Metabolic Consequences of HIV Disease and Treatment

An Overview of Current Knowledge and Research

This report was prepared for the Forum for Collaborative HIV Research by Robert Munk, Ph.D.

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 primarily 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 website at: www.gwumc.edu/chpr and click on HIV Research.

Note from the Director of the Forum for Collaborative HIV Research

Early in the summer of 1997, I had a discussion with a colleague about our anti-viral treatment regimens. While both of us were have an excellent viralogical response to therapy, we were both experiencing changes in our bodies, including weight gain in the abdomen and weight loss in the limbs. We were surprised to hear that we were experiencing the same unusual symptoms. So, we began to call around to other people with HIV and to some of the doctors with larger HIV practices. We found that these symptoms were not that uncommon in patients on antiretroviral therapy. More anecdotal reports turned up on the many computer newsgroups and chat lines. Around the same time, the FDA reported on several cases of diabetes that might be linked to protease inhibitor therapy. It seemed possible that a set of previously unreported, metabolically-associated side effects from protease inhibitors was becoming evident.

In response to these reports, the Forum for Collaborative HIV Research (FCHR) held a meeting in September, 1997 to discuss metabolic consequences of HIV disease and treatment. The meeting brought together representatives from each of the pharmaceutical companies that manufacture protease inhibitors, leading researchers, clinicians, patient advocates and representatives from the NIH. Participants shared whatever data was available, identified the possible causes for these symptoms, and discussed the kinds of studies that need to be done in order to better understand the cause, effect and prevalence of these symptoms. We left the meeting with more questions than answers, but it was an important first step. This was the first organized discussion on what has since become a topic of major interest and importance in HIV research and care.

This report serves as a follow-up to that first meeting. The report describes the kinds of symptoms that have been reported, discusses the various theories as to the cause for these many, disparate symptoms, and describes research and reports that have been presented since that September meeting. It is the hope of the FCHR that the report will serve not only to inform readers about these new developments, but will also serve as a tool for further discussion and research.

David Barr

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INTRODUCTION

The approvals of protease inhibitors marked the beginning of a new era in anti-HIV therapy. The FDA approved saquinavir in 1995, ritonavir and indinavir in 1996 and nelfinavir in 1997. Most of the reports dealing with these drugs focused on the dramatic reductions achieved in plasma viral loads, along with increases in CD4+ T-lymphocyte counts. Substantial decreases in the incidence of opportunistic infections and enhancements in patient well being accompanied these improvements in laboratory markers[1]. The well-publicized side effects of these drugs included a variety of gastrointestinal problems, including nausea, vomiting, and diarrhea, plus circumoral paresthesia with Ritonavir and nephrolithiasis with Indinavir[2]. Changes in several metabolic markers were also noted, including bilirubin, serum glucose, triglycerides, and cholesterol, although these were initially not considered to be significant.

By June 1997, the FDA had collected reports of 83 cases of diabetes mellitus among people receiving protease inhibitor therapy, and issued a warning regarding their use[3], noting that a causal relationship between protease inhibitor therapy and hyperglycemia had not been established. Anecdotal reports of other possible side effects were common in computer e-mail discussions among users of indinavir (the "Crix List"). Anecdotal reports of people using triple-combination antiviral therapy discussed patients who were achieving viral load reductions and CD4+ increases, but were also experiencing significant increases in their abdominal fat, often accompanied by apparent loss of fat from their arms and legs. Others experienced unusual fat deposits or "buffalo hump", lipomas at the base of the neck. Some women reported similar symptoms, along with increases in breast size.

This report presents an overview of reported research into the metabolic consequences of HIV disease and therapies through June 1998, not including studies presented at the XII World AIDS Conference in Geneva. As noted below, interest in this topic is high and many research projects are currently underway.

FCHR Meeting on the Metabolic Consequences of HIV Disease and Treatment

Based on the above noted anecdotal reports, the FCHR convened a meeting on September 14, 1997. The meeting included representatives from pharmaceutical companies that manufacture protease inhibitors, clinicians, government researchers, and patient advocates. The signs and symptoms discussed included elevated triglyceride levels, irregular cholesterol and glucose metabolism, abnormal distribution of body fat including "PI paunch", loss of limb fat and muscle, buffalo hump, and central obesity.

The participants shared their understanding of these symptoms and discussed possible causes. Reports from HIV clinicians to the FDA or to pharmaceutical manufacturers had been rare because most of the symptoms reported were not life threatening, and because no single or unifying syndrome had been characterized,. The reported increases in triglycerides and cholesterol were unusual because these levels had generally decreased in patients with HIV disease prior to the use of protease inhibitors. Although the observations of buffalo hump seemed consistent with Cushing's syndrome, the expected elevations in serum cortisol were not apparent. Symptoms had been observed in patients using any of the approved protease inhibitors, as well as in some using only nucleoside analog therapy and others not using any antiviral medications. The participants agreed that they could not yet determine whether the reported symptoms represented one or numerous syndromes. The causes might include HIV disease, or the HIV therapies, or a metabolic response to successful antiviral therapy.

The meeting continued with a discussion of questions and methodological issues for further research:

1. What is the background prevalence of these symptoms in HIV-infected and in uninfected populations? For example, the risk of diabetes reported by the FDA among users of protease inhibitors did not appear to be disproportionate for the population.
2. To what extent does successful viral suppression and the correction of the underlying chronic HIV disease process lead to weight gain that may be abnormally distributed? Which other symptoms might result from a return to health?
3. What are the relative roles of familial or genetic factors compared to HIV disease or treatment as causes of these metabolic changes?
4. Are the endocrine abnormalities that mimic Cushing's syndrome related to hypersensitivity of the local tissues to cortisol?
5. Assessments of regional body composition are needed to monitor the reported body fat redistribution. These assessments must distinguish between subcutaneous and visceral (omental or intraperitoneal) fat.

6. Patients must be in a fasting state when blood samples are drawn in order to get useful readings of the relevant laboratory parameters. This is not the usual practice in most clinical studies of people with AIDS, meaning that very little existing data from studies of people with HIV will be helpful.
7. Adequate data on weight gain and body composition changes has not been obtained from protease inhibitor studies.
8. The current system for reporting these symptoms is inadequate for several reasons. Clinicians did not consider the individual symptoms to be serious and had not been alerted to monitor them, and there has been no clear definition of any metabolic dysfunction that should be reported. This makes it extremely difficult to assess the prevalence of these symptoms.

DESCRIPTION OF METABOLIC SIDE EFFECTS

The definition of metabolic side effects is not clear. Researchers at the Forum meeting agreed that various symptoms might be associated with HIV disease progression, with the use of antiviral therapies as treatment for HIV infection, or even with the return to health subsequent to successful suppression of viral replication. These symptoms could represent a single syndrome, or multiple syndromes. The absence of a clear definition of metabolic consequences of HIV disease and therapy is reflected in the wide range of incidence rates reported by various researchers, which range from 5% to 64%[4].

For purposes of this report, research on the metabolic consequences of HIV disease and therapies has been divided into three areas 1) hyperglycemia and diabetes mellitus, 2) hepatitis or hepatic failure, and 3) abnormal lipid metabolism and deposition. Neither this discussion nor the tables or bibliography which follow are intended to include all research related to metabolic issues in HIV disease and therapy. The three areas selected appear to be of greatest current concern to patients and clinicians in relation to the use of HIV antiviral therapies.

1) Hyperglycemia and Diabetes Mellitus

Increases in blood glucose levels and new cases of diabetes mellitus were the subject of a FDA Public Health Advisory in June 1997[5]. Based on 83 reported cases, the FDA notified health care professionals of new onset diabetes, hyperglycemia, or exacerbation of existing diabetes in HIV-infected patients receiving protease inhibitor therapy. Researchers have documented varying rates of hyperglycemia and/or diabetes[6,7,8,9,10,11] although most concluded that diabetes induced by protease

inhibitor therapy was rare. One researcher considers the incidence of clinical diabetes mellitus to be surprisingly low considering that insulin resistance is a documented result of protease inhibitor therapy[12]. Selected research is summarized in Table I.

2) Hepatitis or Hepatic Failure

Several researchers have documented hepatitis or hepatic failure apparently linked to protease inhibitor therapy for HIV[13,14,15]. The linkages between hepatitis or hepatic failure and other metabolic effects of HIV disease or therapies are not clear, apart from drug-induced hepatitis. Selected research is summarized in Table II.

3) Abnormal Lipid Metabolism and Deposition

Changes in Blood Lipids

Several researchers have recently documented changes in lipid metabolism associated with antiviral therapies for HIV [16,17,18,19,20,21,22]. However, HIV-associated changes in fat anabolism, triglyceride levels, and endocrine function were documented several years ago, before any protease inhibitor drugs were approved [23,24,25,26]. More recent studies document alterations in lipid metabolism in association with change in body habitus, weight, or composition [27,28,29,30,31].

Perhaps the most troubling change in lipid metabolism is the increase in serum cholesterol in HIV patients using protease inhibitor therapy. Henry [32] recently reported severe premature coronary artery disease with protease inhibitors. In a recent interview[33], Henry suggested that even small increases in serum cholesterol can be serious because they may consist of a large increase in low-density lipoproteins offset by decreases in high-density lipoproteins, and because the high triglyceride levels often found in patients with HIV can cause inaccurate readings of serum cholesterol.

Lipodystrophy

The most visible and best-publicized metabolic abnormality associated with HIV antiviral therapies is an increase in abdominal girth. This was originally referred to as “Crix belly”, because many of those experiencing these changes were taking the protease inhibitor Crixivan (Indinavir). Collection of case reports by various investigators confirmed that similar body changes were occurring in patients taking any of the four FDA-approved protease inhibitors, as well as some who were not using protease inhibitors or any antiviral medications. More recently, the pattern of body changes has been described

as symmetrical loss of subcutaneous fat of the face, limbs, and (in men) the upper trunk, usually accompanied by an increase in abdominal girth and (in women) in breast size. This situation is currently referred to as lipodystrophy. Deposition of fat at the base of the neck, considered to be a related condition, is often called "buffalo hump."

Research to date on these changes in body habitus consists almost entirely of case reports [34,35,36,37,38,39,40,41]. Some of the cases – particularly those involving buffalo hump – appeared similar to Cushing's syndrome. Cushing's is caused by elevated levels of cortisol, often due to adrenal tumors. Serum cortisol levels or dexamethasone suppression tests ruled out Cushing's syndrome in virtually all HIV patients with buffalo hump[42].

Carr [43] has proposed a causal mechanism due to a high degree of similarity between a segment of HIV protease and a lipoprotein receptor-like protein (LRP), which is involved with the transport of circulating lipids. Kotler[44] notes, however, that this does not explain cases of fat redistribution that occur in patients who have never taken a protease inhibitor.

Lipodystrophy is of serious concern because of its impact on patients. In the studies reviewed for this report, most researchers reported that fat redistribution appears fairly early in the course of combination antiviral therapy including protease inhibitors. These changes in body composition have motivated several patients to seek liposuction or surgical removal of fat deposits. Others have discontinued protease inhibitor therapy. With the lack of information on a causative mechanism, there is at present no sound advice to patients regarding the ultimate extent of these body changes, or their reversibility.
Selected research on lipid metabolism and deposition is summarized in Table III.

TREATMENT OF METABOLIC SIDE EFFECTS

Without information on causative mechanisms for the metabolic side effects associated with protease inhibitor or other antiviral use, it is difficult therefore to provide any guidance to clinicians or patients. However, various approaches are being tried for different side effects:

- Although the use of antiviral therapies including protease inhibitors appears to exacerbate hyperglycemia, a significant proportion of cases occurred in people with predisposing factors for

the development of diabetes mellitus. Standard medical therapy has been suggested for diabetes, as well as for hypercholesterolemia [45].

- Abnormal fat deposition has been treated by surgical removal of buffalo humps or by abdominal liposuction. There are anecdotal reports of physicians using cycles of human growth hormone to empirically treat fat redistribution. Mooney[46] has suggested that insulin resistance, induced by protease inhibitor use, is responsible for many of the observed metabolic symptoms.
- It is important to note that no researcher has suggested discontinuation of protease inhibitor or other antiviral therapy as a response to metabolic side effects.

FURTHER RESEARCH

As interest in this topic continues to grow, the number and variety of research projects is increasingly rapidly. In September 1997, a single research report was presented at the Infectious Diseases Society of America conference in San Francisco, and three more at the Interscience Conference on Antimicrobial Agents and Chemotherapy in Toronto. By February 1998, there were 11 posters at the 5th Conference on Retroviruses and Opportunistic infections in Chicago.

In June 1998, in conjunction with the 12th World AIDS Conference in Geneva, Tufts University School of Medicine and the U.S. National Institute on Drug Abuse are sponsoring a daylong "Update on Wasting, Metabolism, and Altered Body Shape in HIV/AIDS." Numerous research reports will be presented at the main conference. Lipodystrophy will be the topic of a symposium presentation at the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy in September 1998. substudies as part of larger antiviral therapies protocols.

The two major federally funded AIDS clinical research organizations are each planning metabolic substudies as part of larger antiviral therapy protocols. These may well be the first large, randomized, prospective studies of metabolic symmptoms. The Adult AIDS Clinical Trials Group (ACTG) is developing a substudy for ACTG 384 to characterize glucose and lipid disorders. The parent study compares various antiviral regimens, including nucleoside analogs plus a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, or both. The sub-study, A5005S, will examine glucose metabolism, lipid disorders and body composition changes in antiretroviral naive subjects receiving nucleosides in combination with efavirenz, nelfinavir, or efavirenz plus nelfinavir. The primary objectives of the study are to compare the metabolic and body composition effects of initiation of an antiretroviral regimen containing a protease inhibitor (nelfinavir) with those of a regimen containing an

NNRTI and no protease inhibitor (efavirenz). Subjects will have evaluation of insulin resistance, fasting lipid profiles, cytokines, cortisol, sex hormones, and body composition by measurements of weight and BIA at baseline and periodically during the study. In addition, oral glucose tolerance testing and regional body compostion by DEXA scanning will be performed at a limited number of sites. Subjects who experience virologic failure on their initial treatment regimen with nelfinavir or efavirenz will be switched to the other drug, allowing the assessment of whether these treatment switches are associated with improvement in metabolic abnormalities. Projected accrual is 345 subjects, to be followed for as long as 3 years. The ACTG hopes that this study will clarify the extent to which metabolic disorders may be a class effect of protease inhibitor drugs.

CONCLUSION

The metabolic effects of HIV disease progression, HIV antiviral therapies, and the restoration of health subsequent to successful antiviral therapy remain undefined. Causal mechanisms have not been identified for metabolic disorders observed in people with HIV disease. Although few of these effects appear to be life threatening, they are of serious concern to many clinicians and patients due to their impact on body image and the possible increased risk of diabetes and coronary artery disease. Further research is urgently needed to clarify the causes, progression, and treatment of metabolic disorders. In the absence of such research, we will likely see an increase in experimentation with potentially dangerous procedures such as liposuction, and in the number of patients discontinuing their antiviral therapy, in an attempt to reverse these side effects.

Table I: Summary of Selected Re search on Hyperglycemia and Diabetes Mellitus

First Author/ Method	Screening for:	N	AV Tx & Duration	Data Collected	Findings
Dever, LL Retrospective chart review	Elevated blood glucose and PI use	121 Subset: 30	IDV 96, SQV 24, RTV 1; duration unknown	Blood glucose Subset: repeated measurements	PI use assoc. with impaired glucose homeostasis, may be assoc. with diabetes in a significant subset of pts. Effect occurs in first few months of tx.
Dong, BJ Review of calls to Nat'l HIV phone consultation svc.	Diabetes cases associated with PI use	6 from over 1000 calls	SQV 3, RTV 1, NFV 2 Minimum 1 month	Unspecified	PI-induced hyperglycemia is rare. Risk factors not consistently present. Difficult to control if PI is continued.
Keruly, JC 1 year longitudinal review of pts. Using Protease Inhibitors	Hyperglycemia with PI use (>140 mg/dl)	6 of 290	PI use 22-230 days, median 53	Blood glucose	Incidence 0.35 per 100 person-months w/ glucose >200 mg/dl; 0.52 for glucose >140 mg/dl. Hyperglycemia is uncommon with PI use but can be severe when it occurs.

Table II: Summary of Selected Research on Hepatitis and Hepatic Failure

First Author/ Method	Screening for:	N	AV Tx & Duration	Data Collected	Findings
Arribas, JR Retrospective chart review	Acute hepatitis (ALT>10 x ULN)	10 of 141 (7%) 8 male, 2 female	Ritonavir 12 to 82 days, median 36.	HC antibody, HBSAg, ALT,	Hepatitis resolved in 7 pts. of 8 who stopped Ritonavir. Recurred in 2 with rechallenge. No recurrence in 7 switched to other PIs.
Barry, C Case report	N/A	1 male	D4T, ddI, IDV; Last regimen 11 wks	Blood lipids, autopsy exam	Fulminant liver failure resulted from one or a combination of drugs.

Table III: Summary of Selected Research on Abnormal Lipid Metabolism and Deposition

First Author/ Method	Screening for:	N	AV Tx & Duration	Data Collected	Findings
Carr, A Patient screening for peripheral lipodystrophy (LD)	Fat wasting of the face and limbs with relative central adiposity	72 of 116 (64%)	One or more PIs 10 mos. Median	Fasting cholesterol triglycerides, glucose, insulin, C-peptide, free fatty acid, fructosamine, cortisol, testosterone, leptin, TNF-alpha, liver enzymes, T cells, viral load, DEXA	LD associated with relative 0.51 kg/month weight loss. LD developed earlier & was more severe w/RTV-SQV than IDV. May result from interaction of protease inhibitors and low density lipoprotein receptor-like protein. Diabetes rare.
Hengel, RL Case Reports of multiple symmetrical lipomatosis	Unencapsulated fat in the neck and shoulder areas	4 (3 male, 1 female)	All on IDV +Stavudine (1) or ZDV/ Lamivudine (3); 6 mo. median on Pis	Glucose, triglycerides, Dexamethasone suppression; others not specified	Woman had increase in breast size and abdominal girth.
Lo, JC Case reports of "buffalo hump"	Dorsocervical fat pad enlargement	7 males	All on antivirals, only 3 on protease inhibitors Unknown	BMI, plasma and urine cortisol, %total fat, %trunk fat, CHOL, TG, DEXA	Cushing's ruled out. May occur in absence of PIs. Found elevated triglycerides and trunk fat proportion.
Mann, M Retrospective review of FDA reports of patients using Pis	Cushing's; change in body habitus, weight, or composition	9; 7 male, 2 female	IDV: 5 RTV: 2 SQV: 2 1-6 months of PI treatment.	Review of clinical data in adverse reaction reports to FDA.	Redistribution of fat to central lower abdomen, neck, back, or retriperitoneal area. One pt. discontinued PI with resolution of symptoms.
Miller, K Evaluation of CT scans in 37 HIV+ men who had CT scans for clinical indications.	Increased abdominal girth without weight gain.	37 men; 10 on IDV with abdominal problems.	13 no IDV; 24 IDV >6 months	total adipose tissue (TAT) and visceral adipose tissue (VAT) by abdominal CT scan, BMI, serum cholesterol and triglycerides	HIV-infected patients on long-term indinavir therapy experience an accumulation of visceral fat that may cause abdominal complaints; abnormal lipid metabolism.

Table III, Continued: Summary of Selected Research on Abnormal Lipid Metabolism and Deposition					
First Author/ Method	**Screening for:**	**N**	**AV Tx & Duration**	**Data Collected**	**Findings**
Mulligan, K Prospective study of metabolic effects of starting PI therapy	Results pre and post PI or 3TC therapy	24; 20 males and 4 females, plus 16 controls	PIs: IDV 12, SQV 2, RTV 2; 3TC 8 PIs: median 4.4 mos; 3TC, 3.9 months.	CD4 count, viral load, glucose, triglycerides, cholesterol, insulin, testosterone, cortisol, DHEA sulfate, DEXA	Suggest PIs have metabolic effects independent of improvements in CD4 count or nutritional status; VL suppression may be involved.
Roberts, AD 4 weekly blood lipid measurements		10 males	IDV plus 2 nukes Tx naïve at start of study	Serum cholesterol, triglycerides, high density and low density lipoproteins	Increases observed in cholesterol, triglycerides, and low density lipoproteins; significance unclear.
Rosenberg, HE Patient screening for "protease paunch"	Increased abdominal girth and stable weight, pts. on PIs	5 of 72 (7%); 3 male, 2 female	Not specified Median 18 mos. of PI therapy	cortisol, growth hormone, somatomedin-C, serum glucose, thyroid: TFT, TSH, FSH, LH; testosterone, DHEA, androstenedione, prolactin	Cushing's ruled out; protease paunch occurred in older pts. (median age 46) receiving long-term PI therapy.
Ruane, PJ Case reports of cervical fat pads	Unusual fat deposits at base of posterior neck	3 males	Extensive history with nukes, IDV added in 1996 2 to 7 months	Serum cortisol, physical examination, MRI of 1 patient	3 patients in one practice found to have striking fatty accumulations at the base of the neck shortly after initiation of PI therapy.

Endnotes and References

[1] See generally, ***Report of the NIH Panel to Define Principles of Therapy of HIV Infection***, MMWR, April 24, 1998/Vol.47/No.RR-5

[2] See generally, ***Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents***, MMWR, April 24,1998/Vol.47/No.RR-5

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[28] *See Note 18*

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