unwilling to resume therapy. Others are refusing to start initial therapy, and this is a public health concern. Changes in body habitus are a major issue for patients. Their concern is not only about body image, but also that these changes identify one as having HIV. Many patients fear having their HIV-positive status disclosed. As news about these symptoms spreads throughout patient communities, it is possible that growing numbers of patients will refuse treatment.

Patient advocates suggested that the pharmaceutical industry should fund research now to help establish whether it is prudent to initiate therapy given the metabolic abnormalities that have been observed rather than to wait for community sentiments to spread and alienate their market. Additionally, many patient advocates felt that the pharmaceutical industry should help fund some of the studies discussed at this meeting.

THE NEED FOR A CASE DEFINITION

a.   Why is a case definition important?

 As therapies change and progress in HIV research continues, a better case definition is essential for better coordination of effort and in order to be able to compare research results in a meaningful

way. In our attempts to develop an interim case definition, the participants were cautioned about the use of a hierarchical model because it is not known whether one can exhibit some of the metabolic abnormalities of the syndrome without showing signs of other adverse events. In some cases there has been poor correlation between physician reports and patient reports of adverse events, particularly for abdominal enlargement. Other studies show a good correlation with physician report and patient self-report. This points to the need for objective rather than subjective definitions.

An interim case definition is necessary to capture adverse event data in a uniform way for clinical trials and ongoing studies to examine outcomes of signs or symptoms such as sexual dysfunction, cardiovascular problems, bone problems, etc. The other purpose for the definition is to determine the prevalence of symptoms and signs against population norms and a seronegative population. For example, comparing waist-hip ratio to a seronegative population would be very useful, but would not enable a physician to determine whether something is wrong in an HIV-positive person who started with an abnormal waist-hip ratio.

b.   Why has it been difficult to establish a case definition?

The dynamic nature of the syndrome makes it difficult to establish a case definition. Over time the syndrome in patients appears to be worsening. While it is reasonable to associate such changes as fat maldistribution and abnormal lipid levels, it is difficult to determine whether other signs and symptoms, such as bilateral vascular necrosis of the hip, are connected.

While lipid and glucose levels are objective measures, other terms, such as lipodystrophy, are not used uniformly. For example, one could have fat depletion in the limbs and fat accumulation in the abdomen. Only by considering fat accumulation and fat depletion separately can we know whether a patient has either symptom or both symptoms.

Many of the signs and symptoms of the syndrome can also occur in seronegative individuals. For example, all of us can gain weight from overeating, so serial waist-hip measurements or radiologic studies [more rigorous clinical studies] might be necessary for different types of central obesity to be considered part of the HIV syndrome.

The history of what has been reported in HIV infection regarding drug therapy is in the absence of body composition changes. If one looks at what is known about body composition changes and its influences on lipid metabolism, then the first lesson may be that this is not a single syndrome. The mechanisms and changes in lipid levels, such as high triglyceride levels, low levels of high-density lipoprotein (HDL), high levels of low-density lipoprotein (LDL), and low levels of very-low-density lipoprotein (VLDL), may be different. Some may be related to drugs, some may be related to HIV disease and some may be related to body composition per se. There are many mechanism studies underway, but these include smaller cohorts than that which will be necessary for a prevalence study. While a prevalence study will not identify the cause(s) of these symptoms, it can provide important information on which of these signs and symptoms are linked to each other.

Part of the problem now is that any abnormalities that are noted in HIV patients that can't be otherwise explained are now lumped under "the syndrome." It was noted that prior to the advent of PIs, peripheral wasting and loss of facial fat were observed. Now that these same events are seen after the advent of PIs, such events are being grouped in the category of body fat redistribution.

There is not enough known about body composition in normals throughout the age span and for all ethnicities to make easy comparisons. For example, many of the original body composition obesity

studies were conducted using skinfold measurements, which may not get at the issue of visceral obesity. There are some clues in large data sets where abdominal computed tomography (CT) scans were done, and these could be viewed as a substudy. A study of change over time makes sense, however, as for the cases of lupus and AIDS wasting, one could start with a static definition that is extremely abnormal. There must be some user-friendliness for a static definition, and these definitions can be elaborated as changes over time are studied, ideally in clinical trials.

c.   Signs and symptoms included in the discussion about an interim case definition

The group was able to reach a consensus on a number of the signs and symptoms that have been postulated to be a part of the global dysmorphic syndrome. A conceptual framework was developed and is included below:

The body composition changes were grouped into the categories of fat maldistribution (including fat accumulation and fat depletion), peripheral wasting, and a category to encompass other changes. Under the subcategory of fat accumulation are buffalo hump (BH); central obesity (CO) or abdominal enlargement (AE); breast enlargement (BE), including gynecomastia; and localized fat accumulation to capture other lipomas such as chin fat accumulation. Fat depletion includes depletion in the face, limbs, buttocks, and other locations. The peripheral wasting category includes that of fat and muscle. The "other" category was added to encompass cutaneous abnormalities such as dry skin, hair loss, and dry lips in order to determine how much is from the disease and how much of this is drug-related.

A second major category of the syndrome is metabolic abnormalities. It was suggested that lipids be left out of the discussion since it is known that the drugs such as ritonavir can raise lipid levels within 2 weeks in HIV-seronegative volunteers. However, the participants decided to include the lipid abnormalities because their inclusion would provide information about their relation to the other events. Metabolic abnormalities include changes in lipid levels, as well as abnormalities in glucose metabolism (both hyperglycemia and insulin resistance). It was stressed to view abnormalities as more than just high levels of a substance, and to view drastic changes in lipid levels as well. Hyperlipidemia is an inappropriate term if one is to determine the mechanism of the syndrome. In addition hormone levels must be determined to note whether such states as menopause are affecting the changes.

The third major category of the syndrome is other physiologic abnormalities. Components of this category include hypertension (HTN), cardiovascular disease (CVD), and other abnormalities.

Working definitions of each of these components should be developed to measure prevalence in a standard fashion. A user-friendly measurement that can be done easily in the field will be necessary to collect prevalence data.

d.   Thoughts about how to measure each component

The underlying assumption that it is imperative to define the syndrome in a cross-sectional fashion with a single look at a single point in time was questioned. Because the underlying mechanism(s) remain unknown and there is variability in the techniques used to measure the abnormalities, it was suggested to study people at two points in time with a defined interval between the timepoints. One would not look at an absolute measure of the amount of BH or CO, but rather a change within the individual over a prescribed amount of time. Several measurement techniques could be used. Ideal measures include DEXA or magnetic resonance imaging (MRI), but skinfold measurements might

be more realistic. The change would be measured and may or may not be correlated with lipid levels. The participants also cautioned that not everything that gets larger is necessarily fat. There are patients who have had swelling for years who will continue to have swelling that won't necessarily be a manifestation of the syndrome.

Prevalence of abdominal enlargement in the general population would be known from the NHANES and CARDIO studies. Measuring AE involves anthropometric measurements. There are sliced CT studies of the abdomen that would enable one to determine the amount of subcutaneous versus visceral fat, as well as total abdominal fat. The control studies do not contain measurements of face, or neck, or buffalo hump area. CT would not be the ideal technique to obtain those measurements because head-to-toe CT would require a significant amount of radiation and not warranted for a prevalence study. There could be objective data from MRI studies that one could couple with patient report and physician report. Coupling DEXA measurements for percent body fat with MRI studies that would capture fat in the face, neck, buffalo hump, and in the breast would provide objective data accumulation.

Anthropometric measurements are useful because a patients' conditions might later turn to wasting and these data could be used for comparison. This points to the need for a continuum of data. If one only collects a single data point from the patient, then there must be an external standard for comparison. Those indicators for which an external standard is feasible should be identified for measurement in a single-point study. Others indicators will be measurable only with longitudinal data from the individual patient. Information could be captured on a continuum ranging from self-report to something that is confirmed by objective longitudinal measured data. An ACTG sub-study is correlating anthropomorphic measurements, self-report, patient distress with these symptoms, and easy self-report variables such as bra cup size, wrist size, and belt size.

Variables to be considered for BE include:
- patient report of increase in breast size;
- physician report;
- comparison of breast size over two timepoints (or more);
- comparison of photos;
- patient report of increase in bra cup size (this may be the best measurement for the prevalence study);
- measurement of circumference that influences the view on the change in cup size (did a person get bigger all over or just in the volume of the breast);
- gynecomastia (note whether unilateral or bilateral); and
- comparison of mammograms (Obtaining mammograms solely for the purpose of this study was not recommended because of the added radiation exposure.).

Variables to be included for CO or AE include:
- patient report;
- physician report;
- anthropometric measurements: waist-hip ratio (circumference), abdominal skinfold;
- photos (does not determine visceral versus subcutaneous fat though);
- sliced CT studies;
- total body MRI;
- time factor (to determine how much of an increase over how long a period of time); and
- total body weight (to help differentiate the therapeutic response to HAART versus what is selective accretion of fat).

AE would have to be correlated with an objective measure such as MRI because the symptom is the accumulation of visceral fat and not subcutaneous fat. Some thought the cost of MRIs would be prohibitive in clinical trials and stated that Dr. Donald Kotler is trying to correlate abdominal skinfold measurements with MRI. In addition Dr. Kotler is trying to correlate patient self-report of AE with anthropometric measurements and particularly the ratio of visceral to subcutaneous fat. There are no good standards for this either in the abdomen or in the body overall. People vary in their body shape both by age and gender, so there is much normal variability.

A time factor would be helpful for patient self-report because correlation with therapy is one kind of indicator but so many symptoms seem to appear rapidly. For example, an increase in waist size over 1 year is different than reports where someone's waist size increases several inches within a few months.

One participant asked 132 patients and their physicians by questionnaire whether the patient had truncal obesity, and through a diagram asked whether the patient experienced increased abdominal size. Physicians said that 66 percent of patients had truncal obesity compared to 42 percent of patients describing themselves as having truncal obesity. This is common in the obesity literature; people don't like to define themselves as obese and use other euphemisms to describe their bodies. A kappa correlation of these 132 patients comparing physician report to patient self-report gave a fair correlation of 0.4. When one asked whether the patient had increased abdominal girth, 80 percent of patients reported affirmatively. These patients did not view themselves as obese but did admit they were getting fatter. It will be very important how questions are asked both of physicians and patients, and unless these variables are tied to objective measures there will be problems.

Variables to be included for BH are:
- patient self-report;
- physician report;
- photographs;
- circumference of neck (this might not necessarily capture BH, because BH is a dorsocervical fat pad); and
- obtaining horizontal and vertical measurements (X-Y axis) at the largest diameter of the hump (Such measurement schemes would have to be "invented" and have not been standardized).

Variables to include for PW are:
- patient report;
- physician report and specification of whether this is in the face, legs, or arms;
- vein palpability and how far up the limb one can palpate a vein (useful to determine fat wasting);
- reports of fat loss from buttocks disproportionately to the rest of their body;
- displacement of water (historically used for progress of acromegalics) by limbs;
- MRI;
- DEXA;
- circumference (a clinically accessible measure)
- skinfold measurements;
- photographs; and
- bioelectric impedance analysis (BIA)

It was asked whether all cases of peripheral wasting would be considered part of the syndrome since wasting was observed in AIDS patients before PI therapy. It was thought that a prevalence study could determine what proportion of individuals who claim they have a given feature are attributable to a drug or disease stage or to family history, etc.

Variables to include for lean body mass are:
- DEXA;
- BIA;
- anthropometric measurements; and
- MRI.

Variables to include under the category of cutaneous changes are:
- Determination of dry lips, dry skin, and hair loss from skin

Total body weight, dietary history, and usual anthropometric measurements must be included to determine whether perhaps a dietary change is causing any of the aforementioned body composition changes.

Variables to include for lipid metabolism abnormalities are:
- total lipid profile- LDL, HDL, triglycerides, cholesterol (fasting);
- patient's historical lipid profile (perhaps they had high triglycerides to begin with);
- HIV treatment history to determine whether these medications might have short-term impacts on lipid levels (for example, Ritonavir's effect on triglyceride levels);
- ultracentrifugal measurements of lipids or fast protein liquid chromatography [FPLC](since many people have high enough levels of triglycerides to invalidate calculations of LDL);
- An incidence study might be necessary to differentiate between the observations of hypertriglyceridemia and hypocholesterolemia in the pre-HAART era and what happens over time. The lipid profile could vary depending on whether a person has 10 T cells and is wasting and then rallies after therapy versus people who have T-cell counts of 500.
- determination of other medications that a person is taking that could influence lipid levels (both prescription and over-the-counter [OTC]);
- A distinction should be made between what measurements can be made with fresh versus frozen samples. Ultracentrifugation and FPLC are done with "fresh" samples, i.e. samples shipped on ice to a central laboratory. One can measure triglycerides, cholesterol, HDL, calculated LDL, and direct-measured LDL.
- dietary history; and
- family history (of high cholesterol, etc.).

Variables to include for glucose metabolism abnormalities are:
- family history of diabetes;
- dietary history;
- determination of other medications that a person is taking that could influence glucose metabolism (both prescription and OTC);
- measurement of glucose, insulin secretion, and insulin resistance;
- glucose tolerance tests;
- measurement of glucose-insulin ratios; and
- Homa method to determine insulin resistance (a calibration based on glucose and insulin for estimating insulin resistance suggested).

There are existing population data against which to compare these levels. The group felt that it was important not to look only at change, but also to determine the proportion of patients with various lipids above a certain level as well as high glucose levels. There are ways of taking body composition data, lipid data, and insulin resistance data in a prevalence study and factoring them, as well as the added influence of the incidence study.

There was also some concern about determining the proportion of patients who have triglycerides above a certain level, since there isn't good agreement across studies about what level would be considered hyperglycemia or hypertriglyceridemia. There are criteria from the National Cholesterol Education Program and the American Diabetes Association (ADA) on what constitutes the definition of either a treatment level (depending on your history for insulin or lipids) or what constitutes the definition for diabetes in terms of hyperglycemia. Those definitions could be easily adapted for the prevalence study.

There are data published that show the levels of LDL, triglycerides, and total cholesterol to HDL ratio in an HIV-negative population to be clearly associated with an increased risk of 5-year and 10-year atherosclerotic complications. This group is interested in the long-term complications of these lipid abnormalities and did not feel the need to calculate a new set of data. They suggested using the levels known in the HIV-negative population to cause atherosclerosis as the limits for classification in the prevalence study.

A category encompassing other metabolic abnormalities besides those of lipids and glucose metabolism was established. Included within this category are:

- sex hormone levels: state of pregnancy, determination of whether someone is pre- or postmenopausal, testosterone levels;
- fasting cortisol levels should be obtained to rule out glucocorticoid excess, particularly for fat maldistribution concerns. (Determine these levels through an overnight dexamethasone suppression test or obtain a 24-hour urine collection for quantitative cortisol evaluation.);and
- measurement of uric acid.

Data obtained using the dexamethasone suppression test and fasting a.m. cortisol levels and 24-hour urinary cortisol levels have ruled out hypercortisolism as an explanation for buffalo hump. Cushing's syndrome has also been ruled out as a cause of "the syndrome." What has not been ruled out is a relative increase in cortisol in individuals, which have not be addressed through current studies. For that reason the group was in favor of retaining the 24-hour urine and cortisol measurement in the prevalence study. Prior to the advent of PIs, there was a series of case reports relating Addison's disease (hypoadrenal state) to AIDS. Fasting cortisol levels or urinary free-cortisol levels were measured in large cohorts prior to the advent of PIs and showed a statistically significant increase in cortisol although not into the Cushing's syndrome range.

A category encompassing other physiologic abnormalities was established and includes:
- determination of cardiovascular disease (CVD) prevalence;
- determination of hypertension; and
- determination of whether excessive bleeding occurs in non-hemophiliacs.

DISCUSSION OF CURRENT ACTIVITIES

Brief descriptions of the substudies that are being conducted within ACTG 384, the CPCRA FIRST protocol, and the INITIO study were given. Each of the parent studies is comparing HAART regimens in treatment-naïve populations. The studies will compare PI vs. NNRTI-containing regimens and will provide long-term follow-up of patients.

ACTG 384 Substudy

The ACTG is planning a substudy for ACTG 384 to characterize glucose and lipid disorders. ACTG 384, the parent study, will randomize patients who are largely antiretroviral-naïve and who have detectable HIV-RNA levels to one of six arms. The arms of the study will be examining two

different nucleoside combinations (lamivudine [3TC]/zidovudine [ZDV] or dideoxyinosine [ddI]/stavudine [d4T]) with an NNRTI and/or a PI for patients who are starting initial therapy. Specifically the study will determine the safety, tolerance, and the virologic benefits of either nelfinavir (NFV) or efavirenz (EFZ) as part of a 3-drug combination versus a 4-drug combination in the treatment of patients with advanced HIV disease who have received limited or no prior antiretroviral therapy. It is a treatment strategy study in that the primary end point will be the time to a salvage regimen. Patients on the three-drug regimens who experience virologic failure will switch to the other two nucleosides, and if they are on EFZ they will switch to NFV and vice versa. If they fail the second regimen, they will go to a salvage regimen. If individuals on the quadruple therapy arms fail, they will go directly to salvage regimens. Each patient will be followed for 2 years, and it is anticipated that the study, which just opened, will be completed within 3 years. The study is blinded as to the treatment assignments with both the NNRTI and PI, but is open label in terms of the nucleoside assignments.

The substudy (A50005S) will examine glucose metabolism, lipid disorders, and body composition changes. The primary objective of the substudy, which has an N = 354 compared to N=800 subjects for the study as a whole, is to compare the effects of an NFV/PI-based regimen to those NNRTI/EFZ-based regimens on measures of insulin secretion and insulin resistance. The effects of initiating one of these regimens on triglycerides and cholesterol levels will also be compared. The secondary objectives include anthropometric measures of body composition to determine whether there are differences in the regimens. The 4-drug regimen will also be analyzed for metabolic variables. The primary analysis of the 4-drug regimen will be the EFZ versus the NFV regimens and will take into account metabolic effects of the different nucleoside regimens as well. The crossover design of ACTG 384 allows in a controlled manner the examination of the effects of regimen switching. Of primary interest are the effects on the metabolic variables of switching from a PI-containing regimen to a non-PI-containing regimen and vice versa. The investigators hope to gain some insight on whether the magnitude of viral suppression and improvement in immune status are associated with effects on metabolic variables.

Measures included in the substudy are: fasting glucose and insulin levels, limited dynamic testing of glucose metabolism in a subset of patients, lipid profiles, anthropometric measurements, BIA, regional DEXA in a subset of patients, a body image questionnaire, recording dietary intake, cytokine levels, cortisol levels, sex hormone levels, and other aspects of endocrine function.

The study design will also analyze the correlation between anthropometric measurements and regional DEXA. Anthropometric measurements include waist-hip ratio, arm, neck, and extremity measurements. Where possible these include procedures used for the NHANES survey. (Procedures for neck size were improvised and obtained with the assistance of Patrick and James Men's Clothiers.) Although breast size will not be measured, this subject will be addressed in the body image questionnaire.

A determination of abnormalities present in untreated individuals will not be part of the study. Patients will have had less than 7 days of prior therapy and could serve as their own controls. The underlying hypothesis that is being tested is whether metabolic and body composition abnormalities are a result of PI therapy per se, or will they occur with the same frequency and/or severity in patients initiated on regimens that do not contain a PI.

There will be no unblinded data available from the substudy until the parent study is unblinded (2 years from accrual or around 2001). Evaluations (viral load and the other measures) will be conducted every 16 weeks and there will be an additional evaluation at 8 weeks following study

entry where lipid and glucose metabolism studies will be repeated. When patient switch regimens the clock will be reset. There is a pharmacology substudy, adherence substudy, and immunologic substudy within the parent trial. The sample size was calculated based on the anticipated changes seen in triglyceride levels. However, there should be an adequate sample size to answer most of the secondary objectives of the study.

In addition to ACTG 384, the ACTG Long-term Longitudinal Randomized Trial (ALLRT) will start soon. This study will enroll 3,000 patients from all of the ACTG antiretroviral trials at all stages of disease. Patients who are treatment naïve as well as those who have failed therapies will be included in the initial randomization where metabolic information will be collected at baseline and every 16 weeks for the 5-year duration of the study. The study results will be unblinded over time. Specific drug regimens will not be examined but rather treatment strategies, dual versus single PI therapy, delayed PI versus immediate PI therapy, etc. Accrual will take place over a year and will draw from many, if not all, of their newly instituted trials.

CPCRA FIRST Substudy

The CPCRA is conducting a parent study, the FIRST protocol (CPCRA058) that will enroll 1,000 patients who are antiretroviral-naïve with no restrictions on CD4+ cell count or HIV-RNA levels. Patients are randomized to a PI or an NNRTI-containing regimen or a combination of a PI and an NNRTI-containing regimen. In addition, patients will choose their background nucleosides. The study does not stipulate which PI or NNRTI must be used. This is a treatment strategy study that is randomized, but the patient and clinician will choose the PI and the NNRTI. The primary outcome of the FIRST study is time to the second virologic failure. The purpose of the metabolic study is to compare the randomized HAART strategy groups in the FIRST protocol for changes in triglycerides, total cholesterol, visceral circumference, and waist-hip circumference.

The power of the study was calculated to determine the primary objective. Total cholesterol, triglyceride levels, and waist-hip circumference ratio will be compared from baseline to one year after randomization to the three HAART strategies used in the FIRST study. One year was chosen for the primary outcome because it is assumed that at one year most of the patients will still be on their assigned randomization arm. Among the secondary objectives are changes in other metabolic indicators including serum glucose, insulin, blood pressure, changes in body composition and body habitus including body weight; ideal body weight; body-mass index (BMI); body cell mass; body fat measured by BIA; body circumferences of arm, waist-hip ratio, and thigh; skinfold measures of triceps, subscapular sites, and the abdominal region. A self-reported diagnosis form will also be used.

Investigators will also examine whether some of these changes will be affected by the baseline characteristics such as initial HAART strategy, specific PI chosen, specific NNRTI chosen, gender, age, ethnicity, substance use, and cigarette smoking history, family history including biological parents and full siblings, HIV-RNA levels, CD4+ cell counts, and self-reported activity level, dietary intake, and the use of dietary supplements and vitamins.

Important secondary objectives include the use of cardiovascular agents, antilipidemics, antidiabetic agents, survival, incidence of myocardial infarction, strokes, and diabetes mellitus.
Measurements will be made at baseline, 1 month, and every 4 months in the FIRST study. In the substudy, study patients will be measured every 4 months for the first year and beyond that every year. Specific measures for the substudy include self-reported physical activity, nutritional and dietary supplements use, cardiovascular and antidiabetic agent use, family history, substance use history, height, weight, body cell mass, and body fat by BIA, 24-dietary recall, body

circumferences, and skinfold thickness. These measures will be performed every 4 months for the first year and annually thereafter. The blood measurements will be fasting measurements and include serum glucose, insulin, total cholesterol, and triglycerides. A baseline elbow breadth will also be measured.

The CPCRA sample size is in the same range as the ACTG 384 study, but the power of the sample size was calculated to answer the primary objective of the study. They hope to overenroll to have the power to answer some of the secondary objective questions. There will be 3 years of accrual (around 280 patients per year).

Measurements that affect the parent study will be blinded in the substudy; for example, examining metabolic changes and trying to associate change in HIV-RNA level or change in CD4 level with those metabolic changes. However, measurements that are truly metabolic ones will be available to the DSMB while the parent study is ongoing, and it will determine whether some results should be unblinded.

INITIO Substudy

The INITIO study, which is being conducted in Europe and Australia, will measure vascular risk factors, lipid profiles, and sugar levels in patients every 12 weeks. Anthropometric measurements and body composition data will be collected on a subset of patients. The study is similar to the ACTG and CPCRA substudies in that this is a treatment strategy study examining times to first and second treatment failures in PI and non-PI-containing regimens with the NNRTI-containing regimens. The coordinating committee still must determine the sample sizes for the study. The data collection is very similar to the ACTG 384 and CPCRA FIRST substudies.

A prevalence study has started in Australia that will enroll in excess of 2,000 patients over a 4-month-period both at hospitals and community sites. Accrual in such a short time is not considered a problem because there are 50 sites representing all of the major teaching hospitals and 25 community practices. Between 10 and 20 percent of patients will have body composition data collected through DEXA and CT scans. Data collected include height, weight, cardiovascular agent use, CD4+ cell counts, viral loads, AIDS-defining events, current and prior antiretroviral use (particularly the duration of the individual drugs), and cumulative duration of PI therapy. Questionnaires for both physician and patient will be collected examining fat wasting, fat accumulation, and other physiologic abnormalities. If a patient gives an affirmative response to those events, he or she will be asked to rate the severity of the event from 1 to 3. The patient and clinician questionnaires will be on separate pages.

Other items to be gathered include fasting lipid and glycemic parameters, skinfold thickness, waist-hip ratios, visceral and subcutaneous fat ratios from a single-cut CT scan, and regional and total body fat determinations obtained with DEXA. The study will include people who are antiretroviral treatment-naïve. It is anticipated that all of the data will be collected by early March 1999. This study will compare data from study participants against a control group.

INCIDENCE STUDIES VERSUS PREVALENCE STUDIES

The issue of conducting incidence studies versus prevalence studies was discussed for this will determine how the problem is approached. For example, in a prevalence study, a one-point

determination of breast enlargement requires reliance on the patient's self-report of an increase in bra size. In an incidence study, measurements or photo comparison would be available.

Another advantage of an incidence study is that one can monitor how lipid levels change over time. The progression observed in the syndrome is that HDL decreases first, then LDL decreases, and then triglyceride levels increase. A disadvantage with an incidence study is that most of the proposed incidence studies have compared antiretroviral-naïve patients (those in the early stages of HIV disease) to those on therapy. One rationale for conducting both incidence and prevalence studies is to know what the prevalence of the syndrome is in the current population versus what is going to happen over the long-term in people who are currently antiretroviral-naïve.

Incidence studies are needed and are primarily underway. However, a prevalence study is necessary so that a broad population can be examined to understand the risk factors that are associated with some of the components of the syndrome. A large prevalence study will examine patients on and off therapy, and at different disease stages.

It was noted that in both the ACTG and CPCRA substudies not only will no data be available for more than 2 years, but also the subjects are a patient population that are thought to have the lowest incidence of lipodystrophy. Results from one study indicate that there is a dramatically increased incidence of lipodystrophy over a 2-year-period after the initiation of therapy. If a PI-naïve population is followed for 2 years, it is not certain whether the data collected from these subjects will be very meaningful to the general HIV population. However, the ACTG and CPCRA studies are crucial to determine whether the syndrome is caused by PI therapy or not. The ALLRT study will obtain initial prevalence of symptoms in all subjects entering into the study because the baseline measurements will reflect subjects at all stages of treatment.

In summary, there was general agreement that in light of the substudy descriptions there was still a need to perform a prevalence study. Some of the reasons are to document the prevalence rate, to begin to understand the linkage between symptoms, to document adverse reactions because patients are starting to discontinue therapy, to point the way toward potential solutions, and to capture a broader population than any existing or proposed studies (including those on different drug therapies and stages of therapy).

DESIGNING A PREVALENCE STUDY

a.   Issues to study

The group was asked what should such an investigation answer. Such issues included: 1) profiling the spectrum of phenotypic and metabolic changes that can occur consequent to therapy, 2) determining a unique identifier to denote among whom and at what point these changes are set in motion, and 3) exploring ethnodemographic differences among the occurrence of the syndrome or whether these occurrences depend on stage of illness or therapy status.

There is enough known about lipid profiles and body composition, and almost enough known about insulin resistance to make some estimates about what the risk would be from a given change. Risk factor questions could be incorporated into the prevalence study.

The case definition for the prevalence study might be different than that used in a longitudinal study, which might be more inclusive. One might want to stratify the results such that the prevalence is given for aspects of the syndrome that are of such severity that they have an impact on people continuing therapy and for aspects of the syndrome that are associated with risk of heart disease, stroke, or diabetes. Developing a better understanding of the effect that body shape changes may have on decisions to stop or not initiate therapy was cited as important.

b.   Patient population and access to patients

A plea was made to use existing cohorts wherever possible. Prevalence data could be collected now, and if the cohort is ongoing one could obtain additional timepoints for long-term comparison. Using studies of existing cohorts, the group could identify what key predictive measures are lacking and find a means to fund those measures. Although the Australian prevalence study will collect much data rapidly, Australia has very few women and children with HIV and has a very small injection drug user (IDU) population; the HIV population in Australia is over 90 percent gay males. There are demographic advantages to conducting an U.S.-based prevalence study particularly for women, children, and IDUs.

Concern was also expressed that body composition data from substance users on PIs were to be compared to normal values from NHANES. Substance users might be malnourished regardless of HIV therapy and such comparisons could confound the results. It is important not to introduce selection bias in the study, for example, by conducting the prevalence study at centers that are studying obesity or are only including those whom self-report the syndrome.

c.   Special considerations in testing

If the study will rely on a physician and/or patient report, then a case-control study on patient report versus physician report of these symptoms is needed along with validation of patient report through total body MRI.

It is important to ask patients when they noticed the development of symptoms. The group must determine how far back they want to make comparisons. The Australian study decided to make a compromise and asked patients to make comparisons from when the patient was diagnosed with HIV to when they started antiretroviral therapy. However, patient advocates noted that it would be difficult to say when a symptom first began. One might suddenly need new clothes or receive comments from people about changes in their appearance. Clinicians reported that some patients would not admit they had symptoms even when it was physically noticeable, and there were patients who reported a whole host of symptoms who appeared normal. Nevertheless, in designing the Australian study there was a good correlation between body fat measured objectively and patient self-report of severity. Patient self-report of severity not only correlates well with body composition data but also with metabolic data.

d.   Measurements needed

The Australian national study is closest conceptually to what the group had in mind for a prevalence study. An improvement to that study that could be included in an U.S.-based study is the collection of body composition data on the full cohort. The group felt that a study should be designed whose results could be translated to other settings. In other words, a study could use CT scans and MRIs to validate findings, but it should also use skinfold thickness or other more accessible measurements that could be applied in non-research settings.

Despite the stated need for incidence and prevalence data, the group felt that a prevalence study including body composition data that are comparable to NHANES and CARDIO should be conducted first. This must include people who have been previously treated and represent the

general population in terms of gender, ethnicity, etc. The study must also have a series of objective data that may approach the areas of the body that are not included in NHANES and CARDIO, but would the serve as the basis for future studies such as the randomized controlled trials. The prevalence study should include funding for high-technology measurements such as MRIs and CT scans that individual researchers in the study could not fund on their own. Second, add onto existing HAART therapy clinical trials some of those same technologies to obtain long-term information that can be compared to the baseline information.

Reasonably good estimates of a variety of risk factors can be identified from the initial evaluation of the patient such as race, ethnicity, age, gender, baseline viral load and CD4 count, family history, etc., and a range of predictors might be identified. It would be preferable to do this in a longitudinal study. However, clues about risk factors and predictors of various components of the syndrome might be obtained in a quicker fashion through the prevalence study. If one could obtain good treatment history, then perhaps the risk attributable to various antiviral therapies might be ascertained. Although some of the signs and symptoms are merely troublesome, the major concerns are whether someone will get a heart attack or a stroke, or whether patients will be so dismayed by their physical appearance that they will discontinue therapy and their HIV disease will progress.

e.   **Costs**

Costs for the prevalence study are a major concern when considering study design. The group felt that MRIs were useful and necessary for obtaining adequate data on full body composition and more useful if conducted in more subjects. The value added from this data would warrant the added expense of the tests. Collaboration between government and industry might provide the necessary funding for these tests. If funds are not spent to obtain important information from the prevalence study now, then researchers won't be able to address the mechanism of action and treatment intervention issues. Funds spent on the prevalence study would not take away from those efforts but will provide the necessary information for those studies.

It was suggested that pharmaceutical sponsors of phase III clinical trials for patients starting new regimens should have study sites obtain screening measurements for 20-50 patients. This should not impact study results for a particular drug since these measurements would be obtained at screening, nor should this interfere with randomization since past drug history would be obtained. A prevalence study could be conducted in this manner, and the burden of the study could be shared across a large number of sponsors.

It was also suggested that the government should sponsor the study coordination, since no one company could undertake this role. One option would be for the NIH to coordinate the study. NIH representatives at the meeting did not think the resources were the insurmountable problem because to determine whether the prevalence was 2 percent or 80 percent not many patients are necessary. Around 1,000 patients are needed, and the cost per patient should be around a few hundred dollars to characterize these patients depending on the tests selected. However, this depends on what measurements need to be done.
Others agreed that the participants were overly concerned about the study cost. A study that compares 500 people at two timepoints or 500 people on PI regimens versus 500 normal controls, and includes single-slice CT scans and a DEXA ($100 for each of those studies at the University of Washington, Seattle) and routine serum analyses, would only cost around $1,000 per patient. The total cost of $1 million is not an extraordinary cost as far as these types of studies goes. Rather than trying to determine how subscapular skinfold thickness correlates with visceral abdominal

subcutaneous ratios the group should choose the best end points using some objective criterion like DEXA, CT scans, or MRI, plan the study, and conduct it.

f.   Possibilities for collaboration

A detailed proposal is necessary before NIH can determine how it can provide assistance. The NIH has many infrastructures that can be brought to bear to help address these questions, but first it must have a detailed proposal to determine where it fits best. The Office of AIDS Research at NIH has always had a keen interest in the metabolic abnormalities associated with HIV infection. They have just formed a working group among the NIH institutes to explore these abnormalities and hope to collaborate with other federal government agencies.

There are many cohorts being followed at the CDC, and with a protocol and cost estimate, the principal investigators for these studies can be approached about incorporating such measures in their studies. These cohorts represent the demographic range that the group desires. The CDC could then approach pharmaceutical representatives for additional funds, if necessary. In addition, the Department of Veterans Affairs is considering conducting a large study and expressed interest in contributing to a prevalence study with its very large patient base and numerous primary care facilities in the United States.

If a more detailed proposal is presented, then the pharmaceutical industry can identify the needs and resources that it can apply to aid study implementation. Industry representatives expressed the desire to continue to be supportive to this process and to support those who have the expertise to define components of the syndrome.

g.   Messages to convey to the HIV/AIDS community

Policymakers and writers within the audience were urged to communicate that researchers do not have the answers yet, but that there is no data indicating that therapy should be discontinued. An important message to convey to the HIV/AIDS community is that researchers are not waiting for a prevalence study to be conducted to start conducting treatment intervention studies or mechanistic studies. Government-funded mechanistic studies and treatment trials are underway that might yield results before the prevalence study does and that might provide further insight into this syndrome.