LIPID AND MORPHOLOGIC ABNORMALITIES ASSOCIATED WITH ANTIRETROVIRAL THERAPY FOR HUMAN IMMUNODEFICIENCY VIRUS INFECTION: PREVALENCE, INCIDENCE, AETIOLOGY AND IMPACT ON TREATMENT PATTERNS

by

KATHERINE VALERIE HEATH
B.Sc. University of BC 1980 M.Sc. University of BC
The University of British Columbia, 2002

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE

REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE STUDIES

Department of Health Care and Epidemiology

We accept this thesis as conforming to the required standard

Robert S. Hogg

Michael V. O'Shaughnessy

Julio S.G. Montaner

Joel Singer

THE UNIVERSITY OF BRITISH COLUMBIA

April 23, 2002

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of HEALTH CARE & EPIDEMIOLOGY

The University of British Columbia
Vancouver, Canada

Date April 25, 2002

ABSTRACT

Objectives: The primary objectives of this study are to determine the prevalence and incidence of the emerging lipid and morphologic abnormalities commonly referred to as human immunodeficiency virus (HIV)-associated lipodystrophy syndrome and to identify possible determinates of prevalent and accrued symptoms among persons receiving treatment for HIV infection in British Columbia. We also aim to describe both physician and patient responses to the occurrence of these and other adverse drug effects particularly in relation to pro-active antiretroviral regimen non-adherence among patients.

Methods: British Columbia's provincial HIV/AIDS Drug Treatment Program provides antiretroviral therapy to all eligible HIV positive persons in British Columbia free of charge. Persons prescribed antiretroviral agents are automatically entered into the drug treatment program database and information regarding prescribed therapies, age, gender, AIDS status and laboratory parameters is maintained for all participants while they remain on therapy. In addition, subjects complete voluntary surveys each year on the occasion of their anniversary of treatment program entry. This captures detailed information regarding socio-demographic characteristics, the occurrence of adverse drug effects, and other parameters. Additional questions regarding medically unsanctioned antiretroviral therapy adjustment and other responses to the occurrence of sub-types of adverse drug effects were incorporated for one year of the survey.

Results: The prevalence of probable HIV-associated lipodystrophy syndrome in British Columbia among antiretroviral recipients is approximately 50% by self-report. Incidence rates of symptoms are also high among both those with an extensive history of therapy and those initiating first antiretroviral therapy. Study findings indicate a primary role of protease inhibitors in the aetiology of symptoms including lipoatrophy, lipohypertrophy and

dyslipidemia. Other factors including patient gender and stavudine use may be related to morphologic abnormalities. Proactive self medication in direct response to adverse drug effects occurs at an annual rate of approximately 11%. This activity is associated with the severity, number and type of symptoms experienced.

Conclusion: Lipodystrophy-associated symptoms are likely a consequence of antiretroviral therapy although their aetiology is complex and multifactorial. Symptoms associated with lipodystrophy and other adverse drug effects are likely to prompt intentional regimen adjustment and require consideration beyond their direct impact on clinical outcomes.

TABLE OF CONTENTS

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to extend my warmest and most sincere thanks to my committee members each of whom provided me with something beyond their direction, support and generous mentorship.

Dr. Robert Hogg, who kept me grounded;
Dr. Joel Singer, who kept me laughing;
Dr. Julio Montaner, who kept me thinking; and
Dr. Michael O'Shaughnessy, who kept me feeling.

I gratefully acknowledge the financial support of the Centre for Excellence in HIV/AIDS and the Izaac Walton Killam Foundation for their support through a Memorial Pre-doctoral Fellowship.

To the participants of British Columbia Drug Treatment Programme who took time from their busy schedules in the face of great obstacles to participate, I am eternally indebted.

I also extend my regards to those anonymous scholars who reviewed the resulting manuscripts prior to publication and the external thesis reviewer for their critical insight.

CHAPTER 1

INTRODUCTION AND THESIS ORGANISATION

1.1 HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN BRITISH COLUMBIA AND TREAMENT HISTORY

Infection with the human immunodeficiency virus (HIV), a pathogenic retrovirus, causes the destruction of CD4 lymphocytes in humans[1,2]. This results in a progressive deterioration of immune function culminating in acquired immunodeficiency syndrome (AIDS), and eventually, death. The progressive loss of immune function renders those infected susceptible to various opportunistic infections caused by other viruses, fungi, parasites and bacteria. AIDS itself is characterised by the presence of an AIDS defining illness in accordance with the Centres for Disease Control and World Health Organisation classification system of HIV infection and additionally, by a CD4 cell count of less than 200 cells/mm^3 in the United States[3].

On an international level, Canada is a country of intermediate cumulative AIDS incidence. As of December 31st, 2001, there have been 17,818 reported cases of AIDS in Canada[4]. With 3,054 AIDS cases reported as of December, 2001, British Columbia has not been spared the full impact of this epidemic[4]. Throughout the epidemics' history, British Columbia has been at the forefront of efforts to meet the social and health care needs of those living with HIV infection. A primary goal of clinical care and research in this province, and world-wide, has been to identify efficacious and effective therapies for HIV disease.

Since the discovery of human immunodeficiency virus as the cause of AIDS in the mid 1980's, substantial research has been directed toward the treatment of HIV infection, primarily the development of drugs which selectively attack the retrovirus after infection. While the

introduction and expanded use of antiretroviral therapies has yielded tangible benefits, many challenges still remain in the successful application of therapy to HIV disease.

Prior to the introduction of antiretroviral therapy, median survival from AIDS index diagnosis to death ranged from approximately 9.5 to 14 months, typically with substantial morbidity resulting from opportunistic infections[5,6]. The course of HIV disease has altered substantially over the last decade with the introduction of antiretroviral therapy. The introduction in 1987 of zidovudine, a nucleoside reverse transcriptase inhibitor (nucleoside analogue) and the first approved HIV antiretroviral agent, significantly improved survival times for AIDS patients. A large cohort study of zidovudine in patients with advanced disease demonstrated a median survival of 21.2 months compared to 9.6 months for untreated patients[6].

Subsequently, other nucleoside analogues were developed such as didanosine and zalcitabine. Despite these advances treatment remained challenging. Rapid development of drug resistant viral strains imposed a relatively short duration of effect and most patients experienced eventual progression[7,8]. These outcomes led to clinical trials of double combination therapies which indicated superiority over monotherapies. For example, the Delta study demonstrated a 21% and 33% reduction in mortality with zidovudine/didanosine and zidovudine/zalcitabine combinations, respectively, in comparison to zidovudine monotherapy[9].

Combination therapy options expanded further with the release of additional nucleoside analogues lamivudine, and stavudine. Mirroring clinical findings, population-based studies subsequently demonstrated that patients who initially received zidovudine, didanosine, or zalcitabine based therapy were 2.5 times more likely to die or progress to AIDS than those initially receiving lamivudine or stavudine inclusive regimens[10].

Initially, the efficacy of novel therapies was monitored by reductions in the occurrence of opportunistic infections or extension of life. Over the first decade of investigation both patient characteristics and a number of clinical and laboratory markers were investigated for their prognostic value. Early studies of survival trends throughout the 1980s found the length of survival to be highly variable, with initial AIDS-defining illness, age, year of AIDS diagnosis, and CD4 cell count identified as independent predictors of mortality[11-13].

Concurrent with later clinical trials of combination therapies, the acceptance and advent of markers of clinical progression such as CD4 cell counts allowed improved and more rapid monitoring of clinical success and disease progression[14]. In a landmark 1996 study, HIV-1 plasma viral load was shown to be a better predictor of progression to AIDS and death than CD4 cell count[15]. Specifically, baseline HIV ribonucleic acid (RNA) levels were found to be highly predictive of prognosis with reduced viral RNA in response to antiretroviral therapy predictive of improved clinical prognosis. Subsequent studies have clearly confirmed a close association between reduction of plasma viral load during the course of antiretroviral therapy and the risk of a new AIDS defining illness or death[16,17]. Investigations of the use of a combination of plasma viral load and CD4 cell count to reflect clinical disease progression revealed that the prognostic interpretation of any given plasma viral load reduction was related to the treatment induced change in CD4 cell count[16]. Current treatment guidelines reflect these observations recommending the use of both plasma viral load and CD4 cell count to guide the timing of therapy initiation and for monitoring treatment response[18].

Concurrent with these advances, the discovery of a new class of antiretrovirals- protease inhibitors, initiated forays into the use of triple combination therapy utilising two nucleosides in conjunction with these newly developed agents. In clinical trials each of the protease inhibitors; saquinavir, indinavir, ritonavir and nevirapine were shown to improve short-term

survival, decrease morbidity, increase CD4 cell counts and reduce plasma viral load when incorporated into triple drug regimens in comparison to dual nucleoside therapy[19-22].

The use of protease inhibitors was followed in rapid succession by the advent of non-nucleoside reverse transcriptase inhibitors including nevirapine, efavirenze and delavirdine. The successful addition of these agents to dual nucleoside analogue regimens as an alternative to protease inhibitor use further expanded regimen options for those with HIV disease[23-25].

These novel triple drug regimens ushered in the current era of highly active antiretroviral therapy. The widespread use of highly active antiretroviral therapy, initiated in 1996, has led to dramatic improvements in HIV-related morbidity and mortality[26] attributed to the extended durability of viral suppression to below detectable levels[27]. Promising results obtained in clinical trials have again been reflected in population-based studies across the developed world. In the United States, death rates among HIV patients decreased from 29.4 per 100 person-years in 1995 to 16.7 per 100 person-years in 1996 and to 8.8 per 100 person-years by mid 1997[28]. In France, a study of more than 7,500 patients attending ten AIDS referral centres from September/October 1995 to September/October 1996 showed a drop in hospitalisation days by 35%, of new AIDS cases by 35%, and of deaths by 46% over the course of the study[29]. Furthermore, comparison of the three centres that adopted highly active therapy earliest to the three centres that introduced it most recently demonstrated a reduction in hospitalisation days of 41%, new AIDS cases of 41%, and deaths of 69%. In Canada, similar trends have been noted, with declining mortality following the wide-spread use of triple combination regimens[30,31].

The development of new antiretroviral agents continues at a rapid pace. Currently an additional six nucleoside analogues, five non-nucleosides and six protease inhibitor agents are in various stages of development and undergoing phase I, II and III clinical trials. In addition,

new classes of agents are being investigated for their antiretroviral activity and their safety and efficacy in HIV-infected individuals. These include integrase inhibitors, fusion inhibitors, chemokine receptor antagonists, ribonucleotide reductase inhibitors and immune modulators. Moreover, novel dosing schedules and combinations are also being explored in an effort to decrease the burden on those using these regimens and to offer an expanded array of therapy options. The therapeutic management of HIV infection, however, remains a unique challenge in clinical care.

1.2 CURRENT ISSUES IN TREATMENT

The full benefits of antiretroviral therapy seen in clinical trials remain difficult to attain in the general population, largely due to imperfect adherence to therapy[32,33]. Treatment is complex, requiring rigorous adherence to demanding multi-drug antiretroviral treatment regimens. Imperfect adherence is related to level of viral suppression and subsequent emergence of drug resistance[23,34-36]. For those who achieve success, continued viral control, even in the short-term, can be troublesome due to the natural development of drug resistance[37-39]. Resistance to individual drugs and cross resistance within drug classes results in cycling through various regimen combinations until such time as resistance to all available therapy classes results in eventual treatment option exhaustion. When failure occurs at this point the only hope for continued suppression is the availability of new drugs.

Recently, however, further limitations to treatment success have become critical. Coincident with the application of advanced treatment regimens, symptoms and health problems not before seen in the HIV affected population have been reported including hyperlactatemia, osteoporosis, avascular necrosis, redistributions in body fat (lipodystrophy), dislipidemia, and cardiovascular events[40-45]. Many of these are suspected to be emerging

drug-related adverse effects[46-54]. Drug toxicities have important implications both for the patient's ability or willingness to use available regimens and for patterns of individual therapy use among those committed to ongoing therapy. Due to these factors the occurrence of adverse drug effects further hampers the ability of patients to achieve the full benefits of currently available antiretroviral therapy.

The occurrence of redistributions in body fat and abnormalities in lipid profiles are of particular interest and are the focus of the research presented here.

1.3 RESEARCH NEEDS AND STUDY JUSTIFICATION

The emergence of novel adverse drug effects represents a turning point in antiretroviral treatment. At a time when concrete advances offer hope to persons living with HIV disease, the occurrence of suspected adverse drug effects are a significant stumbling block in efforts to extend survival while retaining acceptable quality of life.

The emergence of HIV-associated lipodystrophy syndrome, the constellation of symptoms including lipodystrophy, lipomatosis and dislipidemia, is of particular interest given its potential impact on many facets of antiretroviral therapy. At the initiation of this research very little information regarding lipodystrophy-associated symptoms was available. However, preliminary studies suggested that lipodystrophy syndrome-associated symptoms were extremely common among persons being treated with standard antiretroviral regimens[44,55]. No studies of incidence had been conducted and prevalence data was limited to small or highly selected study samples. Moreover, no data regarding the epidemiologic parameters of these symptoms were available for Canada. With a large population of HIV infected individuals and the broad application of state-of-the-art antiretroviral treatment it is important to estimate the

proportion and absolute numbers of individuals who may be experiencing these symptoms in British Columbia.

Thirdly, the aetiology of lipodystrophy-associated symptoms was, and remains, unknown despite a growing body of research. Studies aimed at addressing this question have been limited in terms of sample size, treatment regimens examined, range of population characteristics and by a paucity of data regarding possible confounders or contributing variables.

Lipodystrophy-associated symptoms also provide a unique opportunity to investigate some "non-clinical" aspects of adverse effects. Lipodystrophy-associated morphologic changes in particular are relatively benign and their occurrence is not currently considered reason for treatment changes in and of themselves. Morphologic symptoms are easily identified and are likely to be first noted by patients themselves and do not appear to dissipate to any great extent particularly if severe or of long standing[56,57].

Theoretically, such side effects may be particularly problematic if, due to their relatively innocuous clinical effects, they are under-managed by physicians. Moreover symptoms can be disfiguring and frightening to those experiencing them. These features may prompt individuals to turn to self-management of symptoms through various types of regimen adjustment or non-adherence which may have devastating effects on the clinical efficacy of prescribed regimens.

Finally, the emergence of lipodystrophy-associated symptoms should act as a catalyst for investigating the important role that adverse drug effects are likely to play in the future of antiretroviral therapy. Data regarding the prevalence and incidence of emerging toxicities in the general population of antiretroviral users is scarce. Reporting is subject to selective notification, and dissemination to publication time lags. Detailed investigations of one group

of adverse drug effects such as lipodystrophy symptoms can provide a platform which can be used to design and establish a broader system of surveillance for emerging adverse events.

1.4 STUDY OBJECTIVES AND THESIS ORGANISATION

This thesis is divided into 8 chapters. This first has set the stage for the dissertation work acting as a short introduction to the underlying impetus for the research and its objectives. Chapter 2 provides a detailed review of the current literature regarding emerging adverse effects and discusses their relevance to the future of antiretroviral treatment. The third chapter outlines the study setting. The data resources and specific methods used to address each objective and their limitations are also described. Chapters 4 through 7 address the main study objectives one through four as outlined below and summarise the findings of these various lines of enquiry.

The general aim of this study is to describe the epidemiology of HIV-related lipodystrophy-associated symptoms in British Columbia and address some of the questions regarding the impact of these and other adverse drug effects on physician and patient mediated treatment patterns.

The **first** objective is to estimate the prevalence of morphologic and lipid abnormalities consistent with HIV- associated lipodsytrophy syndrome among persons being treated with antiretroviral therapy for HIV disease in British Columbia and to identify patient and treatment characteristics associated with prevalent morphologic and lipid abnormalities.

The **second** objective is to estimate the annual incidence of morphologic and lipid abnormalities consistent with HIV- associated lipodsytrophy syndrome and to identify patient and treatment characteristics associated with prospectively accrued cases. This analysis is complicated by the multifaceted nature of treatment and wide variation in the extent and

format of treatment history among persons receiving antiretroviral treatment. These features make it difficult to delineate the contribution of treatment-related factors to symptom occurrence. The **working hypothesis** of this research is that the symptoms associated with lipodystrophy are caused by antiretroviral medications prescribed for HIV disease treatment.

The **third** objective is, therefore, aims to ameliorate these problems to some extent. In this study the analytic strategy of the second objective is applied to treatment naïve individuals initiating first antiretroviral therapy. This approach also allows the exploration of issues of temporality which are problematic in the first two studies.

Lastly, it is not known whether, and to what extent, adverse symptoms affect patterns of antiretroviral use and adherence or whether these patterns are dependent on the type of symptoms experienced. The **fourth** and final study objective is to describe physician versus patient approaches to the occurrence of lipodystrophy-associated symptoms and other adverse drug effects. A further aim is to provide preliminary information regarding the proportion of individuals receiving treatment that may be engaging in proactive non-adherence due to the occurrence of adverse effects and to identify possible predictors of this behaviour.

Each applicable chapter (Chapters 2 and 4 through 7) consists of a stand alone manuscript each of which is either published, accepted, or under review with an international, peer-reviewed scholarly journal and in which the candidate is the lead author.

The final chapter, Chapter 8, provides a review of the study results overall and discusses the implications of these findings. The unique contributions of the study and its relevance to current literature are discussed. Lastly recommendations are put forward and the contribution of this work to the implementation of these recommendations is outlined.

1.5 SUMMARY

Despite many advances in HIV-related treatment, successful long-term therapy remains challenging due, in part, to the emergence of adverse drug effects associated with clinically efficacious therapy. At the initiation of this research project in 1998 case series and anecdotal reports of morphologic and lipid abnormalities among persons using antiretroviral agents were beginning to emerge in the medical literature. These abnormalities including changes in body fat distribution and dyslipidemia, as they often appear in constellation, were termed HIV-associated lipodystrophy syndrome. The ultimate goal of the research presented here is to provide a thorough understanding of the epidemiology of HIV-associated lipodystrophy syndrome among HIV positive persons receiving antiretroviral therapy in British Columbia. This includes a description of both the prevalence and incidence of key lipodystrophy-associated symptoms, detailed etiologic investigation, and a broader investigation of how lipodystrophy symptoms and other adverse drug effects may impact on individual treatment patterns.

In the four years between the first reports of lipodystrophy-associated symptoms and the present time many studies have been conducted to investigate these and other emerging adverse drug effects. The manuscripts which form the body of this thesis have contributed to the substantial advances in knowledge in those intervening years and represent the sole source of published observational data regarding the epidemiology of lipodystrophy syndrome in Canada.

In the following chapter we review what is currently known regarding the emerging suspected adverse drug effects of antiretroviral therapy with particular reference to HIV-associated lipodystorphy syndrome.

1.6 REFERENCES

1. Gallo RC, Salahuddin SA, Popovic M et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science* 1984; 224:500-503.
2. Popovic M, Sarngadharan MG, Read E et al. Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. *Science* 1984; 224:497-500.
3. Interim proposal for a WHO Staging System for HIV infection and Disease. *Wkly Epidemiol Rec* 1990; 65:221-224.
4. Surveillance update: AIDS in Canada, Quarterly Report, June, 2001. Ottawa, Ontario: HIV/AIDS Division, Laboratory Centre for Disease Control, Health Canada.
5. Luo K, Law M, Kaldor JM et al. The role of initial AIDS-defining illness in survival following AIDS. *AIDS* 1995; 9:57–63.
6. Vella S, Giuliano M, Pezzotti P et al. Survival of zidovudine-treated patients with AIDS compared with that of contemporary untreated patients. *JAMA* 1992; 267:1232–1236.
7. Concorde Coordinating Committee. Concord: MRC/ARNS randomized double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet* 994; 343:871-881.
8. Volberding PA, Lagakos SW, Grimes JM et al. A comparison of immediate with deferred zidovudine therapy for asymptomatic HIV-infected adults with CD4 cell counts of 500 or more per cubic millimetre. *N Engl J Med* 1995; 333:401-407.
9. Delta Coordinating Committee. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didianosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet* 1996; 348:283–291.

10. Hogg RS, Heath KV, Yip B et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *JAMA* 1998; 279:450–454.

11. Pederson C, Gerstoft J, Tauris P et al. Trends in survival of Danish AIDS patients from 1981 to 1989. *AIDS* 1990; 4:1111–1116.

12. Lemp GF, Payne SF, Neal D et al. Survival trends for patients with AIDS. *JAMA* 1990; 263:402–406.

13. Bindels PJE, Krol A, Roos M et al. The predictive value of T cell function in vitro and pre-AIDS zidovudine use for survival after AIDS diagnosis in a cohort of homosexual men in Amsterdam. *J Infect Dis* 1995; 172:97–104.

14. Mellors JK, Alvaro M, Janis G et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997; 126:946–954.

15. Mellors JW, Rinaldo CR, Gupta P et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science* 1996;272:1167–1170.

16. Marschner IC, Collier AC, Coombs RW et al. Use of changes in plasma levels of human immunodeficiency virus type I RNA to assess the clinical benefit of antiretroviral therapy. *J Infect Dis* 1998; 177:40–47.

17. O'Brien WA, Hartigan PM, Martin D et al. Changes in plasma HIV-1 RNA and Cd4+ lymphocyte counts and the risk of progression to AIDS. *N Engl J Med* 1996; 334:426–431.

18. Carpenter CCJ, Cooper DA, Fischl MA et al. Antiretroviral therapy in adults. Updated recommendations of the International AIDS Society – USA Panel. *JAMA* 2000; 283:381–390.

19. Collier A, Coombs RW, Schoenfeld DA et al. Treatment of human immunodeficiency virus infection with saquinavir, zidovudine, and zalcitabine. AIDS Clinical Trial Group. *N Engl J Med* 196; 334:1011-1017.

20. Gulick RM, Mellors JW, Havlir D et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med* 1997; 337:734-739.

21. Hammer SM, Squires KE, Hughes MD et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 counts of 200 per cubic millimetre or less. *N Engl J Med* 1997; 337:725-733.

22. Cameron DW, Heath-Chiozzi M, Danner S et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. The Advanced HIV Disease Ritonavir Study Group. *Lancet* 1998; 351:543-549.

23. Montaner JS, Reiss P, Cooper D et al. A randomised, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients. The INCAS Trial. Italy, The Netherlands, Canada and Australia Study. *JAMA* 1998; 279:930-937.

24. Staszewski S, Morales-Ramirez JO, Godofsky W et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine plus lamivudine in the treatment of HIV-1 infection in adults. *N Engl J Med* 1999; 341:1865-1873.

25. Wood R, Hawkins DA, Moyle G et al. Second placebo-controlled trial in naïve individuals confirms the role of delavirdine in highly active antiretroviral therapy. *Sixth Conference on Retroviruses and Opportunistic Infections*. Chicago, Illinois 1999 [abstract 624].

26. Michelet C, Arvieux C, Francois C et al. Opportunistic infections occurring during highly active antiretroviral treatment. *AIDS* 1998; 12:1815–1822.

27. Raboud JM, Montaner JSG, Conway B et al. Suppression of plasma viral load below 20 copies/ml is required to achieve a long-term response to therapy. *AIDS* 1999; 12:1619–1624.

28. Palella FJ Jr., Delany KM, Moorman AC et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998; 338:853–860.

29. Mouton Y, Alfandari S, Valette M et al. Impact of protease inhibitors on AIDS-defining events and hospitalizations in 10 French AIDS reference centers. *AIDS* 1997; 11:F101–F105.

30. Hogg RS, O'Shaughnessy MV, Gataric N et al. Decline in death from AIDS due to new antiretrovirals. *Lancet* 1997; 349:1294.

31. Hogg RS, Yip B, Kully C et al. Improved survival among HIV-infected patients after initiation of triple-drug regimens. *CMAJ* 1999; 160:659-665.

32. Descampes D, Flandre P, Calvez V et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. *JAMA* 2000; 283:205-211.

33. Young B, Johnson S, Bahktiari M et al. Resistance mutations in protease and reverse transcriptase genes of human immunodeficiency virus type-1 isolates from patients with combination antiretroviral therapy failure. *J Infect Dis* 1998; 178:1497-1501.

34. Vanhove GF, Schapiro JM, Winters MA, Merigan TC, Blaschke TF. Patient's compliance and drug failure in protease inhibitor monotherapy. *JAMA* 1996; 276:1955-1956.

35. Altice FL, Friedland G. The era of adherence to HIV therapy [Editorial]. *Ann Intern Med* 1998; 129:503-505.

36. Bangsberg DR, Hecht FM, Charlebois ED et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS* 2000; 14:357-366.

37. Coffin JM. HIV population dynamics in vivo: implications for genetic variation, pathogenesis, and therapy. *Science* 1995; 267:483-489.

38. Nunberg JH, Schleif WA, Boots EJ et al. Viral resistance to human immunodeficiency virus type-1-specific pyrimidine reverse transcriptase inhibitors. *J Virol* 1991; 65:4887-4892.

39. Schuurman R, Nijhuis M, van Leeuwen R et al. Rapid changes in human immunodeficiency virus type-1 RNA load and appearance of drug-resistant virus populations in persons treated with lamivudine (3TC). *J Infect Dis* 1995; 171:1411-1419.

40. Chattha G, Arieff AI, Cummings C, Tierney LM. Lactic acidosis complicating the acquired immunodeficiency syndrome. *Ann Intern Med* 1993; 11:37-39.

41. Monier P, Mckown, Bronze MS. Osteonecrosis complicating highly active antiretroviral therapy in patients with human immunodeficiency virus. *CID* 2000; 31:1488-1492.

42. Roudier L, Viard J. Osteonecrosis of the hip, lipodystrophy and antiretroviral treatment [Letter]. *AIDS* 2000; 14:2056.

43. Ho TTY, Chan KCW, Wong KH, Lee SS. Buffalo hump and facial wasting in HIV. *Lancet* 1998; 351:1736-37.

44. Carr A, Samaras K Burton S et al. A syndrome of peripheral lipodystrophy, hyperlipidemia and insulin resistance due to HIV protease inhibitors. *AIDS* 1998; 12:F51-F58.

45. Henry K, Melroe H, Huebsch J et al. Severe premature coronary artery disease with protease inhibitors. *Lancet* 1998; 351:1328.

46. Lewis W, Dalakis MC. Mitochondiral toxicity of antiviral drugs. *Nature Med* 1995; 1:417-421.

47. Carr A, Miller J, Law M, Cooper DA. A syndrome of lipoatrophy, lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS* 2000; 14:F25-F32.

48. Dube MP, Johnson DL, Currier JS, Leedom JM. Protease inhibitor-associated hyperglycaemia. *Lancet* 1997; 350:713-714.

49. Meyer D, Behrens G, Schmidt RE, Stoll M. Osteonecrosis of the femoral head in patients receiving HIV protease inhibitors [Letter]. *AIDS* 1999; 13:1147-1148.

50. Miller KD, Jones E, Yanovski JA, Shankar R, Feurstein I, Falloon J. Visceral abdominal-fat accumulation associated with use of indinavir. *Lancet* 1998; 12:F51-F58.

51. Boxwell DE, Styrt BA, US Federal Drug Administration. Lactic acidosis (LA) in patients receiving nucleoside reverse transcriptase inhibitors (NRTI's). *39th Interscience Conference on Antimicrobial Agents and Chemotherapy*, San Francisco, California 1999 [Abstract 1284].

52. Carr A, Samaras K, Chisholm DJ et al. Pathogenesis of HIV-1 protease inhibitor-associated peripheral lipodystrophy, hyperlipidemia, and insulin resistance. *Lancet* 1998; 131:1881-1883.

53. Maggi P, Serio G, Epifani G et al. Premature lesions of the carotid vessel in HIV-1-infected patients treated with protease inhibitors. *AIDS* 2000; 14:123-128.

54. Depairon M, Chessex S, Sudre P et al. Premature atherosclerosis in HIV-infected individuals- focus on protease inhibitor therapy. *AIDS* 2001; 15:329-334.

55. Thiébaut R, Daucourt V, Malvy D et al. Lipodystrophy, glucose and lipid metabolism dysfunctions, Aquitaine Cohort, 1999. *1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV.* San Diego, California 1999 [Abstract 17].

56. Mallon PWG, Miller J, Carr A, Cooper D. Ansalysis of changes in metabolic and morphological abnormalities in HIV-positive individuals with HIV-associated lipodystrophy, changing regimens. *3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV.* Athens, Greece 2001 [Abstract 83].

57. Behrens GMN Stoll M, Schmidt RE. Lipodystrophy syndrome in HIV infection. What is it, what causes it and how can it be managed? *Drug Saf* 2001; 23:57-76.

CHAPTER 2

BACKGROUND

2.1 FORWARD

This chapter was accepted for publication in February 2002 as: "Emerging Drug Toxicities of Highly Active Antiretroviral Therapy for Human Immunodeficiency Virus (HIV) Infection" in *Current Drug Targets*. While the manuscripts comprising this thesis reflect the state of knowledge at the time of each component's completion, this review includes information available as of early 2002 to provide an up-to-date summary of information. Co-authors included all committee members and Dr. Greg Bondy, a specialist in laboratory medicine with expertise in lipid abnormalities.

2.2 INTRODUCTION

Over the past decade of clinical research into HIV disease efforts have been focused on the development of antiretroviral agents used to attack the virus after infection. The development of the first class of antiretroviral agents- nucleoside reverse transcriptase inhibitors, and their use in mono or dual therapy regimens met with some initial success. Rapid viral rebound due to the development of drug resistance and subsequent treatment failure, however, remained problematic. More recently, the development of protease inhibitors, and non-nucleoside reverse transcriptase inhibitors and their incorporation into regimens combining three or more drugs ushered in the current era of highly active antiretroviral therapy. The widespread use of highly active therapy, initiated in 1996, has led to dramatic improvements in HIV-related morbidity and mortality attributed to the extended durability of viral suppression[1]. While the promising results obtained in clinical trials have

been mirrored to some extent in population-based studies across the developed world[2,3] the full theoretical benefits of antiretroviral therapy remain difficult to attain in the general population. One critical limitation of currently available multi-drug regimens is the occurrence of adverse drug effects.

Since their introduction, antiretroviral therapies have been associated with a broad range of adverse events including, most commonly, gastrointestinal symptoms, neuropathies, rash and hepatic toxicities. With the wide dissemination of highly active antiretroviral therapy the issue of adverse drug reactions has become increasingly important.

Under current treatment regimens, individuals experience greater overall duration of drug exposure. Extended survival due to improved treatment translates to longer overall exposure to antiretroviral therapy. Moreover, individual drugs retain their efficacy when applied as part of a highly active regimen, implying extended exposure to any one commonly used agent. Adverse effects associated with duration of antiretroviral use overall or in relation to a specific agent or associated with threshold effects are likely to become more common. In addition, the use of multiple concomitant therapies may result in direct drug interactions as well as an increased risk of development of multiple adverse drug effects of differing aetiologies. Lastly, the rapid development and introduction of new agents may result in novel adverse events not identified prior to drug approval and general release.

Recent reports in the medical literature describing suspected adverse drug events not previously identified among individuals exposed to antiretroviral therapies indicate that these apprehensions may be well founded. Here we discuss several suspected emerging adverse drug effects; HIV-associated lipodystrophy, hyperlactatemia and lactic acidosis, and bone disorders. These are of special interest as they are newly emerging, of unknown aetiology, not captured through standard care practices and are theorised to have a common mechanism of

occurrence. We review what is known about their distribution, possible causes and approaches to treatment and briefly outline their relevance to the future of antiretroviral treatment. It is important to note that research in the area of HIV therapeutics advances rapidly. This is particularly true in the case of adverse drug effects given the current interest in this topic. This review aims to provide the most up-to-date information possible at the time of publication.

2.3 MORPHOLOGIC AND METABOLIC ABNORMALITIES AND LIPODSYTROPHY SYNDROME

Morphologic abnormalities involving re-distributions in body fat (lipodystrophy) among persons treated with antiretrovirals for HIV disease were first reported in 1998. These abnormalities can include one or more of peripheral fat wasting from the face, arms, legs and buttocks (peripheral lipoatrophy), increased visceral abdominal fat or breast enlargement (central lipohypertrophy), and lipomatosis including enlargement of the dorso-cervical fat pad (buffalo hump)[4-6]. Metabolic events have also been reported, specifically glucose and lipid abnormalities. Glucose abnormalities can present as insulin resistance, impaired glucose tolerance, hyperglycemia and type 2 diabetes mellitus[6-9]. Dyslipidemia includes hypercholesterolemia and hypertryglyceridemia[6-10]. With both morphologic and metabolic abnormalities frequently appearing in various constellations, it has been suggested that these symptoms represent an HIV-associated lipodystrophy syndrome[6,9]. To date it remains unclear whether such symptoms indeed represent a single syndrome, two distinct syndromes or simply unrelated symptoms.

A multi-national study, lead by Australian researchers is underway to devise a definition of lipodystrophy syndrome based on reliable clinically validated diagnostic criteria. Studies to date have used a wide variety of self-reported and clinically identified symptoms and

syndrome definitions. Not surprisingly therefore, prevalence estimates for specific morphologic symptoms or lipodystrophy syndrome overall vary considerably from less than 5% to greater than 80% of patients exposed to various treatment regimens (for a review see[11]). In one large population-based study, among 1035 individuals receiving a wide variety of antiretroviral regimens, 50% were identified as having probable lipodystrophy by self-report[12]. Prevalence rates by symptom were; 36% for peripheral fat wasting, 33% for central lipohypertrophy and 6% for buffalo hump.

True prevalence of metabolic symptoms proves more difficult to describe as most reports provide mean changes or differences between groups in laboratory values rather than frequency of abnormal values. Moreover, some studies may underestimate these events as identification usually requires additional laboratory testing not commonly considered standard practice unless the index of suspicion is high[8,13]. One study based on self-report by patients found the prevalence proportion of dyslipidemia to be 16%, however, patient self-report may underestimate the true prevalence for these abnormalities[12]. The prevalence of insulin resistance measured by intravenous insulin tolerance test has been reported to be as high as 66% among those on protease inhibitor containing regimens as compared to 25% among those on dual nucleoside therapies and approximately 5% among those not on antiretroviral therapy[14]. Carr et al. have reported a prevalence of 16% based on oral glucose tolerance test among persons on protease inhibitor therapy. In contrast, the risk of overt diabetes among persons on antiretroviral medications appears to be lower, approximately 7%, as determined by oral glucose tolerance test among protease recipients[9].

Fewer estimates of symptom incidence are available as long-term prospective evaluation of patients, preferably treatment-naïve individuals, is generally required. One recent study using retrospective-prospective methodology reported a cumulative incidence of 29% for any

morphologic abnormality as identified by patient and physician report among persons on protease inhibitor inclusive triple combination therapy regimens after a median of 20 months of exposure[15]. A further study comparing subjects on dual protease inhibitors only versus two protease inhibitors plus nucleoside analogues reported overall incidence of morphologic changes subjectively identified by study physicians to be 17% over the 96 week follow-up period[16]. These figures vary little from incidence proportions reported among persons initiating therapy for the first time. For instance, a cohort of therapy-naïve patients initiating highly active antiretroviral regimens reported a prevalence of 17% after a median of 18 months based on morphologic changes identified by both the examining physician and the patient[17]. Similarly, a study of 121 persons treated with highly active antiretroviral therapy for more than 6 months during primary HIV infection reported a cumulative incidence of morphologic changes of 18% at 24 months based on clinical exam[18]. While estimates of both prevalence and incidence display some variability, these symptoms appear to affect a substantial proportion of the treated population making the identification of possible risk factors for their development imperative.

Despite active investigation the exact aetiology of various metabolic and morphologic changes associated with lipodystrophy syndrome remains unclear. With the initial identification of symptoms temporally coincident with the wide spread use of highly active antiretroviral therapy, multidrug regimens and their novel components, specifically protease inhibitors, were initially suspected as a likely causative factor. Indeed, several reports indicate a significant increase in patient identified morphological changes associated with protease inhibitor use[9,19,20], and/or identify specific proteases associated with various morphologic and metabolic abnormalities[8,21,22]. Others have concluded that these abnormalities are not associated with type of therapy or may occur in the absence of protease inhibitors[23]. For

example, preliminary cross sectional analysis from the LIPOCO study reported no association between morphologic changes and protease class therapy overall[13]. In detailed analysis of protease inhibitors they also reported no drug specific associations among the 100 protease exposed subjects studied. Similarly, results from a second cohort indicated no effects related to various treatment strategies[24]. For the most part, however, protease use or highly active antiretroviral therapy in general have been implicated in fat redistribution.

Several recent reports indicate that these symptoms may be a function of nucleoside analogue therapy rather than, or in addition to, protease inhibitor use[12,13,25-27]. In one study, those having ever used protease therapies were more than twice as likely to have lipodystrophy than those who had never been exposed, however, the duration of treatment with the nucleoside stavudine was also associated with a 35% increased risk of lipodystrophy for every 12 months of exposure[12].

Several recent studies have included analyses by morphologic phenotype. An ongoing prospective cohort study among 494 persons treatment naïve at baseline has reported associations between highly active antiretroviral therapy duration and both lipodystrophy overall and lipoatrophy as well as a marginal association between indinavir duration and lipohypertrophy[17]. A further study of highly active antiretroviral therapy exposed individuals noted significantly increased risk of lipohypertrophy with protease inhibitor class therapy, however, analysis by protease component was not conducted[28]. The aforementioned LIPOCO study also implicated stavudine use in peripheral lipoatrophy and in morphologic changes overall, however, with only nine subjects experiencing pure lipohypertrophy analysis restricted to this symptom group was not possible[13]. Martinez et al. recently reported a 16% increase in the risk of lipodystrophy with lipoatrophy for every additional six months of stavudine use among individuals on protease containing regimens[17]. This study, however,

concluded that the use of specific drugs is not significantly associated with lipodystrophy overall. Based on cross-sectional data, the HIV Outpatient Study has also reported increased risk of moderate or severe lipoatrophy associated with the use of stavudine and having used indinavir for greater than two years[29]. A prospective study of progressive lipoatrophy has reported increased risk with pre- highly active antiretroviral therapy duration of dual nucleoside analogue therapy and stavudine duration[30].

Several studies have also indicated non-treatment risk factors such as patient age and gender[13,24,29]. Other studies have not confirmed these reports[6,9,12,31]. It has also been suggested that immune recovery during treatment may have an impact on the likelihood of morphologic changes[18,29,32], but others have noted no relationship[15]. It is important to note that the studies reporting positive relationships do not appear to have adjusted analyses for adherence.

When taken in conjunction, studies conducted to date directly implicate antiretroviral agents in the development of symptoms of HIV -related lipodystrophy syndrome. However, data indicates a multifactorial aetiology which may also vary by symptom phenotype. Specifically, protease inhibitors appear to play a larger role in the development of hypertrophy while nucleosides, particularly stavudine, are implicated in lipoatrophy. In response to these findings the United States Food and Drug Administration recently required drug manufacturers to include information on lipodystrophy symptoms in package inserts for all antiretroviral medications.

The specific pathogenesis by which therapy use may result in lipodystrophy symptom development remains unknown. Similarity in clinical features between those with HIV-associated lipodystrophy, persons with inherited or non-HIV-related lipodystrophies and

persons with inherited mitochondrial diseases have recently led to an hypotheses of nucleoside analogue induced mitochondiral toxicity described later in this manuscript.

Regardless of current limitations, the ubiquitous nature of symptoms, high incidence rates and the implication of front line therapeutic agents makes continued investigation of metabolic and morphologic abnormalities a high research priority. Moreover, the possible implication for increased risk of cardiovascular events suggested by abnormal metabolic profiles raises the question of longer-term effects of lipodystrophy-associated symptoms[33].

Over the course of the last decade of the HIV epidemic, the mortality rate among those with HIV infection due to cardiovascular events has increased significantly from approximately 1% in the mid eighties to 9% by the 1994-96 period[34,35]. This may, in part, be explained by treatment mediated declines in mortality from AIDS-related causes such as opportunistic infections and the changing demographics of the affected population. It seems likely however, that HIV infection itself[35], related nutritional deficiencies[36] and other disease-related factors may have a direct impact on cardiac health. Studies of HIV positive patients have found higher frequencies of dyslipidaemia and asymptomatic atherosclerotic lesions in comparison to healthy control subjects[37-39]. Recently, reports implicating antiretroviral therapies in increased cardiovascular risk profiles suggest that cardiovascular disease will become an increasingly important area of concern for those living with HIV/AIDS.

Vascular complications such as stroke, myocardial infarction and angina have been reported among HIV positive persons with few traditional risk factors but prolonged exposure to antiretroviral treatment[40]. A recent study has identified premature atherosclerotic carotid artery lesions associated with the use of protease inhibitors[41]. In contrast, a study conducted among middle aged HIV-positive subjects and HIV-negative controls found a greater proportion of those infected to have peripheral atheroscerlotic plaques and to have

hyperlipidemia[42]. However, neither HIV serostatus nor PI use among HIV-positive subjects were independent predictors of plaque presence, rather, traditional risk factors were identified as the probable underlying cause.

Elevated total cholesterol and triglycerides, low levels of high-density lipoprotein cholesterol, insulin resistance as well as truncal adiposity are known risk factors for cardiovascular disease in the general population[43,44]. Theoretically, dislipidemia and insulin resistance resulting from antiretroviral therapies may well increase risk of cardiovascular disease among persons demonstrating these abnormalities. The indications for morphologic changes are less clear as only central lipohypertrophy would traditionally be expected to contribute directly to cardiac risk. Recently, a case-control analysis of HIV infected individuals with and without morphologic abnormalities was conducted using control subjects from the Framingham Offspring Study matched on age, gender and body mass index[45]. The study concluded that those with morphologically defined lipodystrophy had significantly increased waist-to-hip ratios, fasting insulin levels and diastolic blood pressure. Those with morphologic abnormalities were also more likely to have impaired glucose tolerance, diabetes, hypertryglyceridemia, and lower high-density lipoprotein cholesterol in comparison to control subjects. Moreover, HIV infected subjects without morphologic symptoms did not differ on the basis of these outcomes, with the exception of high-density lipoprotein cholesterol levels, from HIV-negative controls.

The risk of cardiovascular disease or events directly associated with metabolic and morphologic abnormalities seen in HIV-associated lipodystrophy has also not been subject to thorough epidemiologic investigation. Small numbers of hard outcome events, the sometimes invasive or expensive nature of shorter-term surrogate marker measurement and confounding with traditional life-style and genetic risk factors make investigation difficult. One recent

report from the HIV Outpatient Study found an incidence of myocardial infarction of 1.2/100 person-years among those patients receiving protease inhibitor therapy as compared to a rate of 0.5 among those not on protease inhibitor containing regimens[46]. This association remained after adjustment for other cardiovascular risk factors, however, the majority of events occurred among subjects with known risk factors.

It is generally agreed that long-term prospective population-based data is needed to establish whether theoretical increased risk due to antiretroviral agents *per se*, or their sequelae, actually translate into a greater risk of cardiovascular disease and acute events. Large-scale, multinational studies are currently underway in an attempt to address this issue but until such time as data becomes available focus remains on the management of established cardiovascular risk factors.

There is no clinically proven therapy for the metabolic and morphologic complications associated with lipodystrophy syndrome. Approach to management is currently determined by the presence and severity of symptoms and additional cardiovascular risk factors. Treatment-related factors are also important and include the success of current therapy, remaining therapy options and expected future duration of current therapy. Regimen modification presents a possible solution, however, cessation or switching therapies prior to virologic failure may severely curtail future treatment options.

Traditional lipid and triglyceride lowering agents including statins and fibrates such as gemfibrozil have been used to treat the dyslipidemias associated with HIV antiretroviral therapy. One study has reported this approach to be safe and effective for patients with HIV-associated lipid abnormalities[47]. The use of these agents, particularly some statins in conjunction with protease inhibitor therapies is complicated by the possibility of drug interactions as well as the relative toxicity of the combination of both statins and gemfibrozil.

Recently cerivastatin (Baycol® or Lipobay®) was recalled from markets world-wide due to deaths resulting from rhabdomyolysis, and increased risk of this adverse reaction among persons exposed concurrently to gemfibrozil. As diet and exercise are first line therapies in the general population to lower LDL, increase HDL, decrease triglyceride levels and improve insulin resistance these strategies are also being considered[48]. At this time the effect of dietary and exercise based approaches among persons with HIV-related metabolic changes has not been well examined. One recent study comparing dietary advice alone and dietary advice plus pravastatin among men with high cholesterol on protease containing regimens noted no improvement among the those receiving only dietary advice but a significant reduction in total cholesterol of 1.2mmol/L among those receiving dietary advice plus pravastatin[49].

The management of glucose abnormalities is similarly complex. Insulin sensitizers such as metformin and glitazones have been applied as possible treatments. These agents have been shown to reduce serum glucose and decrease glucose intolerance in HIV infected patients[50-52]. Metformin can mobilize abdominal fat in certain individuals, however it may result in overall weight loss[51,53]. Special consideration should be given when using insulin sensitizers in patients with HIV metabolic syndrome. Metformin has been linked to lactic acidosis in non-HIV-infected subjects and should be used with caution in patients with hyperlactatemia[54]. Moreover, some glitazones share metabolic pathways with PIs, thus increasing the risk of pharmacokinetic interactions.

Fat redistribution continues to be particularly troublesome. The potential of glitazones are being studied for their fat re-distribution effects in this population. For example, in one small study glitazones were shown to produce overall weight gain in individuals with non-HIV lipodystrophy or lipoatrophy with much of this gain in subcutaneous peripheral fat[52]. Meanwhile, some patients are resorting surgical options such as cheek implants and

liposuction or excision for fat accumulation, particularly buffalo hump. Exercise may help to reduce central fat accumulation but tends to achieve overall fat loss thus making peripheral lipoatrophy more pronounced[55]. Resistance training and use of growth hormone and androgens including steroids to increase lean body mass and enhance lipid mobilisation have been used with some success in persons experiencing HIV-associated wasting[56,57]. Small preliminary studies of patients with lipodystrophy, suggest that growth hormone may have a positive effect on buffalo hump, abdominal girth and triglyceride levels, however, improvement of peripheral fat loss has not been noted[58].

In summary, the implication of drugs forming the core of highly active triple regimens in the occurrence of metabolic and morphologic abnormalities is of great concern. While standard medications may prove successful in treating some symptoms the possibility of mounting toxicities and drug interactions as well as adding to an already excessive pill burden reduces the acceptability of currently available therapies. As to possible increased cardiovascular risk, until such time as definitive data becomes available, management currently focuses on factors amenable to patient-mediated lifestyle changes. Large prospective multinational studies, needed to delineate the aetiology of abnormalities and estimate associated risks of morbidity and mortality, are currently underway and should provide some insight into these issues.

2.4 HYPERLACTATEMIA AND LACTIC ACIDOSIS

Elevated lactate levels, symptomatic and asymptomatic hyperlactatemia and acute lactic acidosis have been described in persons with HIV infection. Initial reports were associated with the use of zidovudine but these complications have also been described in association with other nucleoside analogues including didanosine and stavudine[59,60]. The mechanism by

which these toxicities arise is well established. Deoxyribonucleic acid (DNA) polymerase is the enzyme responsible for the replication of mitochondrial DNA. Intracellularly, nucleoside antiviral agents are transformed into nucleotides and incorporated into the viral DNA chain during its composition. This terminates DNA elongation and disrupts viral reproduction. Unfortunately, these compounds can theoretically also function as substrates for other enzymes capable of DNA formation including human DNA polymerase γ. Nucleoside analogues have been shown to inhibit human DNA polymerase γ[61]. Nucleoside mediated inhibition of mitochondiral DNA and subsequent disruption of mitochondiral function has recently been described with subsequent adverse events ranging from hepatic steatosis to lactic acidosis[60,62,63].

Hyperlactatemia is usually defined as venous lactate levels >2.1mmol/L, however, the exact cut-offs are dependent to some extent on the specific test being used and individual laboratories. This condition is often asymptomatic and chronic in nature but may present with symptoms of fatigue, weakness, exercise intolerance, weight loss, nausea, vomiting and abdominal pain[64].

Data from several cohorts indicate hyperlactatemia prevalence rates of 8-21% among patients treated with nucleoside-based therapies, and from 1% to 8% among untreated individuals[65]. Information gained to date suggests that the incidence of any hyperlactatemia is approximately 1.5 to 2.1/100 patient-years of nucleoside exposure. In a French study of 867 patients, 14 cases of symptomatic moderate to severe hyperlactatemia were reported over a two year period for an annual incidence of 0.8% overall, and 1.2% among those treated with stavudine[66]. Despite its relatively common occurrence, little is known regarding the natural history of mild or moderate hyperlactatemia and whether and to what extent this condition is a precursor of lactic acidosis. One recent prospective study of 349 patients found five cases of

moderate symptomatic hyperlactatemia with the majority of the remaining patients experiencing chronic, mild elevations over the 18 months of follow-up[67]. Study patients initiating highly active antiretroviral therapy experienced a rise in lactate levels over the first six to 12 months of therapy and stabilised at mild elevations thereafter. This study also found evidence of increased lactate levels with stavudine therapy but not with any other nucleoside analogue agents or protease inhibitor and non-nucleoside therapies in multivariate analyses.

Currently, mild asymptomatic hyperlactatemia is not known to pose a health risk and the recommended management is to monitor lactate levels and symptoms. In cases of moderate hyperlactatemia, the occurrence of symptoms or concurrent acidosis should generally prompt the cessation of antiretroviral therapy until lactate levels fall below 3mmol/L[68]. In a small study of 17 patients receiving stavudine and with symptomatic hyperlactatemia, stavudine was replaced with abacavir, zidovudine or both drugs. Over a six month follow-up period none of the patients experienced symptom or hyperlactatemia recurrence[69].

Lactic acidosis is defined as arterial pH of < 7.35mmol/L with a venous lactate level >2.0 mmol/L. Lactic acidosis, while less common than hyperlactatemia, tends to be acute and may occur suddenly even after long-term exposure to nucleoside therapy[62]. It is symptomatic and often fatal with a mortality rate of greater than 50%. Lactic acidosis, similar to hyperlactatemia, is most often associated with nucleoside class therapies. To June 30, 1998, the American Food and Drug Association reported 60 cases of lactic acidosis (half of whom died) in patients receiving antiretroviral therapy[70]. All patients were receiving dual nucleoside therapy. A retrospective cohort study estimated incidence at 1.3/1000 person years among those exposed to nucleoside therapy[71]. Current research is focused on identifying clinical and personal risk factors so that those at greater risk can be monitored. Treatment approaches have not been well studied due to small numbers of consecutive patients however, a study of 6

patients utilised a combination of nucleoside analogue cessation, intravenous fluid support, L-carnitine and vitamin B complex with excellent results[68].

While the acute condition is rare, the unknown consequences of prolonged hyperlactatemia and life threatening nature of acidosis make gaining a better understanding of this condition a priority. The implication of backbone nucleoside analogues in their aetiology is also worrisome. If, as has been postulated, mitochondrial dysfunction occurs with increasing exposure to nucleosides, the incidence of these complications is likely to increase under current treatment conditions. With increased lactate screening, enhanced symptom awareness and earlier identification of abnormal lactate levels and lactic acidosis it is hoped that some cases may be prevented. Due to the rarity of severe lactic acidosis, multi-site, international collaborative studies will be necessary to investigate treatment strategies for those with acute lactic acidosis and to delineate the relationship between asymptomatic hyperlactatemia and risk of progression to lactic acidosis.

2.5 BONE DISORDERS

Recent reports suggest that persons using potent antiretroviral therapy may experience increased rates of osteopenia and osteoporosis and appear to be at increased risk for osteonecrosis.

Osteonecrosis, commonly referred to as avascular necrosis of bone, is the death of the cellular elements of bone resulting from circulatory insufficiency. The most frequently affected site is the femoral head (often bilaterally), however, involvement of the femoral condyle, proximal tibia and small bones of the hand have also been reported. Diagnosis is made by magnetic resonance imaging or computed tomography of the affected site. Patients typically present with pain but asymptomatic disease also occurs. In the general population

well established non-traumatic risk factors include gender, prolonged corticosteroid use, alcohol abuse, injection drug use and hyperlipidemia[72].

Sporadic cases of necrosis associated with HIV infection have been reported since the late 1980's with a rise in reported cases over the past five years[73]. In a retrospective case review of 600 HIV infected patients, eight were identified as having avascular necrosis[74]. Recent case series reports and preliminary analyses suggest increased frequency temporally associated with use of antiretroviral therapy[75,76]. However recent case-control studies have failed to identify specific associations between antiretroviral therapy and necrosis, identifying traditional risk factors, including hyperlipidemia, as the probable mechanism[77,78].

Despite these findings the apparent increase in the occurrence of necrosis is suggestive. Hyperlipidemia has been associated with osteonecrosis. It is possible that the occurrence of these abnormalities associated with lipodystrophy or its treatment provides the etiologic link between potent anti-HIV therapies and increased reports of necrosis. Regardless of the cause, ongoing investigation is required as treatment for necrosis is generally limited to surgery for severe or disabling disease. Clearly, the reduction of amenable risk factors to prevent initial or further damage is indicated. Increased reported risk associated with recreational injection drug use is particularly pressing as this group constitutes a growing proportion of those newly diagnosed with HIV in many parts of the world. Perhaps most importantly, physicians should be alert to symptoms consistent with osteonecrosis allowing for more rapid diagnosis and earlier and more conservative management.

Osteopenia and osteoporosis refer to decreased bone mineral density with osteopenia being a less severe precursor of osteoporosis. Decreased bone mineral density generally develops when the rate of new bone formation is slower than the rate of resorption in normal bone turnover. Individuals with osteopenia have a risk of fracture approximately two times

normal and those with osteoporosis four to five times normal. The most common sites of osteoporotic fractures are the hip, forearm and spine.

In healthy populations, increased age, female gender and lower body weight are associated with lower bone mineral density. Specific risk factors for decreased bone mineral density include sedentary lifestyle, smoking, alcohol use, decreased testosterone levels, and genetic factors among others. Prior to the introduction of highly active antiretroviral therapy, HIV infection was not reported to affect bone mineral density. For example, a 1997 study compared bone mineral density in 45 HIV infected men with low CD4 counts (median of 90cells/mm^3) and age-matched HIV negative controls[79]. This study found no differences in total body or hip bone mineral density but did demonstrate a 3% lower density in the lumbar spine among HIV positive participants. More recently several studies have reported higher rates of bone demineralisation and a higher prevalence of osteopenia among persons receiving potent anti-HIV therapeutic regimens[80,81]. In one cross sectional study Tebas and colleagues compared whole body, lumbar spine and femur density among 60 HIV infected protease inhibitor recipients, 35 HIV positive men not on protease inhibitors and 17 healthy male controls[80]. They described osteopenia or osteoporosis among 50% of male subjects using protease based on lumbar spine bone mineral density scores with a twofold risk of lower bone mineral density among those treated with protease inhibitors as compared to controls. A second study of 80 patients with lipodystrophy and long-term protease use found prevalence proportions of osteopenia and osteoporosis of 28% and 9% respectively[81].

It appears that the mechanism of decreased bone mineral density in HIV-infected patients may be due to increased bone turnover. Recently reported results indicate that markers of bone formation and resorption are increased in HIV-infected adults in comparison to healthy control subjects[82]. A further study conducted among 40 HIV-infected children (35

treated with highly active triple therapy and five untreated), and healthy control subjects showed significantly lower spine bone mineral density among treated children than either untreated children or control subjects[83]. This group also found significantly higher levels of markers of bone formation and resorption among those using antiretroviral therapy.

The potential for an association between bone disorders and antiretroviral agents is of great importance given increased survival, ageing of HIV positive treatment cohorts, longer duration of antiretroviral exposure and increasing proportion of both women and injection drug users in the HIV positive population. Available data is, at best, preliminary and it has yet to be determined whether apparent increased rates and the possible association with protease inhibitors will be confirmed in large prospective studies. Moreover, similar to the case of lipodystrophy and cardiovascular risk, it remains to be seen whether these abnormalities will translate to a true increased incidence of fractures in those with HIV disease above that which would be expected given the changing demographics of the patient population.

2.6 MITOCHONDIRAL TOXICITY: A UNIFIED THEORY OF EMERGING ADVERSE DRUG EFFECTS?

Nucleoside mediated inhibition of replication of mitochondrial DNA can lead to the creation of dysfunctional mitochondrial DNA encoded proteins, resulting in mitochondrial DNA dysfunction and depletion[84]. The majority of side effects linked directly to nucleoside analogue use including neuropathy, myopathy, pancreatitis, bone-marrow suppression and lactic acidosis are also clinical manifestations of inherited mitochondrial diseases[85]. This is suggestive of tissue specific nucleoside-related mitochondrial toxicities as a common pathogenic mechanism in the development of various therapy-associated adverse effects.

The link between nucleoside induced mitochondrial toxicities and lactic acidosis has been well established. If, as has been hypothesised, persistently elevated lactate levels seen in hyperlactatemia are due to reduced clearance of lactate in the liver because of hepatocyte mitochondrial dysfunction, features seen in some patients with lactic acidosis such as hepatic steatosis may be explained[67,86,87].

It has also been established that acidemia can increase mineral dissolution[88]. It is hypothesised that increased lactate production is being buffered for urinary excretion by calcium hydroxyapatite released from bone. Among HIV infected patients there is some evidence to suggest that lactic acidemia is associated with low bone mineral density[89]. In addition, several recent reports suggest an association between the morphologic complications related to lipodystrophy and bone mineral density. Mora et al have reported that greater bone mineral loss may occur among children with morphologic lipodystrophy-associated symptoms[83]. A cross sectional observational study of HIV positive men with and without morphologic lipodystrophy-associated abnormalities and HIV-negative controls also reported significantly reduced lumbar spine bone density among those with lipodystrophy and an association between increased visceral abdominal fat and reduced bone density in these subjects[90].

It has also been hypothesised that some lipodystrophy-related symptoms may be induced by tissue specific mitochodrial toxicities[85,91]. The clinical presentation of lipodystrophy indicates that there may be differential effects on adipose tissue varying by location. A generalised theory stems from the fact that lipolysis is an energy dependent process and that central lipocytes have greater lipolytic activity than peripheral lipocytes requiring a greater number of mitohondria per cell. If mitochondrial function is disrupted there may be more

rapid turnover in fat cells in the peripheral areas leading to wasting and relatively slower central lipolysis thereby accounting for centripetal fat accumulation.

Some underlying evidence in support of this theory is based on the striking similarities between HIV-associated lipodystrophy and inherited lipodystrophies. The constellation of peripheral wasting, hypertriglyceridemia, insulin resistance and subcutaneous fat masses on the neck and shoulders seen in the HIV-associated form is mirrored in multiple symmetric lipomatosis-type1 (also known as Madelungs disease)[92]. Mutations and deletions in mitochondrial DNA affecting oxidative phosphorylation which may decrease fat turnover allowing for development of lipomas in these patients have been reported[93]. That highly active antiretroviral therapy generally includes nucleoside analogues and reports of lipodystrophy in patients taking only nucleosides in conjunction with the known mitochondrial toxicity of this class of drugs is suggestive. In one small study, Shikuma and colleagues compared mitochondrial DNA content between HIV infected persons on treatment and experiencing peripheral wasting; those on treatment without symptoms; HIV infected persons not on treatment; and non HIV-infected controls[94]. This study, while underpowered to detect meaningful differences, found evidence of substantially lower levels of mitochondrial DNA in the subcutaneous adipose tissue of those reporting peripheral adipose wasting. A similar study of twelve HIV-infected subjects, seven with, and five without, lipodystrophy and comparison to healthy controls found no evidence of mitochondrial DNA depletion but reported structural abnormalities and mitochondrial DNA deletions to be more common among those with lipodsytrophy symptoms[95].

There also exists substantial contrary evidence or interpretation of reported data which weakens the hypothesis of mitochondrial toxicity (for a review see[96]). For instance, in the above study by Shikuma et al., no evidence of large mitochondiral DNA deletions or

insertions was noted in association with the reported mitochondrial DNA depletion[94]. Moreover, overt disease due to inherited mitochondrial DNA disorders usually occurs in conjunction with severe reductions in mitochondrial DNA to <20% of normal; levels substantially lower than those reported in studies of HIV-related lipoatrophy[94,97,98]. Other recent reports also suggest that patients with metabolic abnormalities on protease inhibitor plus nucleoside therapy have normal fat oxidation[99] and lactate and pyruvate recovery after exercise[100] suggesting normal mitochondrial function.

Further investigation of the mitochondrial theory of pathogenesis will be challenging given the multiple phenotypes associated with mitochondiral toxicities, the likelihood of multifactorial causes and the invasive nature of tissue biopsy which remains the gold standard for establishing tissue-specific mitochondrial DNA depletion.

2.7 SUMMARY

As a result of the enhanced therapeutic efficacy of combination antiretroviral therapy, HIV infected patients are exposed to these agents for extended periods of time. These advances have, however, been associated with the emergence of previously unreported drug-related toxicities including lipodystrophy syndrome, mitochondrial toxicities, and bone disorders. The mechanisms by which these metabolic complications arise, and how they may be related remains uncertain.

The increasing prevalence of adverse effects and the implication of first line therapeutic agents is of grave concern. The growing complexity of antiretroviral regimens, rapid introduction of novel therapies and long-term treatment course indicate that patients will be exposed to a large number of therapies over the course of disease and that novel adverse drug effects will continue to emerge. These events will play an increasingly important role in HIV

management. The direct clinical consequences of adverse drug effects contribute to the already substantial burden of morbidity and mortality among those receiving treatment for HIV disease. Moreover, adverse effects may have implications beyond those associated with direct clinical sequellae through changes in patterns of medication adherence and cessation. There remains a clear mandate, therefore, to identify emerging adverse drug reactions early, investigate their aetiology and gain a comprehensive understanding of their possible impact on treatment patterns and long-term clinical outcomes.

2.10 REFERENCES

1. Michelet C, Arvieux C, Francois C et al. Opportunistic infections occurring during highly active antiretroviral treatment. *AIDS* 1998;12:1815–1822.
2. Hogg RS, Heath KV, Yip B et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *JAMA* 1998;279:450–454.
3. Palella FJ Jr., Delany KM, Moorman AC et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998; 338:853–860.
4. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1 protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998; 351:1881-1883.
5. Miller KD, Jones E, Yanovski JA, Shankar R, Feurstein I, Falloon J. Visceral abdominal-fat accumulation associated with use of indinavir. *Lancet* 1998; 12:F51-F58.
6. Carr A, Samaras K, Burton S et al. A syndrome of peripheral lipodystrophy, hyperlipidemia and insulin resistance due to HIV protease inhibitors. *AIDS* 1998; 12:F51-F58.
7. Thiébaut R, Daucourt V, Malvy D et al. Lipodystrophy, glucose and lipid metabolism dysfunctions, Aquitaine Cohort, 1999. *1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV.* San Diego, California 1999 [Abstract 17].
8. Walli RK, Hefort O, Michl GM et al. Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1 infected patients. *AIDS* 1998; 12:F167-F173.

9. Carr A, Samaras K, Thorisdottir A, et al. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidemia, and diabetes mellitus: a cohort study. *Lancet* 1999; 353:2093-2099.

10. Dube MP, Johnson DL, Currier JS, Leedom JM. Protease inhibitor-associated hyperglycemia. *Lancet* 1997; 350:713-714.

11. Safrin S, Grunfeld C. Fat distribution and metabolic changes in patients with HIV infection. *AIDS* 1999; 13:2493-2505.

12. Heath KV, Hogg RS, Chan KJ, Harris M, Montissori V, O'Shaughnessy MV. Lipodystrophy-associated morphologic, cholesterol and triglyceride abnormalities in a population-based HIV/AIDS treatment database. *AIDS* 2001;15:1-9.

13. Saint-Marc T, Partisani M, Poizot-Martin I et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study. *AIDS* 2000; 14:37-49.

14. Goebel FD, Walli R. ART associated insulin resistance: frequency, potential causes and possible therapeutic interventions. *1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV*. San Diego, California 1999 [abstract 005].

15. Rakotoambinina B, Medioni J, Rabian C, Jubault V, Jais JP, Viard JP. Lipodystrophic syndromes and hyperlipidemia in a cohort of HIV-1-infected patients receiving triple combination antiretroviral therapy with a protease inhibitor. *J Acquir Immune Defic Syndr* 2001; 27:443-449.

16. van der Valk M, Gisolf EH, Reiss P et al on behalf of the Prometheus study group. Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. *AIDS* 2000; 15:847-855.

17. Martinez E, Mocroft A, Garcia-Viejo M et al. Risk of lipodystrophy in HIV-1 infected patients treated with protease inhibitors: a prospective cohort study. *Lancet* 2001; 357:592-598.

18. Goujard C, Boufassa F, Deveau C, Laskri D, Meyer L for the Primo Group. Early occurrence of lipodystrophy in HIV-1-infected patients treated during primary infection. *8th Conference on Retroviruses and Opportunistic Infections.* Chicago, Illinois 2001 [Abstract 403].

19. Striker R, Conlin D, Marz M, Wiviott L. Localized adipose tissue hypertrophy in patients receiving immunodeficiency virus protease inhibitors. *CID* 1998; 27:218-220.

20. Schindler JT, Sponer KM, Deker CF. Buffalo humps associated with protease inhibitors [Letter]. *Ann Intern Med* 1998; 129:164.

21. Virben R, Aquilna C. Indinavir-associated lipodystrophy. *AIDS* 1998; 12:F37-F39.

22. Sullivan AK, Feher MD, Nelson MR, Gazzard BG. Marked hypertriglyceridemia associated with ritonavir therapy [Letter]. *AIDS* 1998; 12:1395-1396.

23. Kotler DP, Rosenbaum K, Wang J, Pierson RN. Studies of body composition and fat distribution in HIV-infected and control subjects. *J Acquir Immun Defic Syndr* 1999; 20:228-237.

24. Thiebaut R, Daucourt V, Mercie P et al. Lipodystrophy, metabolic disorders, and human immunodeficiency virus infection: Aquitaine Cohort, France, 1999. *CID* 2000; 31:1482-1487.

25. Polo R, Verdejo J, Gonzalez-Munoz M et al. Lipodystrophy related to NRT inhibitors in HAART therapy. *39th Interscience Conference on Antimicrobial Agents and Chemotherapy.* San Francisco, California 1999 [Abstract 1302].

26. Carr A, Samaras K, Thorisdottir A et al. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidemia, and diabetes mellitus: a cohort study. *Lancet* 1999; 353:2093-2099.

27. Saint-Marc T, Partisani M, Poizot-Martin I et al. A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. *AIDS* 1999; 13:1659-1667.

28. BognerJR, Vielhauer V, Beckman RA et al. Stavudine versus zidovudine and the development of lipodsytrophy. *J Acquir Immun Defic Syndr* 2001; 27:237-244.

29. Lichtenstein KA, Ward DJ, Moorman AC et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS* 2001; 15:1389-1398.

30. Mallal SA, John M, Moore CB, James IR, McKinnon EJ. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS* 2000; 14:1309-1316.

31. Paparizos VA, Kyriakis KP, Botsis C, Papastamopoulos V, Hadjivassiliou M, Stavrianeas NG. Protease inhibitor therapy-associated lipodystrophy, hypertriglyceridaemia and diabetes mellitus [Letter]. *AIDS* 2000; 14:903-905.

32. Boufassa F, Dulioust A, Lascaux AS et al. Lipodystrophy in 685 hiv-1-treated patients: influence of antiretroviral treatment and immunovirological response. *HIV Clin Trials* 2001; 2:339-345.

33. Knopp RH. Drug treatment of lipid disorders. *N Engl J Med* 1999; 341:498-511.

34. Anderson, DW, Virmani R. Emerging patterns of heart disease in HIV infection. *Human Pathology* 1990; 21:253-259.

35. Patel RC, Frishman WH. Cardiac involvement in HIV infection. *Medical Clinics of North America* 1997; 80:1493-1512.

36. Baum MK, Shor-Posner G, Lai S et al. High risk of HIV-related mortality is associated with selenium deficiency. *J Acquir Immun Defic Syndr* 1997; 15:370-374.

37. Constans J, Pellegrin JL, Peuchant E et al. Plasma lipids in HIV infected patients: a prospective study in 95 patients. *Eur J Clin Invest* 1994; 24:416-420.

38. Tabib A, Leroux C, Mornex JF, Loire R. Accelerated coronoary atheroscelrosis and arteriosclerosis in young human-immunodeficiency-virus-positive patients. *Coron Artery Dis* 2000; 11:41-46.

39. Constans J, Marchand JM, Conri C et al. Asymptomatic atherosclerosis in HIV-positive patients: a case-control ultrasound study. *Ann Med* 1995; 27:683-685.

40. Henry K, Melroe H, Huebsch J, et al. Severe premature coronary artery disease with protease inhibitors. *Lancet* 1998; 351:1328.

41. Maggi P, Serio G, Epifani G et al. Premature lesions of the carotid vessel in HIV-1-infected patients treated with protease inhibitors. *AIDS* 2000; 14:123-128.

42. Depairon M, Chessex S, Sudre P et al. Premature atherosclerosis in HIV-infected individuals- focus on protease inhibitor therapy. *AIDS* 2001; 15:329-334.

43. Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986; 256:2823-2828.

44. Howard G, Bergman R, Wagenknecht LE et al. Ability of alternative indices of insulin sensitivity to predict cardiovascular risk: comparison with the "minimal model". Insulin Resistance Atherosclerosis Study (IRAS) Investigators. *Ann Epidemiol* 1998; 8:358-369.

45. Hadigan C, Meigs JB, Corcoran C et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *CID* 2001; 32:130-139.

46. Holmberg S, Moorman AC, Tong T et al. Protease inhibitor drug use and myocardial infarction in ambulatory HIV-infected patients. *39th Annual Meeting of the Infectious Diseases Society of America*. San Francisco, California 2001 [abstract 18].

47. Henry K, Melroe H, Heubesch J et al. Atrovastatin and gemfibrozil for protease inhibitor-related lipid abnormalities. *Lancet* 1998; 352:1031-1032.

48. Ballantyne CM. Current thinking in lipid lowering. *Am J Med* 1998; 104:33S-41S.

49. Moyle GJ, Lloyd M, Reynolds B, Baldwin C, Mandalia S, Gazzard BG. Dietary advice with or without pravastatin for the management of hypercholesterolaemia associated with protease inhibitor therapy. *AIDS* 2001; 15:1503-1508.

50. Walli RK, Michl GM, Rogner JR et al. effects on the PPAR-activator troglitazone on protease associated peripheral insulin resistance. *6th Conference on Retroviruses and Opportunistic Infections*, Chicago, Illinois 1999 [abstract 666].

51. Saint-Marc T, Touraine JL. Effects of metformin on insulin resistance and central adiposity in patients receiving effective protease inhibitor(PI). *6th Conference on Retroviruses and Opportunistic Infections*. Chicago, Illinois 1999 [abstract 608].

52. Arioglu E, Duncan-Morin J, Sebring N et al. Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes. *Ann Intern Med* 2000; 133:263-274.

53. Hadigan C, Corcoran C, Basgoz N, Davis B, Sax P, Grinspoon S. Metformin in the treatment of HIV lipodystrophy syndrome; a randomized controlled trial. *JAMA* 2000; 284:472-477.

54. Derfronzo RA. Parmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999; 131:281-303.

55. Roubenoff R, Weiss L, McDermott A et al. A pilot study of exercise training to reduce trunk fat in adults with HIV-associated fat redistribution. *AIDS* 1999; 13:1373-1375.

56. Strawford A, Barbieri T, van Loan M et al. Resistance exercise and supraphysiologic androgen therapy in eugonadal men with HIV-related weight loss: a randomized controlled trial. *JAMA* 1999; 281:1282-1290.

57. Schambelan M, Mulligan K, Grunfeld C, et al. Recombinant human growth hormone in patients with HIV-associated wasting. *Ann Intern Med* 1996; 125:873-882.

58. Torres R, Unger K. The effect of recombinant human growth hormone on protease inhibitor-associated fat maldistribution syndrome. *6th Conference on Retroviruses and Opportunistic Infections*. Chicago, Illinois 1999 [Abstract 675].

59. Chattha G, Arieff AI, Cummings C, Tierney LM. Lactic acidosis complicating the acquired immunodeficiency syndrome. *Ann Intern Med* 1993; 11:37-39.

60. Bissuel F, Bruneel F, habersetzer F et al. Fulminant hepatitis with severe lactic acidosis in HIV-infected patients on didanosine therapy. *J Intern Med* 1994; 235:367-371.

61. Lewis W, Dalakis MC. Mitochondiral toxicity of antiviral drugs. *Nature Med* 1995; 1:417-421.

62. Sundar K, Suarez M, Banogon PE, Shapiro JP. Zidovudine-induced fatal lactic acidosis and hepatic failure in patients with acquired immunodeficiency syndrome: Report of two patients and review of the literature. *Crit Care Med* 1997; 25:1425-1430.

63. Lenzo NP, Garas BA, French MA. Hepatic steatosis and lactic acidosis associated with stavudine treatment in an HIV patient: a case report. *AIDS* 1997; 11:1294-1296.

64. Carr A, Miller J, Law M, Cooper DA. A syndrome of lipoatrophy, lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS* 2000; 14:F25-F32.

65. Masur H. Metabolic complications in HIV disease: lactemia and bone disease. *International AIDS Society USA: Topics in HIV Medicine* 2001; 9:8-11.

66. Gerard Y, Maulin L, Yazdanpanah Y et al. Symptomatic hyperlactaemia: an emerging complication of antiretroviral therapy. *AIDS* 2000; 14:2723-2730.

67. John M, Moore CB, James IR et al. Chronic hyperlactatemia in HIV-infected patients taking antiretroviral therapy. *AIDS* 2001; 15:717-723.

68. Brinkman K, Vrouenraets SME, Kauffman R et al. The treatment of nucleoside reverse transcriptase inhibitor-induced lactic acidosis. *AIDS* 2000; 14:2801-2802.

69. Lonergan JT, Havlir D, barber E, Mathews WC. Incidence and outcome of hyperlactatemia associated with clinical manifestations in HIV-infected adults receiving NRTI-containing regimens. *8th Conference on Retroviruses and opportunistic Infections*. Chicago, Illinois 2001 [abstract 9].

70. Boxwell DE, Styrt BA. Lactic acidosis (LA) in patients receiving nucleoside reverse transcriptase inhibitors (NRTIs). *39th International Conference on Antimicrobial Agents and Chemotherapy*. San Francisco, California 1999 [Abstract 1284].

71. Fortgang I, Belitsos P, Chaisson R, Moore R. Hepatomegaly and steatosis in HIV-infected patients receiving nucleoside analog antiretroviral therapy. *Am J Gastroenterology* 1995; 90:1433-1436.

72. Steinberg ME. Avascular necrosis: diagnosis, staging, and management. *J Musculoskeletal Med* 1997; 14:13-25.

73. Monier P, Mckown, Bronze MS. Osteonecrosis complicating highly active antiretroviral therapy in patients with human immunodeficiency virus. *CID* 2000; 31:1488-1492.

74. Timpone J, Fluhme D, Nascone J, evans B, Kumar P. Avascular necrosis in HIV-positive patients. A potential link to protease inhibitors. *6th Conference on Retroviruses and Opportunistic Infections*. Chicago, Illinois 1999 [abstract 680].

75. Roudier L, Viard J. Osteonecrosis of the hip, lipodystrophy and antiretroviral treatment [Letter]. *AIDS* 2000; 14:2056.

76. Meyer D, Behrens G, Schmidt RE, Stoll M. Osteonecrosis of the femoral head in patients receiving HIV protease inhibitors [Letter]. *AIDS* 1999; 13:1147-1148.

77. Scribner AN, Troia-Cancio PV, Cox BA et al. Osteonecrosis in HIV: A case-control study. *J Acquir Immune Defic Syndr* 2000; 25:19-25.

78. Glesby M, Vaamonde C. Case-control study of avascular necrosis in HIV-infected patients. *Antiretroviral Therapy* 2000; 5(suppl 5):21.

79. Paton NIJ, Macallan DC, Griffin GE, Pazianas M. Bone mineral density in patients with human immunodeficiency virus infection. *Calcified Tissue International* 1997; 61:30-32.

80. Tebas P, Powderly WG, Claxton S, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. *AIDS* 2000; 14:F63-F67.

81. Hoy J, Hudson J, Law M, Cooper DA. Osteopenia in a randomized, multicenter study of protease inhibitor (PI) substitution in patients with the lipodystrophy syndrome and well-controlled HIV viremia. *7th Conference on Retroviruses and Opportunistic Infections.* San Francisco, California 2000 [Abstract 208].

82. Tebas P, Yarasheski KE, Whyte M, claxton S, DeMarco D, Powderly WG. Serum and urine markers of bone mineral metabolism in HIV-infected patients taking protease

inhibitor containing potent antiretroviral therapy. *Second International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV*. Toronto, Ontario 2000 [Abstract 029].

83. Mora S, Sala N, Bricalli D, Zuin G, Chiumello G, Vigano A. Bone mineral loss through increased bone turnover in HIV-infected children treated with highly active antiretroviral therapy. *AIDS* 2001; 15:1823-1829.

84. Chen C, Vazquez-Padua M, Cheng Y. Effect of anti-human immunodeficiency virus nucleoside analogues on mitochondrial DNA and its implications for delayed toxicity. *Molecular Pharmacology* 1991; 39:625-28.

85. Brinkman K, ter Hofstede HJM, Burger DM, Smeitink JA, Koopmans PP. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as a common pathway. *AIDS* 1998; 12:1735-1744.

86. Lonergan JT, Behling C, Pfander H et al. Hyperlactatemia and hepatic abnormalities in 10 HIV-infected patients receiving nucleoside combination regimens. *CID* 2000; 31:162-166.

87. Brinkman K. editorial response: hyperlactatemia and hepatic steatosis as features of mitochondrial toxicity of nucleoside analogue reverse transcriptase inhibitors. *CID* 2000; 31:167-169.

88. Ginspoon SK, Baum HBA, Kim V, Coggins C, Klibanski A. Decreased bone formation and increased mineral dissolution during acute fasting in young women. *J Endocrinol Metab* 1995; 80:3628-3633.

89. Carr A, Miller J, Eisman JA, Cooper DA. Osteopenia in HIV infected men: association with asymptomatic lactic acidemia and lower weight pre-antiretroviral therapy. *AIDS* 2001; 15:703-709.

90. Huang JS, Rietschel P, Hadigan CM, Rosenthal DI, Grinspoon S. Increased abdominal visceral fat is associated with reduced bone density in HIV-infected men with lipodystrophy. *AIDS* 2001; 15:975-982.

91. Brinkman K, Smeitink JA, Romijin JA, Reiss P. Mitochondiral toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. *Lancet* 1999; 354:1112-1115.

92. Klopstock T, Naumann M, Seibel P, Shalke B, Reiners K, Reichmann H. Mitochondrial DNA mutations in multiple symmetric lipomatosis. *Mol Cell Biochem* 1997; 174:271-275.

93. Becker-Wegrerich P, Steuber M, Olbrisch R, Ruzicka T, Auburger G, Hofhaus G. Defects of mitochondiral respiratory chain in multiple symmetric lipomatosis. *Arch Dermatol Res* 1998; 290:652-55.

94. Shikuma CM, Ningjie H, Milne C et al. Mitochondiral DNA decrease in subcutaneous adipose tissue of HIV-infected individuals with peripheral lipoatrophy. *AIDS* 2001; 15:1801-1809.

95. Zaera MG, Miro O, Pedrol E et al. Mitochondrial involvement in antiretroviral therapy-related lipodystrophy. AIDS 2001; 15:1643-1651.

96. Moyle G. Mitochondrial toxicity hypothesis for lipoatrophy: a refutation[letter]. AIDS 2001; 15:413-415.

97. Walker UA, Bickel M, Lutke-Volksbeck SI et al. Decrease of mitochondrial DNA content in adipose tissue of HIV-1 infected patients treated with NRTIs. *2nd International Workshop on Adverse Drug Interactions and Lipodystrophy.* Toronto, Ontario 2000 [Abstract 06].

98. Chinnery PF, Howell N, Andrews RM et al. Clinical mitochondiral genetics. *J Med Genet* 1999; 36:425-436.

99. Ware LJ, Morelese J, Burdge G et al. Differences in postprandial lipid metabolism in patients with PI-associated and NRTI associated lipodystrophy. *2nd International Workshop on Adverse Drug Interactions and Lipodystrophy.* Toronto, Ontario 2000 [Abstract 020].

100. Roge BT, Calbert J, Moller K et al. Mitochondrial function in HIV-infected patients with lipodystrophy during exercise and recovery. *2nd International Workshop on Adverse Drug Interactions and Lipodystrophy.* Toronto, Ontario 2000 [Abstract P22].

101. Bassetti S, Battegay M, Furrer H et al. Why is highly active antiretroviral therapy (HAART) not prescribed or discontinued? Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr* 1999; 21:114-119.

102. Harrington M, Carpenter CCJ. Hit HIV-1 hard but only when necessary. *Lancet* 2000; 355:2147-2152.

103. Aversa1 S, Kimberlin C. Psychosocial aspects of antiretroviral medication use among HIV patients. *Patient Educ Couns* 1996; 29:207-219.

104. Aversa2 S, Kimberlin C, Segal R. The medication attribution scale: perceived effects of antiretrovirals and quality of life. *Qual Life Res* 1998; 7:205-214.

105. Morris LS, Schulz RM. Medication compliance: the patient's perspective. *Clin Ther* 1993; 15:593-606.

106. Burgos M, Revsin NS, VilasA, Fontan L. Obstacles in treatment adherence: patient reasons. *International Conference on AIDS.* Geneva, Switzerland 1998 [abstract 32400].

107. Vanhove GF, Schapiro JM, Winters MA, Merigan TC, Blaschke TF. Patient's compliance and drug failure in protease inhibitor monotherapy. *JAMA* 1999; 276:1955-1956.

108. Bangsberg DR, Hecht FM, Charlebois ED et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS* 2000; 14:357-366.

CHAPTER 3

STUDY SETTING, OVERVIEW OF METHODS AND LIMITATIONS

3.1 STUDY SETTING- THE BRITISH COLUMBIA CENTRE FOR EXCELLENCE IN HIV/AIDS

The British Columbia Centre for Excellence in HIV/AIDS (the Centre), housed at St. Paul's Hospital in Vancouver, British Columbia, is a working group dedicated to HIV disease research. The Centre provides education and training to health care professionals, distributes drugs to those with HIV/AIDS, and is actively engaged in furthering our understanding of HIV disease through clinical trials, epidemiological studies and laboratory research as well as direct clinical involvement in patient care.

The British Columbia HIV/AIDS Drug Treatment Program is the single largest undertaking of the Centre. The primary goals of the program are to ensure that British Columbians living with HIV/AIDS have access at no charge to the drugs used to treat HIV infection, to provide physicians with state-of-the-art treatment guidelines and to make projections for the coming years. As of January 1, 2002, some 5866 persons have ever received treatment through the treatment program and some 2561 are actively enrolled.

With many individuals receiving treatment in British Columbia, the large number of persons continuing to become infected each year, an injection drug using population numbering in the thousands and a mandate to continue to provide antiretroviral therapy to all eligible persons, the Centre and its drug treatment program offer a unique research setting and source of data.

In the following section we turn to a discussion of the methods by which the data collected through the Centre can be used to meet the study objectives outlined in Chapter 1.

3.2 Data requirements and methodologic approaches

It is important that factors of methodological validity, cost effectiveness and possible future research plans be considered in the selection of methodological approaches. To meet the objectives of this study we require information about: a) the presence or absence of symptoms of lipodystrophy at specified points in time; b) physician responses to the occurrence of adverse drug effects; c) patient responses to adverse drug effects and; d) complete data regarding possible predictors of the outcomes of interest or confounders including socio-demographic characteristics, treatment history, current treatment regimens, and clinical values.

In the absence of systematic surveillance for adverse drug effects, options include direct elicitation of information from physicians, and/or from patients, and use of existing databases. The combination of direct solicitation from patients in conjunction with existing databases is most appropriate for this study. Physicians were not selected as a source of data for several reasons. Firstly, information regarding a large number of subjects is required to establish population-based estimates of incidence and prevalence and to allow for sub-group analyses in etiologic investigations. In British Columbia, physicians specialising in HIV/AIDS provide care to the vast number of patients receiving treatment and may each have up to several hundred patients. Data collection would place excessive burden on these HIV care providers. Secondly, patients may not convey or physicians may not remember the occurrence of many adverse effects. Thirdly, patients are unlikely to disclose adjustments to therapy made without medical sanction to their physician. It was also believed that giving the option of response directly to patients was superior in terms of ethical considerations. Lastly, this approach was more logistically feasible as annual patient questionnaires are currently part of the drug treatment program mandate (see following section).

The second primary methodologic issue is how and in what format data should be collected. For the purposes of this study, patient self-administered survey data was felt to be most appropriate. The Centre holds that the privacy of persons living with HIV/AIDS is of the utmost importance. For this reason patients included in the drug treatment program can not be directly contacted by the Centre or any research organisation or individual. All correspondence must be directed through the primary HIV care giver and provided to the patients under the usual conditions of physician-patient confidentiality. Therefore, face-to-face questionnaires administered by researchers are not feasible. Moreover, these methods or survey administration by primary care giver can be both costly and excessively time consuming given the number of subjects. Survey administration by the primary care physician also carries the same problems of disclosure associated with direct elicitation of data from physicians. Due to the sensitive nature of questions it is imperative that confidentiality of respondents be assured. Self-administered surveys preserve the confidentiality of respondents thereby enhancing participation and encouraging frank responses. Written questionnaires also lend themselves well to the collection of longitudinal data.

While the most appropriate method for the present study, gathering data directly from patients and the use of self-reported written questionnaires have important limitations. These are described in section 5 of this chapter.

3.3 DATA SOURCES

This study used three data sources: patient self report through voluntary responses to annual treatment program participant surveys; the drug treatment program patient database; and laboratory records. For each sub-study included in this project, the required data from each data source was merged to form a single data-set as the platform for subsequent analyses.

3.3.i Drug treatment program patient database

All persons in British Columbia who are eligible to receive antiretroviral therapy and wish to do so at no cost are automatically entered into the treatment program database when first prescribed antiretroviral therapy by a physician in British Columbia. Data recorded at entry includes age, gender and whether the patient has been diagnosed as having AIDS. Each individual is given a treatment program identification code and entered into a non-nominal database by this code. At baseline and each follow-up, typically occurring every two to three months, the database also records each medication prescribed. In addition, first occurrences of AIDS defining events for those AIDS-free at entry are submitted by the treating physician at the time of diagnosis. In this way a complete prospective record of antiretroviral treatment history and disease progression is maintained.

3.3.ii Annual drug treatment program participant survey

In addition to the above information, at baseline and at each year thereafter on the anniversary of their initial enrolment until death or the cessation of therapy, participants are asked to voluntarily complete a detailed questionnaire. Surveys are distributed to patients through their physician and returned to the centre directly by the respondent to ensure confidentiality. Surveys are updated each year to reflect changing data needs. Typically, each year, some 40% of all participants respond to these annual surveys.

These annual questionnaires for the years 1998/99, 1999/00 and 2000/01 are provided in Appendices 1 through 3. Briefly, data collection includes: socio-demographic profiles, information on quality of life and depression, current health status, the presence of concomitant disease, use of complementary alternative therapies and risk group information.

Since 1998/99 surveys have also asked about the occurrence of more than 40 possible adverse drug effects including symptoms associated with lipoystrophy syndrome.

For the purposes of the final sub-study, further amendments were made to the 200/01 questionnaire (see Question 39, Survey 2000/2001, Appendix 3). First a variable was added to assess the self-reported categorisation of each symptom as mild, moderate or severe. Second, adverse effects were classified through a consensus process by tertiary care HIV care providers as either subjective or objective. Subjective symptoms were those that physicians felt would not be identifiable through clinical examination or medical tests, relying primarily on patient report for identification. Each was then classified as clinically requiring or not requiring physician action. For an adverse effect to require action it must pose some direct threat to patient health. Clearly whether action is taken and in what form may depend on the severity or duration of the event. Generally action was categorised as waiting and monitoring, applying or recommending treatment to ameliorate symptoms, investigating symptoms for cause, changing antiretroviral therapy or cessation of therapy. This process yielded 4 sub-groups of adverse effects: subjective/action (group A); subjective/no action (group B); objective/action(group C) and; objective/no action (group D).

For each category of symptoms A through D, two questions were posed. The first asked what the patient's physician did or recommended in response to symptoms in that group and the second asked patients to describe what they, themselves actually did in response to the same symptoms.

3.3. iii Laboratory linkage

At each clinical follow-up, HIV care providers are advised to order CD4 cell count and plasma viral load assessments for each patient in accordance with care guidelines and patient needs, typically several times each year. The centre accesses this data directly from

laboratories for all patients who provide their consent to do so including lipid profiles and glucose tolerance tests for patients for whom these tests are ordered.

The following section outlines methodology specific to each of the studies undertaken to meet thesis objectives.

3.4 OVERVIEW OF STUDY SAMPLE SELECTION

Recall that each sub-study comprises a chapter of this document. While the specific methods used for each sub-study are described in the methods section of each of these manuscript chapters, an overview of the various samples of patients eligible for each study is provided below. In addition a schematic overview is given in Appendix

In any given year the Centre's drug treatment program has approximately 3,000 active participants currently on antiretroviral therapy. The drug treatment program observational cohort is dynamic, with individuals entering treatment as they become eligible, or present for treatment, and current participants being lost from the program as they move out of the province, die or stop therapy. Due to the voluntary nature of the participant survey, respondents also represent a dynamic cohort with some individuals completing surveys every year, others rarely responding, and others completing the survey in some years and not in others.

The initial study regarding prevalence of lipodystrophy associated symptoms and preliminary etiologic investigation (Chapter 4) is based on a cross sectional analysis of all treatment program participants who returned an annual survey over the October 1998 through September 1999, period. To be eligible participants had to have complete data for all variables of interest and have plasma viral load and CD4 determinations in the six months prior to survey completion in conjunction with consent to retrieve these laboratory values.

For the first incidence study (Chapter 5) the sample included all individuals from the prevalence study sample who completed a second successive annual survey over the period October 1, 1999 to December 31, 2000, i.e., completed two surveys approximately one year apart. Individuals reporting no instance of each specific symptom in the first survey and reporting that symptom in the successive survey were considered incident cases for that symptom. The denominator for each calculation was defined as the total number of individuals at risk for that event i.e., those without the symptom of interest at the time of the first survey. The cumulative incidence of each specific subjective symptom or class of symptom including HIV-associated lipodystrophy related morphological changes was estimated as: λ= r in one year interval / d; with 95%CI =$\lambda \pm 1.96$ (se). Where: λ = incidence, r = incident cases, d = individuals at risk, and standard error = $\sqrt{r}/pm$.

The third study comprises a brief report regarding incidence of symptoms among previously therapy naïve individuals initiating highly active antiretroviral therapy (Chapter 6). Study subjects included all those who had initiated antiretroviral therapy between October 1998 and May 2001 and provided completed data regarding the occurrence of adverse drug effects at least three months and no more than twenty-four months after therapy initiation.

The final sub-study (Chapter 7), again, utilizes a cross sectional design. The sample included all those who responded to the 200/01 survey over the first 10 months of its availability; December 2000 through September 2001. Again, subjects were required to have complete data for all variables of interest.

3.5 STUDY LIMITATIONS

It is important to keep in mind as we review the results of the sub-studies included in this investigation that the study as a whole is subject to several important limitations.

3.5.i External Validity

Drug treatment program survey respondents in any one study may not be representative of all treatment program participants. Due to the voluntary nature of the survey used non-response is an obvious problem and can not be ameliorated. Response rates to mail surveys are often low, particularly among subjects who are coping with debilitating illness. In the drug treatment program annual response rates are generally in the range of 30 to 45%. The absolute number or proportion of respondents, while important in terms of the adequacy of the sample size for statistical analysis, is not as pivotal a concern as the prospect of responder bias which may be a threat to internal validity.

3.5.ii Response Bias

If responders and non-responders are systematically different on the basis of variables which are linked to the outcome variables of interest then bias may occur. One can only describe such differences and speculate as to their impact on the findings. To these ends, those comprising the various study samples were compared to excluded treatment program participants on the basis of age, gender, plasma viral load, CD4, AIDS status, history of antirteroviral therapy and current therapy.

3.5.iii Validity of survey responses: misclassification, under- and over-reporting and loss to follow-up

The survey question regarding side effects asks whether individuals have experienced various symptoms as a result of their current drug regimen. If symptoms are permanent or long lasting, as the morphologic symptoms associated with lipodystrophy appear to be, individuals suffering these adverse events may not report them if subjects believe them to be a result of prior rather than current therapy. Lipid abnormalities may be under-reported if subjects are not told by their physician that they have higher than normal cholesterol or

triglyceride levels. Conversely, the reliance on self report may overestimate the occurrence of morphologic abnormalities. Loss of muscle mass and increased abdominal girth are commonly associated with normal ageing, particularly among men. General AIDS-associated wasting may also confound findings regarding peripheral wasting.

A further problem is a form of "product recognition" bias. As patients become increasingly aware of lipodystrophy-syndrome over time, reporting of symptoms may become more common. More importantly, if subjects attribute symptoms to particular medications, those using regimens including the suspected agent may be more likely to report symptoms- a form of exposure suspicion bias. This would bias results towards a positive association between symptoms and the suspected agent(s).

Lastly, if those experiencing symptoms decide to abandon all therapy as a direct result of experiencing symptoms they are unlikely to respond to annual surveys as they may no longer consider themselves "active" drug treatment program members. This may result in overall under-reporting and underestimation of prevalence and incidence as those with symptoms are preferentially lost to follow-up. Since lost subjects can not be contacted there is little one can do to ascertain the extent to which this may occur, although these subjects are incorporated into baseline comparisons of respondents and non-respondents.

3.5.iv Temporality

The greatest challenge to the findings reported here is the inability to establish true temporality in regards to particular antiretroviral regimens and the occurrence of symptoms. Symptom reports are elicited on an annual basis and the timing of symptom onset is unknown. Therefore, it is possible that individuals may have changed therapy due to lipodystrophy-related symptoms or to have changed therapy several times between symptom onset and

reporting. Many studies to date, however, have relied on retrospective data collection and are subject to both diagnostic suspicion and exposure suspicion as well as recall biases.

An attempt has been made to address the issue of temporality to some extent by including, in all analyses of prevalence and incidence (Chapters 4 and 5 and 6), all available treatment data with particular reference to current therapy use, recent therapy and long term treatment history and by detailed examination of antiretroviral agent by class and agent.

In addition, in Chapter 6, among treatment naïve subjects, a sub analysis is performed which includes only naïve patients who maintained their initial treatment regimen throughout the study follow-up period.

3.6 Summary

The following four studies attempt to provide and overview of the epidemiology and consequences of lipodystrophy-associated symptoms among persons being treated with antiretroviral therapies in British Columbia. Data is derived from British Columbia's HIV/AIDS Drug Treatment Program database, annual surveys of treatment program participants and available laboratory records, all of which are overseen by the British Columbia Centre for Excellence in HIV/AIDS. Various sampling strategies have been used depending upon the study outcomes of interest and eligibility requirements. It is important to recognise limitations in the study database and methodologic approaches and possible sources of bias in the review and interpretation of the study findings.

CHAPTER 4

PREVALENCE OF MORPHOLOGIC AND LIPID ABNORMALITIES AMONG PERSONS TREATED FOR HIV DISEASE IN BRITISH COLUMBIA

4.1 FORWARD

This chapter has been published as: "Lipodystrophy-Associated Morphologic, Cholesterol and Triglyceride Abnormalities In a Population-Based HIV/AIDS Treatment Database." In: *AIDS* 2001; 15:1-9. The study was initiated April of 1999 and completed in June of 2000. Co-authors of the study include Keith Chan, committee members and Drs. Valentino Montessori and Marianne Harris, two clinicians involved in clinical research and patient care. Statements describing the role of primary co-authors can be found in Appendix 5 and transfer of copyright from AIDS in Appendix 6.

4.2 INTRODUCTION

In an era of highly active antiretroviral therapy, persons with HIV/AIDS are utilising novel therapies in ever increasingly complex regimens. Consequently, they may experience significant repression of HIV replication translating to increased survival times[1,2]. Coincident with these advances, reports have identified the emergence of morphologic abnormalities involving re-distributions in body fat (lipodystrophy) characterised by peripheral fat wasting, increased visceral abdominal fat, breast hypertrophy in women, and enlargement of the dorso-cervical fat pad (buffalo hump)[3-10]. Metabolic abnormalities have also been reported including hypercholesterolimia and hypertryglyceridemia[10,11]. With abnormalities appearing in constellations, it appears that these symptoms represent a syndrome of HIV-associated lipodystrophy[5,10-12].

Reports estimating the prevalence of symptoms or lipodystrophy syndrome vary widely, with abnormalities occurring among 18% to 70% of patients exposed to protease inhibitor containing regimens[13-17]. While initial identification was coincident with the wide spread use of protease inclusive therapy, the aetiology of these abnormalities remains obscure. Several reports indicate a significant increase in patient identified morphological changes associated with protease inhibitor use[18-20], and/or identify specific proteases associated with various morphologic[5,21] and metabolic[22-27] abnormalities. Others have concluded that these abnormalities are not associated with type of therapy or may occur in the absence of protease inhibitors[3,26-30]. Several recent reports indicate that these symptoms may be a function of nucleoside analogue reverse transcriptase inhibitor therapy rather than, or in addition to, protease use[31-33].

In-depth studies of select patient groups can contribute to our understanding of the natural history of symptoms and help to frame etiologic investigation. Small clinical samples may allow for assessment of validity and reliability of outcome measures and extensive data collection through clinical evaluation based on standardised protocol.

Such studies however, have inherent limitations. Clinical follow-up is costly and time consuming for both clinicians and subjects making large scale or long term commitment economically and logistically unfeasible. Smaller studies are also often hampered by lack of statistical power. Meta-analysis is often inapplicable due to variations in outcomes assessed, measurement tools, information regarding confounders and sample populations. More importantly non-random sample selection of clinical study participants may make study results susceptible to biases which can be difficult to identify or ameliorate.

Large, population-based observational data bases can make a unique contribution to our understanding of emerging patterns of adverse events. At their best, such databases include

large samples or entire populations of interest. Due to the large number of subjects followed issues of sample size are negated and sub samples are amenable to hypothesis generating analyses. Broad-based observational studies also include a wide spectrum of individuals without the constraints of age, gender, disease stage and therapeutic regimen often imposed or occurring by chance or selection processes in clinical studies; thereby reducing risk of associated biases. Lastly, findings of observational studies are useful in fulfilling additional criteria for causal inference establishing consistency in comparison to studies of differing design and coherence with results of studies using similar but based on other populations.

In this study we report on estimates of prevalence and correlates of self-reported lipodystrophy and constituent symptoms within a large, population-based cohort of persons treated with antiretroviral therapies.

4.3 METHODS

The HIV/AIDS drug treatment program of British Columbia, Canada provides antiretroviral medications free of charge to all eligible province residents. To receive antiretroviral therapies at no cost individuals must be confirmed HIV positive, have a CD4 count of ≤ 500 cells/mm^3 and/or plasma viral load of $> 5{,}000$ copies/ml as is commensurate with current recommendations[34,35].

Individuals are automatically entered into the treatment program when first prescribed any antiretroviral agent. At program entry and subsequent physician visits the participant's complete history (if any) of antiretroviral use, CD4 count, plasma viral load, and disease stage are recorded. Typically patients are followed-up at three-month intervals at which time prescriptions are renewed or altered based on treatment success and other clinical factors. For all patients a complete prospective record of antiretroviral therapy prescription is thus

maintained including the exact medications prescribed, date of each prescription and actual prescription fill dates.

At treatment program entry and at each annual anniversary participants are requested to voluntarily provide additional information through a self-administered mailed questionnaire. Data collection includes information about socio-demographic characteristics, general health, the use of alternative therapies and detailed information regarding established therapy-related side-effects as well as the occurrence of health problems or symptoms which may be attributed to HIV medications. Since 1998, these have included instances of symptoms considered to be key possible identifiers of lipodystrophy syndrome[36], specifically: fat wasting in the face, arms or legs; abdominal weight gain or breast enlargement; buffalo hump; increased triglycerides and increased total cholesterol.

Information regarding abnormalities is reliant on self report, however, patients were directed to report metabolic disturbances only if they had been confirmed by their physician. In British Columbia, provincial guidelines for the treatment of HIV are distributed to all physicians who have prescribed antiretrovirals and recommend fasting laboratory tests for total cholesterol and triglyceride levels as standard care, however, the actual fasting state at the time of tests can not be verified[35]. Local laboratory standards define the upper limit of normal for triglycerides and total cholesterol as 2.3 mg/dL and 5.2 mg/dL respectively.

As no standard definition of lipodystrophy exists, for the purposes of this analysis patients were deemed to have probable lipodystrophy if they had at least one of; peripheral wasting, weight gain confined to the abdomen or breast enlargement in women, buffalo hump and/or; both of increased triglycerides and increased total cholesterol. Instances of high blood pressure, type 2 diabetes mellitus, peripheral neuropathy, sexual dysfunction (men only), menstrual changes, loss of hair, dry skin, high blood pressure or ingrown toenail were

recorded but because of their non-specific association with lipodystrophy were not included in our case definition.

Identification of correlates of prevalent symptoms and lipodystrophy syndrome (dichotomised as present or absent) was achieved through initial univariate comparisons. Explanatory variables and possible confounders investigated included: Participant's age (continuous); gender; ethnicity (Caucasian, Aboriginal Canadian or other); transmission risk group (homosexual sex, heterosexual sex, injection drug use, or medical procedure); most recent CD4 count in cells/mm^3; plasma viral load in copies/ml; whether the patient had ever had an AIDS diagnosis; and their use of ingested alternative therapies (those not generally prescribed within Western medicine including Chinese and other herbs, Coenzyme Q10, N-acetyl-cystiene and Dinitrochlorobenzene). Finally past, current and duration of use of antiretrovirals was investigated. This included having ever used, current use of, total real-time duration of exposure in months and number of concurrent therapies of three classes of agents protease inhibitors, nucleoside analogues and non-nucleosides. Past use, current use and duration of exposure to each individual antiretroviral agent was also recorded. Adherence to the current regimen was considered as a continuous measure calculated as the percentage of prescriptions written that were actually filled in 10% increments. Chi squared or Fishers exact tests were used to identify univariate associations between dichotomous or categorical variables and Wilcoxin Rank Sum tests for continuous explanatory variables.

Subsequent forward stepwise logistic regression assessed independent effects of explanatory variables on the presence of lipodystrophy. All variables significant at the 0.05 level in univariate analysis were offered for inclusion in multivariate models. In cases in which variables were found to be collinear only one variable (that considered most clinically

relevant to the outcome or the one most strongly associated with the outcome in univariate analysis) was included in each model building run. All p-values reported are 2-sided.

4.4 RESULTS

From October 1998 through September 1999, 1091 annual questionnaires were returned, 1,035 (95%) with complete data regarding side effects. The majority (92%) were male, 78% were Caucasian, 10% Canadian Aboriginal and 12% other ethnic groups. The median age of participants was 41 years (IQR 36-47). A small majority (59%) had greater than a high school education and 44% were employed. The majority, (80%) reported sexual contact as the most likely mode of infection while 12% reported injection drug use. Ingested alternative therapies were used by 21% of participants. The median CD4 count was 370 cells/mm^3 (IQR 210-525), some 26% had been diagnosed as having AIDS, and 50% of patients had plasma viral load below 400 copies/ml.

In terms of treatment modalities, 642 participants (62%) were currently using protease inclusive regimens and 74% of participants had ever used protease inhibitors. Of current protease inhibitor users, 63% were using regimens containing one protease and 37% were using two protease inhibitors in combination. Indinavir was most commonly used (57%), while nelfinavir, ritonavir and saquinavir were each used by approximately 20% of current users. The remaining 393 participants were restricted to nucleoside analogue or non-nucleoside based regimens of whom 273 were protease inhibitor naïve.

Among those who had ever utilised protease inhibitors the median duration of protease inclusive therapy was 18.5 months (IQR 11.3 – 24.9) with median duration of nucleoside and non-nucleoside inclusive therapies prior to protease inhibitor use of 9.1 and 0 months

respectively. Among protease naïve participants the median durations of nucleoside or non-nucleoside therapy were 25.4 and 0 months respectively.

Overall, 518 or 50% of participants were identified as having probable lipodystrophy syndrome. Peripheral fat wasting or abdominal fat accumulation occurred among 36% and 33% of participants respectively. Buffalo hump was noted by 6%. Increased triglyceride and cholesterol levels were reported by 10% and 12% respectively.

Other symptoms were reported by 673 participants and included high blood pressure (6%), type 2 diabetes mellitus (4%), peripheral neuropathy (29%), sexual dysfunction (23% of men), menstrual changes (28% of women), loss of hair (16%), dry skin (38%) or ingrown toenail (10%).

Individuals reporting peripheral wasting (Table 4.4.1) were older, more likely to be Caucasian, to have not completed high school, to be unemployed, and to be using complementary therapies. In terms of antiretroviral regimens, lipoatrophy was associated with having ever used protease inhibitors, current use of protease inhibitors, and duration of protease inhibitor and nucleoside analogue therapies (all $p<0.001$).

Lower education level and alternative therapy use were also associated with centripetal or breast fat accumulation (Table 4.4.2). Those who had used protease inhibitors (ever or currently), and who had greater duration of treatment with either protease inhibitor or nucleoside inclusive regimens as well as those who had ever used non-nucleosides were more likely to experience this symptom (all $p<0.05$).

Older age and unemployment were associated with dorso-cervical fat pad enlargement (Table 4.4.3) as was use and duration of protease inhibitor therapy and duration of nucleoside therapy ($p\leq0.02$).

Similar results were noted for metabolic abnormalities (data not shown) with older age, less than a high school education, Caucasian ethnicity, protease inhibitor use (ever and current) and duration of protease inhibitor therapy associated with both increased triglyceride and cholesterol levels (all $p<0.05$).

Factors associated with probable lipodystrophy syndrome (Table 4.4.4) included older age, being unemployed, the use of alternative therapies, past or current use of protease containing regimens, duration of protease therapy, and duration of nucleoside therapy. In a sub analysis of each of the four specific protease inhibitors available, current use of each was significantly associated with lipodystrophy univariately (all $p<0.02$, data not shown).

CD4 cell count, plasma viral load and diagnosis of AIDS were not associated with any specific symptom or with lipodystrophy syndrome overall.

Table 4.4.5 summarises the finding of multivariate analysis. The initial analysis (a) indicates that each additional year of age was associated with a 3% increase in risk (adjusted odds ratios [AOR] 1.03; 95%CI 1.01, 1.04) of lipodystrophy. Current employment (AOR 0.56; 95%CI 0.42, 0.73) and the use of ingested alternative therapies (AOR 1.46; 95%CI 1.06, 2.01) were independently associated with a decreased and increased risk of lipodystrophy respectively. In terms of independent effects of treatment, those having ever used protease inhibitor therapies were more than twice as likely to suffer lipodystrophy (AOR 2.63; 95%CI 1.89, 3.66) than those who had never been exposed. The duration of treatment with stavudine was associated with a 35% increase in risk of lipodystrophy for every 12 months of stavudine exposure (AOR 1.35; 95%CI 1.15, 1.58).

No significant interactions were observed.

A second model (b) was developed to further investigate the contribution of various protease therapies and their combinations to the risk of lipodystrophy among participants who

had ever been exposed to protease inhibitors. Additional variables offered for inclusion were number of proteases taken concomitantly, cumulative duration of all protease inhibitor therapies with months on each drug summed, and the contribution of each of the four protease inhibitors both individually and in therapy regimens including more than one protease inhibitor. Older age (AOR-1.03; 95%CI 1.01, 1.05), current employment (AOR 0.67; 95%CI 0.49, 0.91) and the use of ingested alternative therapies (AOR 1.51; 95%CI 1.05, 2.19) were again significantly associated with lipodystrophy. In this sub-group however, each year of exposure to lamivudine treatment was associated with a 32% increase in risk (AOR 1.32; 95%CI 1.13, 1.53). Again, no significant interactions were observed.

The consistent relationships between increased risk of lipodystrophy and both unemployment and the use of complementary therapies was further explored as these factors may be associated with disease stage despite the lack of association with AIDS diagnosis, CD4 count and plasma viral load in univariate analyses. This analysis revealed no associations between either complementary therapy use or employment status and these markers of disease stage (all $p>0.05$, data not shown).

Table 4.4.1: Prevalence of Lipodystrophy-Associated Wasting and Correlates Among 1035 Participants

Wasting	Yes n=376 n (%)	No n=659 n (%)	P value
Gender			0.731
Male	348 (93)	606 (92)	
Female			
Age	43 (38-49)	40 (35-46)	<0.001
Education			0.013
< High school	137 (36)	292 (44)	
≥ High school	239 (63)	367 (56)	
Employed			<0.001
Yes	126 (34)	332 (52)	
No	245 (66)	309 (48)	
Ethnicity			0.046
Aboriginal	30 (8)	76 (12)	
Caucasian	310 (82)	500 (76)	
Other	36 (10)	83 (13)	
Alternative Rx			0.002
Yes	100 (28)	122 (19)	
No	260 (72)	517 (81)	
Protease Inhibitor			
Ever used			<0.001
Yes	318 (85)	444 (67)	
No	58 (15)	215 (33)	
Current use			<0.001
Yes	275 (73)	367 (56)	
No	101 (27)	292 (44)	
Duration (IQR)	18 (8-25)	11 (0-21)	<0.001
Nucleoside			
Ever used*			1.00
Yes	373 (99)	654 (99)	
No	3 (1)	5 (1)	
Current use			0.955
Yes	345 (92)	604 (92)	
No	31 (8)	55 (8)	
Duration (IQR)	34 (22-51)	26 (13-30)	<0.001
Non-nucleoside			
Ever used			0.230
Yes	118 (31)	231 (35)	
No	258 (69)	478 (65)	
Current use			0.228
Yes	103 (27)	204 (31)	
No	273 (73)	455 (69)	
Duration (IQR)	0 (0-2)	0 (0-2)	0.270

0 Fishers Exact Test

Table 4.4.2: Prevalence of Lipodystrophy-Associated Fat Accumulation and Correlates Among 1035 Participants

Fat accumulation	Yes n=346 n (%)	No n=689 n (%)	P value
Gender			0.227
Male	314 (91)	640 (93)	
Female	32 (9)	49 (7)	
Age	41 (36-48)	41 (35-47)	0.109
Education			0.028
< High school	127 (37)	302 (44)	
≥ High school	219 (63)	387 (56)	
Employed			0.052
Yes	138 (41)	320 (47)	
No	199 (59)	355 (53)	
Ethnicity			0.268
Aboriginal	28 (8)	78 (11)	
Caucasian	278 (80)	532 (77)	
Other	40 (12)	79 (12)	
Alternative Rx			0.023
Yes	133 (20)	89 (26)	
No	529 (80)	248 (74)	
Protease Inhibitor			
Ever used			<0.001
Yes	299 (86)	463 (67)	
No	471 (14)	226 (33)	
Current use			<0.001
Yes	265 (77)	377 (55)	
No	81 (23)	312 (45)	
Duration (IQR)	17 (8-25)	11 (0-22	<0.001
Nucleoside			
Ever used*			0.725
Yes	344 (99)	683 (99)	
No	2 (1)	6 (1)	
Current use			0.257
Yes	322 (93)	627 (91)	
No	24 (7)	62 (9)	
Duration (IQR)	32 (16-47)	27 (14-43)	0.013
Non-Nucleoside			
Ever used			0.041
Yes	102 (30)	247 (36)	
No	244 (70)	442 (64)	
Current use			0.125
Yes	92 (27)	215 (31)	
No	254 (73)	474 (69)	
Duration (IQR)	0 (0-1)	0 (0-2)	0.076

*Fishers Exact Test

Table 4.4.3: Prevalence of Lipodystrophy-Associated Dorso-Cervical Fat Pad and Correlates Among 1035 Participants

Fat accumulation	Yes n=59 n (%)	No n=976 n (%)	P value
Gender*			0.802
Male	54 (92)	900 (92)	
Female	5 (9)	76 (8)	
Age	43 (39-43)	41 (36-47)	0.026
Education			0.504
≤ High school	22 (37)	407 (42)	
> High school	37 (63)	569 (58)	
Employed			0.038
Yes	22 (32)	439 (46)	
No	40 (68)	514 (54)	
Ethnicity			0.403
Aboriginal	3 (5)	103 (11)	
Caucasian	49 (83)	761 (78)	
Other	7 (12)	112 (12)	
Alternative Rx			0.311
Yes	16 (28)	206 (21)	
No	42 (72)	735 (78)	
Protease Inhibitor			
Ever used			0.021
Yes	51 (86)	711 (73)	
No	8 (14)	265 (27)	
Current use			0.009
Yes	46 (78)	596 (61)	
No	13 (22)	380 (39)	
Duration (IQR)	22 (12-26)	13 (0-23)	<0.001
Nucleoside			
Ever used			1.00
Yes	59 (100)	968 (99)	
No	0 (0)	8 (1)	
Current use*			0.470
Yes	56 (95)	893 (92)	
No	3 (5)	83 (9)	
Duration (IQR)	43 (26-57)	28 (15-43)	<0.001
Non-Nucleoside			
Ever used			0.244
Yes	24 (41)	325 (33)	
No	35 (59)	651 (67)	
Current use			0.304
Yes	21 (36)	286 (29)	
No	38 (64)	590 (71)	
Duration (IQR)	0 (0-3)	0 (0-2)	0.313

* Fishers Exact Test

Table 4.4.4: Prevalence of Lipodystrophy Syndrome and Correlates Among 1035 Participants

Lipodystrophy	Yes n=518 n (%)	No n=517 n (%)	P value
Gender			0.901
Male	474 (92.0)	476 (92.3)	
Female	41 (8.0)	40 (7.8)	
Age	43 (37-49)	40 (35-46)	<0.001
Education			0.084
< High school	201 (38.8)	228 (44.1)	
≥ High school	317 (61.2)	289 (55.9)	
Employed			<0.001
Yes	189 (37.2)	269 (53.4)	
No	319 (62.8)	235 (46.6)	
Ethnicity			0.198
Aboriginal	46 (8.9)	60 (11.6)	
Caucasian	417 (80.5)	393 (76.0)	
Other	36 (10.6)	64 (12.4)	
Alternative Rx			0.004
Yes	130 (26.0)	92 (18.4)	
No	370 (74.0)	407 (81.6)	
Protease Inhibitor			
Ever used			<0.001
Yes	435 (84.0)	327 (63.2)	
No	83 (16.0)	190 (36.8)	
Current use			<0.001
Yes	380 (73.4)	262 (50.7)	
No	138 (26.6)	255 (49.3)	
Duration (IQR)	16.9 (7.3-24.7)	8.4 (0-20.1)	<0.001
Nucleoside			
Ever used			1.000
Yes	514 (99.2)	513 (99.2)	
No	4 (0.8)	4 (0.8)	
Current use			0.646
Yes	477 (92.1)	472 (91.3)	
No	41 (7.9)	45 (8.7)	
Duration (IQR)	32.6 (18.7-47.0)	25.7 (12.1-41.4)	<0.001
Non-Nucleoside			
Ever used			0.039
Yes	159 (30.7)	190 (36.8)	
No	359 (69.3)	327 (63.2)	
Current use			0.046
Yes	139 (26.8)	168 (32.5)	
No	379 (73.2)	349 (67.5)	
Duration (IQR)	0 (0-1.4)	0 (0-2.5)	0.052

Table 4.4.5: Results of 2 Stepwise Logistic Regression Procedures- Possible Predictors of Lipodystrophy Syndrome Among All Participants (a), and Among Participants Ever Exposed to Protease Inhibitor Therapy (b)

a[§1]

Variable	Adjusted Odds Ratio	95% Confidence Interval	P value
Older Age (per yr)	1.03	1.01 1.04	<0.01
Employed	0.56	0.42 0.73	<0.01
Alternative Rx	1.46	1.06 2.01	0.02
Protease Ever	2.63	1.89 3.66	<0.01
*Duration of Stavudine Therapy	1.35	1.15 1.58	<0.01

* Per 12 months of therapy

b. [§2]

Variable	Adjusted Odds Ratio	95% Confidence Interval	P value
Older Age (per yr)	1.03	1.01 1.05	<0.01
Employed	0.67	0.49 0.91	0.01
Alternative Rx	1.51	1.05 2.19	0.02
*Duration of Lamivudine Therapy	1.32	1.13 1.53	<0.01

* Per 12 months of therapy
[§1] Based on 977 of 1035 individuals with complete data
[§2] Based on 725 of 762 individuals with complete data

4.5 DISCUSSION

To our knowledge this study is the first to estimate prevalence and describe correlates of HIV-related lipodystrophy syndrome based on patient self-report through systematic inquiry within a large population-based sample. Patient report of adverse reactions are traditionally monitored through open-ended questioning, systematic symptom checklists or spontaneous report. Systematic inquiry, while optimising event capture may be associated with increased risk of false positives while other techniques may result in underestimates[37-40]. This technique, in conjunction with what may be a liberal definition of lipodystrophy in comparison to that recently proposed[18] may overestimate the prevalence of morphological symptoms in our population. As regards metabolic abnormalities, these may be under reported here as above normal triglyceride and cholesterol levels may not be communicated to patients or recall of such communications may be poor. Reliance on self-reported data for morphological abnormalities in the absence of clinical evaluation and validation can also be problematic. Clearly, however, clinical validation can only occur when adverse events are associated with measurable signs with well defined boundaries. The limits of morphological changes that indicate lipodystrophy have yet to be clarified. Moreover, the use of individual clinical examination is impracticable for broad scale population-based monitoring of known abnormalities or in routine post-marketing surveillance for emerging side effects in general. In terms of morphological abnormalities associated with lipodystrophy, in the most comprehensive study to date, Carr and colleagues reported a 98% concordance between patient self-report using systematic inquiry and the findings of clinical examination[18].

We have estimated that lipodystrophy affects approximately one half of individuals accessing antiretroviral therapy in British Columbia. The most commonly reported symptoms were changes in fat distribution in the form of either peripheral wasting or centripetal obesity

while buffalo hump and laboratory abnormalities were less commonly reported. Others have reported similar[41,42] or higher[4,43] rates of prevalent morphological changes while most clinical studies indicate a greater rate of triglyceride and cholesterol abnormalities[4,24,43].

Among participants naïve to protease inhibitors, 27% were identified as having probable lipodystrophy illustrating that key symptoms of lipodystrophy may occur among persons never exposed to protease inhibitors. This finding is consistent with that of studies which have identified symptoms in protease naïve populations or specifically related to nucleoside or non-nucleoside therapies[3,4,12,29,31,44,45].

Univariate analyses revealed statistically significant associations between patient and treatment characteristics and symptoms providing an important basis for comparison to prior reports. Most notably, use of specific protease inhibitors has been associated with various morphologic and metabolic abnormalities[5,10,21,22,27]. In univariate analyses our findings were similar with significantly increased risk of lipodystrophy associated with each protease inhibitor examined, a finding not confirmed in multivariate analysis. This exemplifies the importance of adjustment for confounding and collinear variables.

In multivariate analysis, older age, unemployment and use of alternative therapies were associated with increased risk of prevalent lipodystrophy. While many studies have not reported on factors other than treatment modalities, older age has been identified as a risk factor by others[17,32]. The stability of this association after comprehensive adjustment for clinical and therapeutic factors indicates either a complex function of duration of infection, disease stage at therapy initiation and therapeutic strategies or, conversely, a true age effect. The latter is consistent with the notion that symptoms of lipodystrophy may be associated with mitochondrial abnormalities which may accrue with age[46].

The increased risk of lipodystrophy among those using ingested alternative treatments is intriguing. The use of such therapies has been related to disease stage among individuals with HIV/AIDS[47]. These analyses however, included non-invasive/ non-ingested therapies. In fact further analysis revealed no significant association between adjunct utilization and AIDS diagnosis, CD4 count or plasma viral load. A second possibility- an association between compliance with antivirals and use of complementary therapies- was also ruled out in our cohort. It may be that the relationship is a function of temporality with those suffering from side effects implementing alternative therapies to treat these adverse responses. Additional research is currently underway to explore factors motivating the use of ingested complementary therapies. Lastly, these findings may be the result of reporting bias with those using adjuncts being more aware of morphological alterations.

The role of employment status has not previously been reported. In all likelihood the observed relationship is a function of temporality, with those experiencing morphological abnormalities being more likely to cease work as a result. It does not appear that employment acts as a marker of disease stage or severity in this cohort as no associations between employment status and CD4 count, viral load or AIDS diagnosis were found. Given the Canadian system of universal and free access to primary and specialised health care in conjunction with the centralised overseeing by experts of all antiretroviral prescriptions written within the drug treatment program, it is unlikely that this population is receiving sub-optimal or differential care. Nor does employment act as a marker of inadequate nutrition resulting in weight loss which might be interpreted as lipodystrophy-associated wasting. No difference was found in lipodystrophy status based on participant's responses to a survey question asking directly whether they had experienced weight loss due to inadequate nutrition (Chi squared $p=0.413$).

Increased risk of lipodystrophy was associated with protease inhibitor use and stavudine therapy duration after adjustment for duration of any therapy, use and duration of class specific therapies, adherence and clinical characteristics. Among those not naïve to protease inhibitors the risk of lipodystrophy was associated with the duration of lamivudine therapy after adjustment for duration of protease inhibitor use, duration of use of each specific antiretroviral therapy and number of concurrent therapies. Duration of stavudine and lamivudine therapy do not appear to simply reflect total therapy or nucleoside duration as a repeated analysis forcing the entry of these latter two variables resulted in similar odds ratios and 95% confidence intervals for all previously significant variables.

The results implicating nucleoside analogue use are in agreement with others who have identified an increased risk of symptoms associated with these agents[31,44]. Recently presented data indicates that the duration of stavudine and lamivudine as well as indinavir and saquinavir are associated univariately with increase risk of lipodystrophy[17]. Carr and colleagues showed stavudine use to be associated with peripheral lipoatrophy and lamivudine duration with abdominal obesity and buffalo hump while protease inhibitor duration was associated with all three symptom groups[32]. The preliminary results of a French study also indicate a relationship between lipoatrophy and stavudine use[33].

Caution is warranted in interpreting these findings as the cross-sectional nature of the study precludes drawing conclusions regarding causality. Moreover, while this study is population-based it is reliant on voluntary responses from participants who may not be representative of all persons treated in British Columbia or elsewhere.

These issues not withstanding, the inordinately high prevalence of both lipodystrophy syndrome and its component symptoms identified through self-report within a large observational, population-based treatment program by individuals representing a broad

spectrum of those living with HIV/AIDS and utilizing a wide variety of antiretroviral regimens is of grave concern. Most pressing is the implication of protease inhibitors and nucleoside analogues, drugs widely prescribed both as first line agents and throughout disease. At a time when these therapies can finally offer some hope to persons with HIV/AIDS, the emergence of such side effects further complicates an already difficult task. Morphologic abnormalities can be disfiguring and often frightening as they may be experienced as one of the first overt physical manifestations related to HIV disease. The subjective perception of these events by those receiving therapy may be of importance beyond that of strict clinical relevance. Significant declines in morbidity and mortality noted among those living with HIV/AIDS directly attributable to therapeutic advances may be offset if individuals decide to alter, abandon or eschew highly active antiretroviral therapy due to the occurrence or fear of such events. Prevention and treatment of side effects as well as an understanding of their impact on treatment decisions is imperative if we are to continue successfully towards a goal of long term care through pharmacological management.

4.6 SUMMARY

Symptoms consistent with lipodystrophy syndrome are highly prevalent. Based on a cross-sectional analysis of prevalent cases, this study provides preliminary information about factors which may be associated with the symptoms of HIV-associated lipodsytrophy syndrome. In the next chapter estimates of incidence are determined and we refine our analysis, identifying possible predictors of symptoms using prospectively accrued cases.

4.7 REFERENCES

1. Hogg RS, Heath KV, Schechter MT, Yip B, Craib KJP, O'Shaughnessy MV, Montaner JSG. Improved survival among HIV infected individuals following initiation of antiretroviral therapy. *JAMA* 1998; 279 (6): 450-454.
2. Hammer SM, Squires KE, Hughes MD et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell founts of 200 per cubic millimetre or less. *New Engl J Med* 1997; 337:725-733.
3. Kotler DP, Rosenbaum K, Wang J, Pierson RN. Studies of body composition and fat distribution in HIV-infected and control subjects. *J Acquir Immune Defic Synd* 1999; 20(3):228-237.
4. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1 protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998; 351:1881-1883.
5. Miller KD, Jones E, Yanovski JA, Shankar R, Feurstein I, Falloon J. Visceral abdominal-fat accumulation associated with use of indinavir. *Lancet* 1998; 12:F51-F58.
6. Rosenburg HE, Mulder J, Stepowitz KA, Giordano MF. "Protease paunch" in HIV+ persons receiving protease inhibitor therapy: incidence, risks and endocrinologic evaluation. *5th Conference on Retroviruses and Opportunistic Infections.* Chicago, Illinois 1998 [Abstract 408].
7. Roth VR, Kravcik SA, Angel JB. Development of cervical fat pads following therapy with human immunodeficiency virus type 1 protease inhibitors. *CID* 1998; 27:65-67.
8. Hengel RL, Geary JAM, Vuchetich MA et al. Multiple symmetrical lipomatosis associated with protease inhibitor therapy. *5th Conference on Retroviruses and Opportunistic Infections.* Chicago, Illinois 1998. [Abstract 407]

9. Ho TTY, Chan KCW, Wong KH, Lee SS. Buffalo hump and facial wasting in HIV. *Lancet* 1998; 351:1736-37.

10. Carr A, Samaras K, Burton S et al. A syndrome of peripheral lipodystrophy, hyperlipidemia and insulin resistance due to HIV protease inhibitors. *AIDS* 1998; 12:F51-F58.

11. Thiébaut R, Daucourt V, Malvy D et al. Lipodystrophy, glucose and lipid metabolism dysfunctions, Aquitaine Cohort, 1999. *1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV.* San Diego, California 1999 [Abstract 17].

12. Carr A, Miller J, Law M, Cooper DA. A syndrome of lipodystrophy (LD), lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue reverse transcriptase inhibitor therapy: contribution to PI-related LD syndrome. *1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV.* San Diego, California 1999 [Abstract 11].

13. Rozenbaum W, Gharakhanian S, Salhi Y et al. Clinical and laboratory characteristics of lipodystrophy in a French cohort of HIV-infected patients treated with protease inhibitors. *1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV.* San Diego, California 1999 [Abstract 12].

14. Dong K, Flynn MM, Dickinson BP et al. Changes in body habitus in HIV+ women after initiation of protease inhibitor therapy. *12th World AIDS Conference*, Geneva, Switzerland 1998 [Abstract 12373].

15. Thiébaut R, Malvy D, Mercié P, daucourt V, Marimoutou C, Dabis F. Factors influencing the evolution of plasma triglyceride in the era of HAART, Aquitaine Cohort 1996-1998. *1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV.* San Diego, California 1999 [Abstract 15].

16. Daucourt V, Thiébaut R, Mercié P et al. Prevalence of lipodystrophy and relation with clinical, anthropometric data and treatment, Aquitaine Cohort, 1999. *1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV*, San Diego, California 1999 [Abstract 16].

17. Ward DJ, Delancy KM, Moorman AC et al. Description of lipodystrophy in the HIV Outpatient Study (HOPS). *1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV*, San Diego, California 1999 [Abstract 14].

18. Carr A, Samaras K, Thorisdottir A, et al. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidemia, and diabetes mellitus: a cohort study. *Lancet* 353:2093-9, 1999.

19. Striker R, Conlin D, Marz M, Wiviott L. Localized adipose tissue hypertrophy in patients receiving immunodeficiency virus protease inhibitors. *CID* 1998; 27:218-220.

20. Schindler JT, Sponer KM, Deker CF. Buffalo humps associated with protease inhibitors [Letter]. *Ann Int Med* 1998; 129:164.

21. Virben R, Aquilna C. Indinavir-associated lipodystrophy. AIDS 1998; 12:F37-F39.

22. Sullivan AK, Feher MD, Nelson MR, Gazzard BG. Marked hypertriglyceridemia associated with ritonavir therapy [Letter]. *AIDS* 1998; 12:1395-6.

23. Cameron DW. Antiretroviral safety and durability of ritonavir-saquinavir in protease inhibitor-naïve patients in year two of follow-up. *5th Conference on Retroviruses and Opportunistic Infections.* Chicago, Illinois 1999 [Abstract 388].

24. Pollner J, Aronson NE, McHugh S et al. Significant increases in serum cholesterol are seen among HIV patients taking protease inhibitors. *12 World AIDS Conference.* Geneva, Switzerland 1998 [Abstract 12269].

25. Walli RK, Hefort O, Michl GM et al. Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1 infected patients. *AIDS* 1998; 12:F167-F173.

26. Doung M, Petit JM, Piroth L et al. Lipid evaluation and glucose metabolism in HIV-infected patients before and after initiation of protease inhibitor therapy. 39th *Interscience Conference on Antimicrobial Agents and Chemotherapy*, San Francisco, California 1999 [Abstract 1291].

27. Youle M, Mocroft A, Johnsom M et al. Lipid profiles in patients on ritonavir-containing salvage regimens. 39th *Interscience Conference on Antimicrobial Agents and Chemotherapy*, San Francisco, California 1999 [Abstract 1290].

28. Carter V, Adams F, Hoy J, Nyulasi I, Mijch A. The prevalence of lipodystrophy in an outpatient population. *1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV*, San Diego, California 1999 [Abstract 37].

29. Mercié P, Malvy D, Daucourt D et al. Case report of lipodystrophy observations in patients naïve of protease inhibitor treatment, Aquitaine Cohort, 1999. *1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV*. San Diego, California 1999 [Abstract 18].

30. Grunfeld C. Dyslipidemia due to HIV infection and its therapy. 1st *International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV*, San Diego, California 1999 [Abstract 4].

31. Polo R, Verdejo J, Gonzalez-Munoz M et al. Lipodystrophy related to NRT inhibitors in HAART therapy. *39th Interscience Conference on Antimicrobial Agents and Chemotherapy*, San Francisco, California 1999 [Abstract 1302].

32. Carr A, Miller J, Law M, Cooper DA. A syndrome of lipoatrophy, lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS* 2000; 14:F25-F32.

33. Saint-Marc T, Partisani M, Poizot-Martin I et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study. *AIDS* 2000; 14: 37-49.

34. Carpenter CCJ, Cooper DA, Fischl MA et al. Antiretroviral therapy in adults: Updated recommendations of the International AIDS Society- USA Panel. *JAMA* 2000; 283:381-390.

35. Montaner JSG and O'Shaughnessy MV. *Therapeutic Guidelines for the Treatment of HIV/AIDS and Related Conditions*. British Columbia Centre for Excellence in HIV/AIDS, June 1999.

36. http://www.intmedpress.com Consensus meeting on the case definition for lipodystrophy. Conducted in conjunction with the *1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV*. San Diego, California 1999.

37. Keith MR, Bellanger-McCleery RA, Fuchs JE. Multidisciplinary program for detecting and evaluating adverse drug reactions. *Am J Hosp Pharm* 1989; 46:101-110.

38. Brewer T, Colditz GA. Postmarketing surveillance and adverse drug reactions: Current perspectives and future needs. *JAMA* 1999; 281:824-829.

39. Fisher S, Bryant SG, Kluge RM. Detecting adverse drug reactions in post-marketing surveillance: interview validity. *Drug Info J* 1987; 21:173-183.

40. Wallin J, Sjovall J. Detection of adverse drug reactions in a clinical trial using two types of questioning. *Clin Ther* 1981; 3:450-452.

41. Christeff N, Melchior J, de Truchis P, Perronne C, Nunez EA, Gougeon M. Lipodystrophy defined by a clinical score in HIV-infected men on highly active antiretroviral therapy: correlation between dyslipidaemia and steroid hormone alterations. *AIDS* 1999; 13:2251-2260.

42. Bernasconi E, carota A, Magenta L, et al. Metabolic changes in HIV infected patients treated with protease inhibitors. 12th *World AIDS Conference.* Geneva, Switzerland 1998 [Abstract 12375].

43. Miller JE, Emery S, French M, Baker D, Cooper DA. The Australian prevalence survey of lipodystrophy syndrome. 7th *Conference on Retroviruses and Opportunistic Infections.* San Francisco, California 2000 [Abstract 201].

44. Saint-Marc T, Partisani M, Poizot-Martin I, et al. A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. *AIDS* 1999; 13:1659-1667.

45. Madge S, Kinloch-de-loes S, Mercey D, Johnson MA, Weller IVD. Lipodystrophy in patients naïve to protease inhibitors [Letter]. *AIDS* 1999; 13:735-737.

46. Wallace, D. Mitochondrial genetics: A paradigm for ageing and degenerative diseases? *Science* 1992; 5057:628-632.

47. Ostrow MJ, Corneliesse PGA, Heath KV et al. Determinants of complementary therapy use in HIV-infected individuals already on antiretroviral, anti-opportunistic or prophylactic agents. *J Acquir Immune Defic Synd* 1997; 15:115-120.

CHAPTER 5

INCIDENCE OF LIPODYSTROPHY-ASSOCIATED MORPHOLOGIC AND LIPID ABNORMALITIES

5.1 FORWARD

This manuscript is currently under review as "Antiretroviral Treatment Patterns and Incident HIV-Associated Morphologic and Lipid Abnormalities in a Population-Based Cohort." with the *Journal of Acquired Immune Deficiency Syndromes*. This study was initiated in August of 2000 and completed in September of 2001. Co-authors include all thesis committee members and Mr. Keith Chan.

5.2 INTRODUCTION

Standard care with potent multi-drug regimens has resulted in reduced morbidity and mortality among persons with HIV infection[1]. Such advances, however, have been tempered by reports of adverse events associated with highly active antiretroviral therapy. Of particular concern is the emergence of morphologic and metabolic abnormalities often referred to as HIV-related lipodystrophy syndrome. Morphologic changes, include localised lipohypertrophy (fat accumulation) in the abdomen and breasts and dorso-cervical region ("buffalo hump"), and lipoatrophy (fat wasting) in the face, arms, legs and buttocks[2-5]. These re-distributions in body fat (lipodystrophy) often occur with concurrent metabolic changes including, but not limited to, hypercholesterolemia and hypertryglyceridemia[2,4,6].

Estimates of symptom prevalence vary widely with abnormalities reported among 18% to 70% of study subjects[7]. Initial reports regarding the etiology of lipodystrophy syndrome-related symptoms were similarly variable. Temporal coincidence as well as case series or

clinic based studies suggested an association between various symptoms and the use of protease inhibitors[4, 8-13]. Conversely, others noted symptoms among subjects naïve to proteases[3,14,15] or related to nucleoside analogue reverse transcriptase inhibitor therapy[16,17]. More recent studies and those of more inclusive and rigorous design have yet to clarify the etiology of these symptoms with continued findings of symptoms related to either or both of protease inhibitor[15,17-21] use and exposure to nucleoside analogues[15,17,21-26] as well as other patient and clinical characteristics. Continued uncertainty recently prompted the United States Food and Drug Administration to require the makers of antiretrovirals to include information regarding symptoms associated with lipodystrophy with all antiretroviral medications.

The noted inconsistencies may, in part, be due to variations in diagnostic criteria, study sample selection methods, and outcome measurement techniques. Even well designed studies often continue to be based on cross sectional[15,21,27,28], and/or retrospective[18,19,24,26] analyses. Many focus on highly selected subjects in terms of disease stage, treatment facility and current or past treatment exposure[23-26]. Such studies can provide important data and have many advantages, however, they are subject to biases due to recall, diagnostic and exposure suspicion and are limited in terms of the generalizability of study findings.

Studies based on unselected patient populations, while susceptible to other limitations, are needed to provide complimentary data regarding the occurrence and possible predictors of these symptoms under conditions of broad access to standard clinical care. We report here the annual incidence of lipodystrophy-associated symptoms in a population-based observational cohort under conditions of universal access to treatment among persons representing a broad spectrum of historical and recent treatment patterns. Factors associated with incident symptomology are identified and the implications of these findings discussed.

5.3 METHODS

The HIV/AIDS drug treatment program of British Columbia, Canada provides antiretroviral medications free of charge to all eligible province residents and is the only source of no-cost anti-HIV medications in the province. To be eligible, individuals must be confirmed HIV positive, have a CD4 count of ≤ 500 cells/mm^3 and/or plasma viral load of $>$ 5,000 copies/ml as is commensurate with current recommendations[29]. All medical visits and laboratory monitoring are also provided at no cost.

Individuals are automatically entered into the treatment program when first prescribed any antiretroviral agent by a physician in British Columbia. At entry and subsequent physician visits complete history of antiretroviral use, baseline CD4 count and plasma viral load, and disease stage are recorded. Typically patients are followed-up at one to three-month intervals at which time prescriptions are renewed or amended and laboratory parameters are re-evaluated. For all patients a complete prospective record of antiretroviral therapy utilisation and clinical status is thus maintained.

At entry and at each annual anniversary, program participants provide additional data through a voluntary self-administered questionnaire. Data collection includes socio-demographic characteristics, general health, body weight, and the occurrence of more than 40 established and possible therapy-related symptoms. These last include: fat wasting in the face, arms or legs; abdominal weight gain; breast enlargement; buffalo hump; increased triglycerides; and increased total cholesterol.

Information regarding possible or known adverse drug effects is reliant on self-report. Patients are, however, instructed to report increased triglyceride and cholesterol levels only if they have been told that they have these abnormalities by their physician. Guidelines

distributed to all antiretroviral prescribers recommend fasting lipid tests as standard care. Local laboratory standards define the upper limit of normal for fasting triglycerides and total cholesterol as 2.3 mg/dL (mmol/L) and 5.2 mg/dL (mmol/L) respectively.

The study sample was comprised of all individuals who completed annual questionnaires between September 1998 and November 1999 and second successive annual questionnaire between November 1999 and December 2000.

Outcomes of interest included incident cases of lipoatrophy, lipohypertrophy, any lipodystrophy (either lipoatrophy or lipohypertrophy) and lipid abnormalities (increased triglycerides and/or cholesterol). Incident cases by symptom were defined as those not reporting the symptom(s) of interest at baseline but reporting the symptom(s) at one year follow-up. To determine whether change in body weight might contribute to self-report of morphologic changes, incidence of lipoatrophy and lipohypertrophy were re-calculated excluding patients with weight changes of greater than ten pounds over the study period.

Initially, correlates for incident cases of each of lipoatrophy, lipohypertrophy and lipid abnormalities were identified using Chi squared or Fishers exact tests for dichotomous or categorical variables and Wilcoxin Rank Sum tests for continuous variables. Explanatory variables and possible confounders investigated for each outcome included: age; gender; ethnicity (Caucasian, Canadian Aboriginal or other); transmission risk group; baseline CD4 count (cells/mm^3) and plasma viral load (copies/ml); change in CD4 and plasma viral load between baseline and follow-up; and baseline AIDS diagnosis. History of antiretroviral use was also examined including total real-time duration in months of any antiretroviral therapy and of three therapy classes: protease inhibitors; nucleoside analogues; and non-nucleoside reverse transcriptase inhibitors. Recent therapy conditions examined use and duration of therapy by class in the two years prior to follow-up. Similar agent-specific analyses were

conducted for each of the four protease inhibitors, five nucleosides and three non-nucleoside agents commonly available.

Subsequent backwards stepwise logistic regression assessed independent effects of explanatory variables on the presence of lipoatrophy, lipohypertrophy and lipid abnormalities. For each model building run all variables found to be significant at the $p<0.05$ level in symptom group-specific univariate analyses were offered for inclusion. All reported p-values are 2-sided.

5.4 RESULTS

Baseline data was provided by 1261 individuals of whom 745 (59%) completed one year follow-up and were eligible for the present study. Baseline comparison of eligible and excluded individuals (Table 5.4.1) indicated variation in socio-demographic and clinical characteristics, however, no significant differences in therapeutic regimens were found.

Table 5.4.2 summarises incidence rates by symptom among individuals not reporting the symptom at baseline. Incidence was 20.8% for lipohypertrophy (with an incidence of 6% for buffalo hump alone), 27.3% for lipoatrophy, 10.0% for elevated triglycerides and 16.9% for high cholesterol. Twenty seven percent reported having lost, and 23.3% having gained at least 10 pounds in the year preceding follow-up. After exclusion of subjects with weight change from the calculation of lipohypertrophy and lipoatrophy, the incidence of these symptoms declined to 16.9% and 24.0% respectively.

Overall, 368 (49%) of the 745 individuals reported at least one symptom associated with lipodystrophy at baseline. The majority of the remaining 377 individuals at risk for development of first lipodystrophy-related symptom were Caucasian and male (Table 5.4.3). Sixty four percent had greater than a high school education and 57% were employed. Sexual

contact was reported as the most likely mode of infection in 73% of cases while 25% cited injection drug use. Median CD4 count was 400 cells/mm^3 (IQR 240-550), 21% had been diagnosed as having AIDS, and 72% of patients had plasma viral load below 400 copies/ml.

In terms of past treatment use, 64.5% of the 377 subjects had ever used protease inhibitors, 100% had ever used nucleosides and 49.6% had been exposed to non-nucleoside therapies. Regarding therapy strategies in the two years preceding final follow-up, 63.1% had used protease inhibitor, 98.9% nucleoside, and 49.3% non-nucleoside inclusive regimens.

In an overall comparison of individuals with any incident symptom and those remaining symptom-free (Table 5.4.3), none of the personal (age, education level, employment or ethnicity) or clinical factors including plasma viral load, change in plasma viral load, CD4 at entry or change in CD4 count over follow-up period or baseline therapeutic class or strategy with the exception of male gender and diagnosis of AIDS, were associated with symptom development. Recent use of either protease or non-nucleoside class therapies, however, appeared to impose increased risk (both $p<0.02$) of incident symptomology. None of the variables related to nucleoside use were of statistical significance, however, exposure to this therapy class was ubiquitous.

Detailed univariate evaluation of recent therapy by symptom is shown in Table 5.4.4. In general terms this analysis indicates increased unadjusted odds ratios for lipoatrophy, lipohypertrophy and lipid abnormalities among those having used any protease inhibitor in the prior two years. Moreover, results were relatively consistent across individual drugs in this class. In contrast, among nucleosides, only stavudine use was associated with morphologic symptoms, but had no effect on lipid profiles. Non-nucleoside class therapies overall, and nevirapine and efavirenz in particular, were marginally implicated only in lipohypertrophy.

Tables 5.4.5a through c summarise the findings of multivariate analysis for each of peripheral wasting, lipohypertrophy and cholesterol and triglyceride abnormalities. Incident lipoatrophy was associated with duration of stavudine use in the past two years with increased risk of 18% for every 3 months of use (AOR 1.18; 95%CI 1.09, 1.27) and having been diagnosed with AIDS (AOR 2.07; 95%CI 1.20, 3.56). Risk of lipohypertrophy increased with use in the past two years of protease inhibitor class (AOR 3.53; 95%CI 1.81, 6.86) and stavudine containing regimens (AOR 3.67; 95%CI 1.61, 8.38). Newly occurring cholesterol or triglyceride abnormalities were associated with the use of protease inhibitor class inclusive therapy in general (AOR 7.17; 95%CI 2.46, 20.96) and the duration of ritonavir specifically (AOR 1.12; 95%CI 1.04, 1.21).

In sub-analysis limited to those without weight change (data not shown), any morphologic change was associated with stavudine (AOR 3.45 95%CI 1.33, 9.03) and ritonavir (AOR 3.20 95%CI 1.59, 6.43) use in the past two years and duration of nelfinavir inclusive regimens in particular over the past two years (AOR 1.23 95%CI 1.02, 1.48).

No significant interactions were observed in these analyses.

Table 5.4.1: Characteristics of 745 Study Subjects and Remaining 516 Drug Treatment Programme Participants

Characteristic	Excluded Subjects n (%)	Study Subjects n (%)	P value
Gender			<0.001
Male	455 (88)	701 (94)	
Female	61 (12)	44 (6)	
Age	40 (35-45)	42 (37-49)	0.001
Education			<0.001
< High school	264 (51)	267 (36)	
≥ High school	252 (49)	478 (64)	
Employed			<0.001
Yes	198 (39)	360 (49)	
No	306 (61)	368 (51)	
Ethnicity			<0.001
Aboriginal	79 (15)	31 (8)	
Caucasian	368 (71)	368 (82)	
Other	69 (13)	79 (11)	
Alternative Rx			0.100
Yes	99 (20)	171 (24)	
No	393 (80)	537 (76)	
Median CD4 (IQR)	350 (190-510)	420 (280-590)	<0.001
AIDS Diagnosis	127 (40)	189 (25)	0.760
Plasma viral load<400 copies/ml	308 (60)	549 (74)	<0.001
Baseline Therapy Class			
Protease inhibitor	299 (58)	425 (57)	0.701
Nucleoside	484 (94)	709 (95)	0.413
Non-nucleoside	195 (38)	308 (41)	0.222
Baseline Strategy			0.257
Monotherapy	1 (0.2)	1 (0.1)	
Dual therapy	65 (13)	75 (10)	
Triple or more	426 (87)	645 (89)	

Table 5.4.2: Annual Incidence of Lipodystrophy Associated Symptoms Among 745 Participants

Symptom	(A) Symptom free 98/99 n	(B) Symptomatic 99/00 n	Annual Incidence B/A (100%) All subjects
Lipohypertrophy*	481	100	20.8
Lipoatrophy	474	129	27.2
Any lipodystrophy†	377	124	32.9
Elevated triglycerides	670	67	10.0
Elevated cholesterol	654	104	15.9

*Lipohypertrophy includes central hypertrophy, breast enlargement and buffalo hump
†Any morphologic change (lipohypertrophy or lipoatrophy)

Table 5.4.3: Characteristics of 377 Participants Without Symptoms at Baseline: Incident Cases and Those Remaining Symptom Free

Characteristic	Incident Symptoms (n=124) n (%)	Asymptomatic (n=253) n (%)	P value
Gender*			0.033
Male	122 (98)	236 (93)	
Female	2 (2)	17 (7)	
Age	41 (37-48)	41 (36-47)	0.247
Education			0.240
≤ High school	50 (40)	86 (34)	
> High school	74 (60)	160 (66)	
Employed			0.294
Yes	64 (53)	146 (59)	
No	56 (47)	101 (41)	
Ethnicity			0.658
Aboriginal	12 (10)	21 (8)	
Caucasian	95 (76)	204 (81)	
Other	17 (14)	28 (11)	
Protease inhibitor			
Used past 2 yrs			
Yes	94 (76)	144 (57)	<0.001
No	30 (24)	110 (43)	
*Duration (IQR)	21 (3-35)	10 (0-32)	0.003
Nucleoside			
Used in past 2 yrs			
Yes	124 (100)	248 (98)	0.127
No	0(0)	5 (2)	
*Duration (IQR)	43 (29-63)	21 (24-59)	0.169
Non-nucleoside			
Used past 2 yrs			0.005
Yes	74 (60)	112 (44)	
No	50 (40)	141 (56)	
*Duration (IQR)	3 (0-18)	0 (0-13)	0.029

* Total duration in months since first therapy initiation

Table 5.4.3 Cont.: Characteristics of 377 Participants Without Symptoms at Baseline: Incident Cases and Those Remaining Symptom Free

Characteristic	Incident Symptoms (n=124) n (%)	Asymptomatic (n=253) n (%)	P value
Median baseline CD4 (IQR)	370 (200-570)	410 (250-545)	0.218
Change in CD4	50 (-20, 130)	30 (-25, 120)	0.424
Plasma viral load < 400 copies/ml	87 (70)	183 (72)	0.661
Change in viral load	-314 (-1365, -4)	-314 (-400, -4)	0.390
AIDS			0.001
Yes	38 (31)	42 (17)	
No	86 (69)	211 (83)	
Baseline Therapy Class			
Protease inhibitor	72 (58.1)	127 (50)	0.151
Nucleoside	122 (98)	242 (96)	0.235
Non-nucleoside	47 (38)	78 (31)	0.171
Baseline Strategy			0.071
Monotherapy	0 (0)	1 (.5)	
Dual therapy	18 (15)	50 (24)	
Triple or more	105 (85)	187 (76)	

Table 5.4.4: Unadjusted Odds Ratios of Select Clinical and Therapy Variables for Incident Cases of Lipoatrophy, Lipohypertrophy and Lipid Abnormalities

Variable*f*	N on therapy	Lipoatrophy OR (95% CI)	Lipohypertrophy OR (95% CI)	High Lipids OR (95% CI)
Protease inhibitor				
Any protease	238	2.2 (1.3-3.7)	3.8 (2.0-7.4)	10.1 (3.6-28.7)
*[1]Duration		1.1 (1.0-1.1)	1.1 (1.0-1.2)	1.3 (1.2-1.4)
Nelfinavir	79	1.8 (1.0-3.0)	2.7 (1.5-4.7)	1.9 (1.0-3.4)
Ritonavir	116	1.5 (0.9-2.5)	2.1 (1.2-3.5)	3.9 (2.2-7.0)
Saquinavir	90	1.5 (0.8-2.3)	2.1 (1.2-3.7)	2.4 (1.3-4.3)
Indinavir	154	1.9 (1.2-3.0)	2.0 (1.2-3.4)	1.8 (1.0-3.1)
Nucleoside analogue				
Any nucleoside	373	NA	NA	NA
*[2]Duration		1.1 (1.0-1.3)	1.0 (0.8-1.1)	1.1 (0.9-1.4)
Stavudine	281	3.7 (1.8-7.5)	4.1 (1.8-9.2)	1.3 (0.6-2.1)
Didanosine	128	1.6 (1.0-2.6)	1.6 (1.0-2.7)	0.9 (0.5-1.6)
Lamivudine	328	1.2 (0.6-2.4)	1.3 (0.6-2.9)	0.8 (0.4-1.7)
Zalcitabine	13	1.3 (0.4-4.4)	1.2 (0.3-4.5)	1.0 (0.2-4.5)
Zidovudine	139	0.6 (0.3-0.9)	0.6 (0.3-1.1)	0.6 (0.3-1.1)
Non-nucleoside				
Any non-nucleoside	186	1.6 (1.0-2.5)	1.9 (1.2-3.3)	1.1 (0.6-1.9)
*[3]Duration		1.1 (1.0-1.2)	1.0 (1.0-1.1)	1.0 (0.9-1.1)
Efavirenz	28	2.0 (0.9-4.5)	2.4 (1.1-5.5)	1.9 (0.8-4.7)
Delavirdine	33	2.1 (0.9-4.4)	2.5 (1.2-5.5)	1.8 (0.8-4.3)
Nevirapine	169	1.5 (1.0-2.4)	1.6 (1.0-2.7)	0.8 (0.5-1.4)
AIDS (yes vs. no)		2.0 (1.1-3.3)	1.6 (0.9-2.8)	2.4 (1.3-4.3)

*f*All refer to use of agent in the past two years

*Cumulative duration in past 24 months (per quarter year increment) of Protease[1], Nucleoside analogue[2] or Non-nuceoside[3] containing therapy

Table 5.4.5: Possible Predictors of Incident Lipoatrophy (a); Lipohypertrophy (b); and Lipid Abnormalities (c) Among 377 Participants not Symptomatic at Baseline.

a. Lipoatrophy

Variable*	Adjusted Odds Ratio	95% Confidence Interval	P value
Stavudine duration*f* (past 2 years)	1.18	1.09, 1.27	<0.001
AIDS	2.07	1.20, 3.56	0.009

*f*By quarter year increments

b. Lipohypertrophy

Variable*	Adjusted Odds Ratio	95% Confidence Interval	P value
Protease inhibitor	3.53	1.81, 6.86	<0.001
Stavudine	3.67	1.61, 8.38	0.002

c. Lipid Abnormalities

Variable*	Adjusted Odds Ratio	95% Confidence Interval	P value
Protease inhibitor	7.17	2.46, 20.96	<0.001
Ritonavir duration*f* (past 2 years)	1.12	1.04, 1.21	0.003

*All therapy variables refer to use in the past 2 years unless otherwise indicated.

f By quarter year increments

5.5 DISCUSSION

The data presented here based on prospectively accrued incident cases of lipodystrophy-associated symptoms suggests that morphologic and lipid abnormalities have a high rate of incidence in the general population of patients using antiretroviral therapies. Emergence of symptoms is associated with exposure both to protease inhibitors and stavudine containing regimens after adjustment for multiple explanatory variables providing evidence of a causal relationship.

The use of a large population-based sample representing a broad spectrum of subjects, including detailed treatment information, and analyses adjusted for a large number of possible confounders are unique aspects of this study as is the prospective nature of case accrual. The importance of these features has been established in relation to epidemiologic coherence in studies of lipodystrophy[30]. Our study and its findings are, however, not without limitations. This sample is not necessarily representative of all persons receiving treatment in British Columbia or elsewhere. Comparison of eligible and ineligible treatment program participants indicated differences in personal and clinical characteristics, however, treatment patterns- the variables clearly of greatest relevance here- were similar. Lipid abnormalities may be under reported in our cohort if physicians did not apprise patients of these findings or if patient recall was poor. Self report of morphologic abnormalities via systematic inquiry, while it optimises event capture, may lead to over-reporting. However, self-report of morphologic symptoms has been shown to be highly concordant with findings of physician exam in clinical studies[11]. Furthermore, while clinical validation would be considered the "gold standard", self report has some unique features. Most importantly, the subjective perception of morphologic changes as measured using self-report methods is likely to be of greater relevance to actual treatment patterns. Secondly, until such time as clear diagnostic criteria for case identification are

developed and widely accepted, self report may prove to be more consistent in any particular cohort or patient group.

The inordinately high incidence of lipodystrophy and its component symptoms is of great concern. Many studies have provided estimates of prevalence, however, few have reported incidence data based on prospective follow-up. Available estimates based on pre-treated individuals are similar to those obtained in the present study. One recent study using retrospective-prospective methodology reported a cumulative incidence of 29% for any morphologic abnormality among persons on protease inhibitor inclusive triple regimens after a median of 20 months of exposure[26]. A further study comparing dual protease inhibitor only versus dual protease plus a nucleoside reported overall incidence of morphologic changes subjectively identified by study physicians to be 17% over the 96 week follow-up period[25]. These figures vary little from incidence proportions reported among persons initiating for therapy for the first time. For instance, a cohort of therapy naïve patients using highly active antiretroviral regimens reported a prevalence of 17% after a median of 18 months[31]. Similarly, a study of 121 persons treated with highly active antiretroviral therapy for more than 6 months during primary HIV infection reported a cumulative incidence of morphologic changes of 18% at 24 months[32].

Univariate analyses revealed associations between treatment characteristics and both incident peripheral fat wasting and lipohypertrophy. Early studies based on univariate analyses as well as more recent studies have related use of specific protease inhibitors or this class of therapy in general or the use of nucleosides to the occurrence of the general features of lipodystrophy syndrome[2,11,15,16,19,22,33,34].

Several recent studies have included analyses by morphologic phenotype. Our findings suggest an independent effect of protease inhibitor class therapy in the development of both

lipohypertrophy and above normal triglyceride and cholesterol levels. Moreover, multivariate analyses controlling for confounding and collinear variables indicated protease inhibitor class use in the previous two years being of primary importance. We did not confirm any independent protease agent-specific associations, nor association with total duration of protease inhibitor use or therapy exposure overall. Some studies have not found associations between protease inhibitor therapy and morphologic symptoms. For example preliminary cross sectional analysis from the LIPOCO study reported no association between morphologic changes and protease inhibitor class therapy overall[28]. In detailed analysis of protease inhibitors they also reported no drug specific associations among the 100 protease exposed subjects studied. Similarly, results from the Aquitaine cohort indicated no effects related to various treatment strategies[27]. For the most part, however, protease inhibitor use or highly active antiretroviral therapy in general have been implicated in fat redistribution. An ongoing prospective cohort study of 494 persons treatment naïve at baseline has reported associations between triple therapy duration and both lipodystrophy overall and lipoatrophy as well as a marginal association between indinavir duration and lipohypertrophy[31]. A further study of individuals exposed to highly active antiretroviral therapy noted significantly increased risk of lipohypertrophy with protease inhibitor class therapy, however, analysis by protease component was not conducted[35].

Above normal triglyceride and cholesterol levels in our cohort were related only to protease inhibitor inclusive regimens and, specifically, the duration of therapy with ritonavir. These findings are compatible with previous reports regarding these abnormalities in the context of lipodystrophy syndrome and with the generalised effects of protease inhibitors on lipid profiles[11,12,36,37]. This consistency is also reassuring in light of the self-reported nature of laboratory abnormalities presented here.

Our findings indicate the independent role of stavudine in both incident lipoatrophy and lipohypertrophy. These findings concur with a recent case-control study of protease inhibitor naïve, nucleoside exposed individuals which implicated current stavudine use with both symptom phenotypes[17]. The aforementioned LIPOCO study also implicated stavudine use in peripheral lipoatrophy and in morphologic changes overall, however, with only nine subjects experiencing pure lipoatrophy analysis restricted to this symptom group was not possible[28]. Martinez et al. recently reported a 16% increase in the risk of lipodystrophy with lipoatrophy for every additional six months of stavudine use, a finding similar to the 18% increased risk per quarter reported here[31]. This study, however, was restricted to individuals on protease inhibitor containing regimens and concluded that the use of specific drugs is not significantly associated with lipodystrophy overall. The HIV Outpatient Study has also reported increased risk of moderate or severe lipoatrophy, assessed cross sectionally, associated with the use of stavudine and having used indinavir for greater than two years[21]. A prospective study of progressive lipoatrophy has reported increased risk with pre-highly active therapy duration of dual nucleoside therapy and stavudine duration[20]. This study also noted shorter time to onset of symptoms among those using triple regimens including a protease inhibitor and two nucleosides, particularly those containing stavudine in comparison to zidovudine. Conversely, a second study directly comparing zidovudine and stavudine as the backbone nucleoside component of highly active therapy regimens found no independent effect of stavudine on the development of any symptoms[35].

Several studies have also indicated non-treatment risk factors such as patient age and gender[21, 27, 31]. In agreement with the findings presented here, other studies have not confirmed these reports[2,18,11]. It has also been suggested that immune recovery during treatment may have an impact on the likelihood of morphologic changes[15,21,32], but others have

noted no relationship[26,30]. We found no significant differences in change from baseline of either CD4 or plasma viral load associated with incident symptomology. It is important to note that the studies reporting positive relationships do not appear to have adjusted analyses for adherence. If lipodystrophy-related symptoms are indeed direct adverse effects of antiretroviral agents we might expect to see both increased rates of lipodystrophy symptoms and the greatest clinical gains in among those highly adherent to therapy or at least with higher than mean plasma drug levels.

The sub-analysis of those without changes in weight had patterns of association similar to those seen in our cohort overall with the exception that AIDS was no longer independently associated with morphologic changes. This may indicate some difficulty in distinguishing disease associated weight loss from lipodystrophy-specific adipose wasting. Others have noted decreases and increases in body mass index associated with clinically validated reports of lipoatrophy and lipohypertrophy respectively[17,21,27]. These findings may suggest that changes in body weight are a true feature of some aspects of lipodystrophy syndrome for some individuals.

In general, it remains difficult to compare study findings regarding treatment impact on lipodystrophy-associated morphological changes due to variations in sample selection, diagnostic criteria, outcome measurement tools, selection of historical and current treatment variables and methodological differences in retrospective, cross sectional and prospective approaches. Despite these variations, the data presented here in conjunction with other recent studies suggest a coherent epidemiologic picture. High incidence rates of lipodystrophy-associated abnormalities, the indication of first line therapeutic agents in their occurrence and the possible relative unimportance of patient demographic characteristics, clinical status or immune reconstitution have implications for evolving treatment patterns.

High risk of eventual symptom occurrence may result in fear of adverse events thus impacting patterns of treatment seeking and initiation. The psycho-social impacts of self-perceived morphologic changes also require consideration. The relevance, if any, of these events to patterns of therapy discontinuation or change and adherence have not been well described. Improved surveillance, further etiologic inquiry and an understanding of the interrelationships between treatment acceptance and utilisation and lipodystrophy is imperative in our continued efforts to provide effective and acceptable long-term pharmacological management to those living with HIV disease.

5.6 SUMMARY

This study indicates that the incidence of morphologic and metabolic abnormalities is high among persons utilising antiretroviral therapy. However, it is difficult to delineate treatment effects. This cohort is comprised of individuals who have initiated therapy recently as well as those exposed to prolonged duration of treatment. It is also challenging to determine whether emerging events are due to current or past treatments given that regimens change frequently. In an attempt to limit the roles of long term therapy including a wide variety of agents the next chapter presents findings based on a sample of individuals with relatively short duration of treatment and, in a sub-analysis, exposure to a single therapeutic regimen.

5.7 REFERENCES

1. Hogg RS, Heath KV, Schechter MT, Yip B, Craib KJP, O'Shaughnessy MV, Montaner JSG. Improved survival among HIV infected individuals following initiation of antiretroviral therapy. *JAMA* 1998; 279 (6): 450-454.
2. Carr A, Samaras K, Burton S et al. A syndrome of peripheral lipodystrophy, hyperlipidemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS* 1998, 12;F51-F58.
3. Kotler DP, Rosenbaum K, Wang J, Pierson RN. Studies of body composition and fat distribution in HIV-infected and control subjects. *J Acquir Immune Defic Syndr* 1999; 20(3):228-237.
4. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1 protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998; 351:1881-1883.
5. Ho TTY, Chan KCW, Wong KH, Lee SS. Buffalo hump and facial wasting in HIV. *Lancet* 1998; 351:1736-37.
6. Dube MP, Johnson DL, Currier JS, Leedom JM. Protease inhibitor-associated hyperglycemia [Letter]. *Lancet* 1997; 350:713-714.
7. Safrin S, Grunfeld C. Fat distribution and metabolic changes in patients with HIV infection. *AIDS* 1999; 13:2493-2505.
8. Miller KD, Jones E, Yanovski JA, Shankar R, Feurstein I, Falloon J. Visceral abdominal-fat accumulation associated with use of indinavir. *Lancet* 1998; 12:F51-F58.
9. Roth VR, Kravcik SA, Angel JB. Development of cervical fat pads following therapy with human immunodeficiency virus type 1 protease inhibitors. *CID* 1998; 27:65-67.

10. Rozenbaum W, Gharakhanian S, Salhi Y et al. Clinical and laboratory characteristics of lipodystrophy in a French cohort of HIV-infected patients treated with protease inhibitors. *1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV.* San Diego, California 199 [Abstract 12].

11. Carr A, Samaras K, Thorisdottir A, et al. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidemia, and diabetes mellitus: a cohort study. *Lancet* 1999; 353:2093-9.

12. Sullivan AK, Feher MD, Nelson MR, Gazzard BG. Marked hypertriglyceridemia associated with ritonavir therapy [Letter]. *AIDS* 1998; 12:1395-6.

13. Walli RK, Hefort O, Michl GM et al. Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1 infected patients. *AIDS* 1998; 12:F167-F173.

14. Mercié P, Malvy D, Daucourt D et al. Case report of lipodystrophy observations in patients naïve of protease inhibitor treatment, Aquitaine Cohort, 1999. *1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV.* San Diego, California 1999 [Abstract 18].

15. Boufassa F, Dulioust A, Lascaux AS et al. Lipodystrophy in 685 HIV-1-treated patients: influence of antiretroviral treatment and immunovirological response. *HIV Clin Trials* 2001; 2:339-345.

16. Heath KV, Hogg RS, Chan KJ, Harris M, Montessori V, O'Shaughnessy MV. Lipodystrophy-Associated Morphologic, Cholesterol and Triglyceride Abnormalities In a Population-Based HIV/AIDS Treatment Database. *AIDS* 2001; 15:1-9.

17. Carr A, Miller J, Law M, Cooper DA. A syndrome of lipoatrophy, lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS* 2000; 14:F25-F32.

18. Paparizos VA, Kyriakis KP, Botsis C, Papastamopoulos V, Hadjivassiliou M, Stavrianeas NG. Protease inhibitor therapy-associated lipodystrophy, hypertriglyceridaemia and diabetes mellitus [Letter]. *AIDS* 2000; 14:903-905.

19. Tsiodras S, Mantzoros C, Hammer S, Samore M. Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: a 5-year cohort study. *Arch Intern Med* 2000; 160:2050-2056.

20. Mallal SA, John M, Moore C, James IR, McKinnon EJ. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS* 2000; 14:1309-1316.

21. Lichtenstein KA, Ward DJ, Moorman AC et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS* 2001; 15:1389-1398.

22. Saint-Marc T, Partisani M, Poizot-Martin I et al. A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. *AIDS* 1999; 13:1659-1667.

23. Polo R, Verdejo J, Martinez-Rodriquez S, Madrigal P, Gonzalez-Munoz M. Lipodystrophy, fat accumulation, and mixed syndrome in protease inhibitor-naïve HIV-infected patients [Letter]. *J Acquir Immune Defic Syndr* 2000; 25:284-286.

24. Mulligan K, Tai VW, Algren H, Abrams DI, Leiser RJ, Lo JC, Schambelan M. Altered fat distribution in HIV-positive men on nucleoside analog reverse transcriptase inhibitor therapy. *J Acquir Immune Defic Syndr* 2000; 26:443-448.

25. van der Valk M, Gisolf EH, Reiss P et al on behalf of the Prometheus study group. Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. *AIDS* 2000; 15:847-855.

26. Rakotoambinina B, Medioni J, Rabian C, Jubault V, Jais JP, Viard JP. Lipodystrophic syndromes and hyperlipidemia in a cohort of HIV-1-infected patients receiving triple combination antiretroviral therapy with a protease inhibitor. *J Acquir Immune Defic Syndr* 2001; 27:443-449.

27. Thiebaut R, Daucourt V, Mercie P et al. Lipodystrophy, metabolic disorders, and human immunodeficiency virus infection: Aquitaine Cohort, France, 1999. *CID* 2000; 31:1482-1487.

28. Saint-Marc T, Partisani M, Poizot-Martin I et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study. *AIDS* 2000; 14(1): 37-49.

29. Carpenter CCJ, Cooper DA, Fischl MA et al. Antiretroviral therapy in adults: Updated recommendations of the International AIDS Society- USA Panel. *JAMA* 2000; 283:381-390.

30. Gharakhanian S. The HIV-associated lipodystrophy syndrome: research, results, yet more questions. *AIDS* 2001; 15:271-273.

31. Martinez E, Morcroft A, Garcia-Viejo MA et al. Risk of lipodystrophy in HIV-1 infected patients treated with protease inhibitors: a prospective cohort study. *Lancet* 2001; 357:592-598.

32. Goujard C, Boufassa F, Deveau C, Laskri D, Meyer L for the Primo Group. Early occurrence of lipodystrophy in HIV-1-infected patients treated during primary infection.

8th Conference on Retroviruses and Opportunistic Infections. Chicago, Illinois 2001 [Abstract 403].

33. Striker R, Conlin D, Marz M, Wiviott L. Localized adipose tissue hypertrophy in patients receiving immunodeficiency virus protease inhibitors. *CID* 1998; 27:218-220.

34. Polo R, Verdejo J, Gonzalez-Munoz M et al. Lipodystrophy related to NRT inhibitors in HAART therapy. *39th Interscience Conference on Antimicrobial Agents and Chemotherapy*, San Francisco, USA 1999 [Abstract 1302].

35. Bogner RJ, Vielhauer V, Beckmann RA et al. Stavudine versus zidovudine and the development of lipodystrophy. *J Acquir Immun Defic Syndr 2001*; 27:237-244.

36. Danner SA, Carr A, Leonard J, et al. Safety, pharmacokinetics and preliminary efficacy of ritonavir, an inhibitor of HIV-1 protease. *N Engl J Med* 1995; 333:1528-1533.

37. Bernasconi E. Metabolic effects of protease inhibitor therapy. *AIDS Reader* 1999; 9:254-269.

CHAPTER 6

CUMULATIVE INCIDENCE OF LIPODYSTROPHY-ASSOCIATED MORPHOLOGIC AND LIPID ABNORMALITIES AMONG TREATMENT NAÏVE INDIVIDUALS INITIATING ANTIRETROVIRAL THERAPY

6.1 FORWARD

This manuscript is currently under review as "Incidence of Morphologic and Lipid Abnormalities: Gender and Treatment Differentials After Initiation of First Antiretroviral Therapy" with *The International Journal of Epidemiology*. This study was initiated in July of 2001 and completed in November of 2001. Co-authors include all thesis committee members.

6.2 INTRODUCTION

Standard care with highly active triple combination antiretroviral therapy for HIV infection has been linked to the emergence of morphologic and lipid abnormalities often appearing in constellation as a syndrome of HIV-associated lipodystrophy[1]. Morphologic changes include localised lipohypertrophy of the abdomen, breasts and dorso-cervical region, and peripheral lipoatrophy of the face, buttocks, arms and legs[1-3]. Metabolic changes include increased cholesterol and triglyceride levels[1,3].

Cross sectional and retrospective analyses indicate prevalence rates ranging from less than 10% to greater than 80% for these abnormalities (for a review see[4]). While the etiology of these abnormalities remains obscure, reports have identified increased risk associated with exposure to protease inhibitors[1,2,5-8] and nucleoside analogue reverse transcriptase inhibitors (nucleosides)[7,9-11] among other factors.

Inconsistencies in study findings may be due to variations in diagnostic criteria or outcomes assessment. While objective methods such as DEXA, computed tomography, and magnetic resonance imaging have been used, the resulting data is not well standardised in the context of HIV-associated lipodystrophy. These techniques can also be prohibitively costly and difficult to access. Therefore, many larger studies have relied on patient self-report and subjective/semi-qualitative clinical exam[6,11-18]. Patient self-report, while subject to misclassification, has been shown to be highly concordant with clinical findings of morphologic abnormalities[5]. Variability may also be due to differences in study design. Many etiologic investigations have relied on cross sectional[10,13,16,19], and/or retrospective[17,18,20] analyses or have included highly selected study subjects[15,18,20].

Neither the incidence of lipodystrophy-associated abnormalities nor the possible predictors of emerging symptoms subsequent to first initiation of standard therapy have been well described. Here we report the cumulative incidence and possible predictors of lipodystrophy-associated symptoms based on prospective self-report data from an observational cohort of persons initiating a variety of antiretroviral regimens.

6.3 METHODS

In British Columbia, Canada, the distribution of antiretrovirals free of charge to all eligible province residents is centralised in a provincial HIV/AIDS drug treatment program. All patients are registered in the program when first prescribed any antiretroviral agent. A complete prospective record of all therapies prescribed is maintained in addition to demographic and clinical data. Consenting patients provide additional information, including the occurrence of known or suspected adverse drug effects, through annual voluntary self-administered questionnaires. Since October of 1998, these have included symptoms

associated with lipodystrophy syndrome including lipoatrophy of the face, arms or legs, lipohypertrophy (weight gain in the abdomen or breasts and/or buffalo hump) and increased cholesterol and triglycerides.

The study population for the present analysis included antiretroviral naive individuals who initiated treatment between October 1998 and May 2001 and provided completed data regarding the occurrence of adverse drug effects at least three months and no more than twenty-four months after therapy initiation.

A broad range of socio-demographic and clinical characteristics were investigated in preliminary bivariate analyses. These included patient age, ethnicity, gender, employment status, education level, transmission risk group, plasma viral load and CD4 cell count at baseline, and change in plasma viral load and CD4 over follow-up. Treatment variables assessed included initial prescription of therapy by regimen makeup, therapy class inclusion and total duration by class and by agent for each of four protease inhibitors, five nucleosides and three non-nucleoside reverse transcriptase inhibitors. Variables significant at the $p<0.05$ level were offered for inclusion in logistic modelling to assess independent contributions to each of four incidence outcomes: lipoatrophy; lipohypertrophy; dyslipidemia; and mixed lipodystrophy (defined as having both peripheral lipoatrophy and one or more areas of lipohypertrophy). Initial models were conducted as intent-to-treat, retaining all subjects grouped for analysis by initial treatment regimen. A sub-analysis was restricted to those persons who remained on the initial treatment regimen throughout follow-up.

6.4 RESULTS

Table 6.4.1 summarises initial prescribed regimens, the proportion of subjects remaining on initially prescribed therapy and duration of follow-up for the 366 subjects eligible for

analysis. Thirty percent of individuals initiated antiretroviral treatment with regimens including two or three nucleosides and one non-nucleoside, 49% with two or three nucleosides plus a protease inhibitor, 10% used two protease inhibitors including ritonavir as a boosting agent, and 11% were restricted to dual nucleoside therapy. Overall, 59% of subjects initiated therapy with protease inhibitor containing regimens, 30% with non-nucleosides, and 100% utilised nucleoside inclusive regimens. In terms of non-treatment characteristics median age was 38 years, 68% were Caucasian, 89% male, 52% had greater than a high school education and 47% were employed. Median CD4 count at entry was 320 cells/mm^3 (IQR 100-430), median plasma viral load was 66,500 copies/ml and 16% had been diagnosed as having AIDS. Over the course of follow-up the median decline in plasma viral load was 66,298 copies/mL and CD4 cell counts increased by 120 cells/mm^3

In total, 216 (59%) of those initiating treatment remained on their first prescribed regimen at follow-up. These subjects did not differ substantially from the study group overall in terms of baseline characteristics or changes in laboratory markers (data not shown).

After a median duration of therapy of 12 months (range 3 to 23 months) the cumulative incidence was 29% for lipohypertrophy, 23% for lipoatrophy, 9% for increased cholesterol or triglycerides and 13% for mixed syndrome.

Table 6.4.2 summarise the findings of multivariate analysis for each of lipohypertrophy, lipoatrophy, dyslipidemia and mixed lipodystrophy in the cohort overall. Both incident lipoatrophy and lipohypertrophy were independently associated with use of protease inhibitor containing regimens (AOR 1.94; 95% CI 1.25, 3.03) and (AOR 1.76; 95% CI 1.09, 2.85) respectively. Risk of lipoatrophy and lipohypertrophy were also significantly greater for women (AOR 2.06; 95% CI 1.03, 4.12) and (AOR 2.36; 95% CI 1.17, 4.74) respectively. Mixed lipodystrophy was associated only with protease inhibitor inclusion in the treatment

regimen (AOR 2.27; 95% CI 1.14, 4.53) as was the occurrence of dyslipidemia (AOR 2.14; 95% CI 1.26, 3.65).

In the sub-sample of individuals remaining on initial treatment throughout follow-up univariate analysis revealed protease inhibitor use, female gender and use of triple therapy to be significantly associated with various outcomes of interest. For purposes of direct comparison, in final model building runs protease inhibitor use was forced into all models and gender was included in those for lipohypertrophy and lipoatrophy. No other variables retained significance after adjustment for these variables. As shown in Table 6.5.2, trends were consistent with those noted in the comprehensive analysis. However, protease inhibitor use and gender displayed marginal significance except for the relationship between protease inhibitor use and lipoatrophy (AOR 2.08; 95% CI 1.11, 3.56).

Table 6.4.1: Initial Treatment Regimens and Duration of Follow-up

Regimen	n (%)	On initial therapy at follow-up n(%)	Person months follow-up on initial therapy	Total person months follow-up*
2 or 3 Nucleosides/ 1 Non-nucleoside	107 (30)	97 (89)	968	1375
2 or 3 Nucleosides/ 1 Protease	176 (49)	134 (76)	1948	2330
2 or 3 Nucleoside/ Protease/Ritonavir	37 (10)	18 (48)	278	447
2 Nucloeosides only	39 (11)	16 (41)	333	406
Protease (n=217)				
Indinavir	141 (39)	94 (67)	1639	1900
Nelfinavir	35 (10)	23 (66)	247	377
Saquinavir	31 (9)	22 (67)	295	459
Ritonavir	49 (13)	29 (59)	415	636
Non-nucleoside (n=111)				
Nevirapine	104 (28)	91 (88)	905	1231
Delavirdine	1 (0)	1 (100)	10	25
Efavirenz	7 (2)	6 (86)	65	148
Nucleoside (n=366)				
Stavudine	255 (70)	225 (88)	2493	3284
Didanosine	50 (14)	36 (72)	456	642
Zalcitabine	2 (1)	1 (50)	25	29
Zidovudine	104 (28)	75 (72)	1040	1289
Lamivudine	308 (84)	280 (91)	2998	3894

* For individuals initiating therapy with specified regimen format

Table 6.4.2: Possible Predictors of Incident Symptoms Among 366 Participants in Intent to Treat and 216 Participants Remaining on Initial Treatment Regimen

Lipoatrophy

	Intent to Treat			Remaining on initial regimen		
Variable	**AOR**	**95% CI**	**P value**	**AOR**	**95% CI**	**P value**
Protease class	1.94	1.25, 3.03	0.003	1.99	1.11, 3.56	0.020
Female	2.06	1.03, 4.12	0.042	2.08	0.91, 4.74	0.082

Lipohypertrophy

	Intent to Treat			Remaining on initial regimen		
Variable	**AOR**	**95% CI**	**P value**	**AOR**	**95% CI**	**P value**
Protease class	1.76	1.09, 2.85	0.022	1.73	0.91, 3.27	0.094
Female	2.36	1.17, 4.74	0.016	2.19	0.94, 5.05	0.069

Lipid Abnormalities

	Intent to Treat			Remaining on initial regimen		
Variable	**AOR**	**95% CI**	**P value**	**AOR**	**95% CI**	**P value**
Protease class	2.14	1.26, 3.65	0.005	1.94	0.97, 3.89	0.063

Mixed Lipodystrophy

	Intent to Treat			Remaining on initial regimen		
Variable	**AOR**	**95% CI**	**P value**	**AOR**	**95% CI**	**P value**
Protease class	2.27	1.14, 4.53	0.020	1.80	0.71, 4.57	0.217

6.6 DISCUSSION

Our results indicate a high incidence of morphologic and lipid abnormalities among those initiating first-time antiretroviral therapy. Few comparable estimates of incidence are available, although reported figures are in agreement with the data presented here. A similar study of therapy naïve patients initiating triple drug regimens reported a prevalence of morphologic changes identified subjectively by both physician and patient of 17% after a median of 18 months of therapy[14]. Similarly, a study of 121 persons treated with triple therapy for primary HIV infection reported a cumulative incidence of morphologic changes of 18% at 24 months based on clinical exam[12]. Studies conducted among non-naïve subjects utilising protease inhibitor inclusive therapy report comparable rates of incidence[15,18].

Multivariate analyses indicate protease inhibitor class exposure in each of the symptom groups examined here. While some studies have not implicated treatment-related factors in the occurrence of morphologic abnormalities[10,19], the majority have identified specific protease inhibitors or protease inhibitor use in general as possible predictors of prevalent symptoms[1,5,7,8,17,21]. Studies utilising symptom specific analyses have also noted associations between duration of protease inhibitor exposure in both lipoatrophy and abdominal obesity[9], and between protease inclusive triple therapy duration and any lipodystrophy and lipoatrophy[14]. One study of highly active antiretroviral therapy exposed individuals has reported significantly increased risk of lipohypertrophy with protease inhibitor class therapy[6].

Reported dyslipidemia in our cohort was also independently associated only with use of protease inhibitor inclusive regimens. These findings are consistent with the known effects of protease inhibitors on lipid profiles and prior reports describing lipid abnormalities among those with treatment-related lipodsytrophy[5,22,23].

The occurrence and differential rates of presentation of lipodystrophy symptoms among women have been well described[24,25]. Unfortunately, many etiologic studies have not included substantial numbers of female subjects or have not assessed gender as an independent variable. Despite restricted power in our study (n=40 women), we noted a greater than two-fold increased risk of both lipoatrophy and lipohypertrophy among women. Martinez et al have similarly reported a relative hazard of 1.87 among women for lipodystrophy overall among pre-treated subjects exposed to protease inclusive triple therapy[14]. Three other studies that have included analysis by gender noted no increased risk among women, however, these studies were also limited by power constraints[11,13,18]. While reporting bias is a possible explanation for our findings, no increased risk of mixed lipodystrophy among women was noted suggesting that simple over-reported is not likely to have occurred.

The data presented here do not indicate a role of immune reconstitution as indicated by improvements in plasma viral load and/or CD4 cell count in the development of symptoms as has been suggested in some reports[13,16]. It is important to note that such previously published results were not adjusted for treatment adherence and that our findings are consistent with those of further studies[17,18].

The data reported here are based on patient self-report. Identification of morphologic abnormalities in clinical practice and large cohort studies is likely to remain reliant on relatively subjective measures. Moreover, patient assessment of morphologic abnormalities has been shown to correspond well to findings of physical exam[5]. To assess the accuracy of self-reported dyslipidemia, however, survey responses were compared to actual laboratory values for 134 individuals with laboratory data available in the three months prior to survey. Of those reporting high cholesterol or high triglycerides 94% and 84% had laboratory values indicating high cholesterol (defined as > 5.2mm/dL) or triglycerides (defined as >2.3mm/dL)

respectively. These findings indicate a low rate of false positives for self-reported dyslipidemia in this study.

The data presented here indicate a high incidence of lipodystrophy-associated abnormalities among persons initiating antiretroviral therapy. Increased risk associated with initiation of protease inhibitor inclusive regimens and among women is cause for concern. The long term clinical consequences of these disorders are not clear at this time. However, morphologically defined lipodystrophy has been associated with cardiovascular risk factors such as increased fasting insulin levels and diastolic blood pressure, impaired glucose tolerance, diabetes and hypertryglyceridemia among HIV positive subjects[26]. Moreover, there is some evidence that women may be more susceptible to the adverse metabolic effects of protease inhibitor containing regimens[27]. Clearly, large prospective studies of women need to be undertaken to determine whether the traditional consideration of female gender as a protective factor in terms of cardiovascular risk applies equally to those receiving protease inhibitor inclusive antiretroviral therapy for HIV infection.

6.7 SUMMARY

This study and the previous 2 chapters indicate that the morphologic and metabolic symptoms of "lipodystrophy syndrome" are common among those receiving antiretroviral therapy. Symptoms emerge at a high rate among those with variable histories of antiretroviral therapy and among naïve subjects initiating therapy. It also appears clear that these symptoms are, at least in part, a consequence of antiretroviral therapy *per se*.

In the following chapter we investigate the indirect effects of these and other adverse events and identify and describe patterns of adverse event report and the reaction of both physician and patients to the occurrence of adverse events of various types.

6.8 REFERENCES

1. Carr A, Samaras K, Burton S et al. A syndrome of peripheral lipodystrophy, hyperlipidemia and insulin resistance due to HIV protease inhibitors. *AIDS* 1998; 12:F51-F58.
2. Virben R, Aquilna C. Indinavir-associated lipodystrophy. *AIDS* 1998; 12:F37-F39.
3. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1 protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998; 351:1881-1883.
4. Safrin S, Grunfeld C. Fat distribution and metabolic changes in patients with HIV infection. *AIDS* 1999; 13:2493-2505.
5. Carr A, Samaras K, Thorisdottir A et al. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidemia, and diabetes mellitus: a cohort study. *Lancet* 1999; 353:2093-2099.
6. Bogner RJ, Vielhauer V, Beckmann RA et al. Stavudine versus zidovudine and the development of lipodystrophy. *J Acquir Immune Defic Syndr* 2001; 27:237-244.
7. Heath KV, Hogg RS, Chan KJ, Harris M, Montissori V, O'Shaughnessy MV. Lipodystrophy-associated morphologic, cholesterol and triglyceride abnormalities in a population-based HIV/AIDS treatment database. *AIDS* 2001; 15:1-9.
8. Striker R, Conlin D, Marz M, Wiviott L. Localized adipose tissue hypertrophy in patients receiving immunodeficiency virus protease inhibitors. *CID* 1998; 27:218-220.
9. Carr A, Miller J, Law M, Cooper DA. A syndrome of lipoatrophy, lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS* 2000; 14:F25-F32.

10. Saint-Marc T, Partisani M, Poizot-Martin I et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study. *AIDS* 2000; 14:37-49.

11. Mallal SA, John M, Moore C, James IR, McKinnon EJ. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS* 2000; 14:1309-1316.

12. Goujard C, Boufassa F, Deveau C, Laskri D, Meyer L for the Primo Group. Early occurrence of lipodystrophy in HIV-1-infected patients treated during primary infection. *8th Conference on Retroviruses and Opportunistic Infections*. Chicago, Illinois 2001 [Abstract 403].

13. Boufassa F, Dulioust A, Lascaux AS et al. Lipodystrophy in 685 HIV-1-treated patients: influence of antiretroviral treatment and immunovirological response. *HIV Clin Trials* 2001; 2:339-345.

14. Martinez E, Morcroft A, Garcia-Viejo MA et al. Risk of lipodystrophy in HIV-1 infected patients treated with protease inhibitors: a prospective cohort study. *Lancet* 2001; 357:592-598.

15. van der Valk M, Gisolf EH, Reiss P et al on behalf of the Prometheus study group. Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. *AIDS* 2000; 15:847-855.

16. Lichtenstein KA, Ward DJ, Moorman AC et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS* 2001; 15:1389-1398.

17. Tsiodras S, Mantzoros C, Hammer S, Samore M. Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: a 5-year cohort study. *Arch Intern Med* 2000; 160:2050-2056.

18. Rakotoambinina B, Medioni J, Rabian C, Jubault V, Jais JP, Viard JP. Lipodystrophic syndromes and hyperlipidemia in a cohort of HIV-1-infected patients receiving triple combination antiretroviral therapy with a protease inhibitor. *J Acquir Immune Defic Syndr* 2001; 27:443-449.

19. Thiebaut R, Daucourt V, Mercie P et al. Lipodystrophy, metabolic disorders, and human immunodeficiency virus infection: Aquitaine Cohort, France, 1999. *CID* 2000; 31:1482-1487.

20. Mulligan K, Tai VW, Algren H, Abrams DI, Leiser RJ, Lo JC, Schambelan M. Altered fat distribution in HIV-positive men on nucleoside analog reverse transcriptase inhibitor therapy. *J Acquir Immune Defic Syndr* 2000; 26:443-448.

21. Schindler JT, Sponer KM, Deker CF. Buffalo humps associated with protease inhibitors [Letter]. *Ann Intern Med* 1998; 129:164.

22. Sullivan AK, Feher MD, Nelson MR, Gazzard BG. Marked hypertriglyceridemia associated with ritonavir therapy [Letter]. *AIDS* 1998; 12:1395-6.

23. Behrens G, Dejam A, Schmidt H et al. Impaired glucose tolerance, beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors. *AIDS* 1999; 13:F36-F70.

24. Hadigan C, Miller K, Corcoran C et al. Fasting hyperinsulinemia and changes in regional body composition in human immunodeficiency virus-infected women. J *Clin Endocrinol Metab* 1999; 84:1932-1937.

25. Dong KL, Bausserman LL, Flynn MM et al. Changes in body habitus and serum lipid abnormalitites in HIV-positive women on highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 1999; 21:107-113.

26. Hadigan C, Meigs JB, Corcoran C et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clinical Infectious Diseases* 2001; 32:130-139.

27. Pernerstorfer-Schoen H, Jilma B, Perschler A et al. Sex differences in HAART-associated dyslipidaemia. *AIDS* 2001; 15:725-734.

CHAPTER 7

PROACTIVE NON-ADHERENCE TO ANTIRETROVIRALS DUE TO SYMPTOMS OF ADVERSE DRUG EFFECTS

7.1 FORWARD

This chapter is currently under review as "Intentional and Pro-active Non-adherence Due to Adverse Symptoms Associated With Antiretroviral Therapy." with the *Journal of Acquired Immune Deficiency Syndromes*. This study was initiated in November of 2001 and completed in February 2002. Co-authors include all thesis committee members.

7.2 INTRODUCTION

Antiretroviral agents used in the treatment of HIV disease are associated with a wide range of adverse drug effects[1-3]. The relevance of drug toxicities with direct consequences in terms of morbidity or mortality is clear- generally prompting clinical action such as treatment, antiretroviral change or cessation dependent on the type and severity of the symptoms. Other adverse drug effects, however, are considered relatively benign in terms of direct health effects. In these cases, patients may be encouraged to continue virologically successful treatment[4,5]. For example, lipodystrophy-related morphologic changes can be disfiguring and may raise issues of disclosure and stigmatization for those affected, potentially impacting both social relationships and self perception of health[4,6,7]. Despite these features, morphologic abnormalities are not considered by many physicians to threaten physical health or impact HIV-related clinical outcomes.

Theoretically, however, even relatively benign symptoms associated with the use of antiretroviral agents may have important implications for long-term clinical outcomes if they are associated with reduced antiretroviral adherence. Studies of medication-taking behaviour

indicate that patients may alter treatment in order to decrease side effects and improve quality of life[8]. Several reports indicate that both antiretroviral regimen adherence and continuation to be negatively affected by the occurrence of drug-related toxicities[8-12].

These and other studies, however, do not describe the extent of adverse events in the general population of antiretroviral users, patient's responses to symptoms, or whether these vary depending upon the type of symptoms experienced. Nor have prior investigations differentiate between purposeful and unintentional non-adherence. These distinctions are of great importance. While high pill burden, complex dosing schedules and caveats as to timing of medications may result in unintentional imperfect adherence, these problems, for the most part, are not currently amenable to change[13,15]. In theory, proactive or intentional self-management may be curtailed if underlying causes, such as the occurrence of adverse drug effects, can be identified and addressed.

In the present study we describe the frequency of symptom report for a variety of adverse drug effects, the action taken or recommended by physicians and the actual response of patients in a large observational cohort of persons receiving antiretroviral therapy. Furthermore we identify occasions of patient reported antiretroviral self-management i.e., proactive and purposeful alterations in antiretroviral medication, in direct response to adverse drug effects. and examine factors associated with these activities.

7.3 Methods

In British Columbia, Canada the distribution of antiretrovirals free of charge to all eligible province residents is centralised in a provincial HIV/AIDS drug treatment program. The drug treatment programme thus maintains a complete prospective record of therapy prescription and basic demographic and clinical data. Consenting patients provide additional

information through annual voluntary self-administered questionnaires. The study population for this cross sectional analysis included all drug treatment program participants who responded to an annual participant survey between January 1 and November 1, 2001.

For the purpose of this study, annual questionnaires included detailed information regarding physician and patient response to adverse drug effects. A list of 42 known or suspected adverse drug effects associated with antiretroviral therapy were compiled. These were then classified through a consensus process by three tertiary HIV care providers as being either subjective or objective. Subjective symptoms were defined as those that would not be identifiable through clinical examination or medical tests, relying primarily on patient report for identification. Each symptom was then further classified depending on whether, in its usual form, it would or would not prompt clinical action. This process yielded 4 sub-groups of adverse effects: subjective/action (SA); subjective/no action (S); objective/action (OA) and; objective/no action (O). Symptoms typical of each category are exemplified in Table 7.3.1.

Patients were asked to record the occurrence and general severity (mild, moderate or severe) for each of the 42 symptoms over the past year. For each of the four symptom categories, patients were then asked to respond to two questions. The first asked what the patient's physician did or recommended in response to symptoms in that group. These responses were classified as: not applicable (physician was not informed of symptoms); did nothing; investigated symptoms and/or monitored; did not think symptoms were antiretroviral therapy-related; recommended or prescribed treatment for symptoms; stopped antiretrovirals; interrupted antiretroviral therapy and; changed antiretroviral therapy.

The second question asked patients to describe what they actually did in response to these same symptoms. Patient responses were classified as: did nothing; followed doctor's advice; treated symptoms; stopped all therapy indefinitely; interrupted therapy temporarily (or

"drug holiday") and; sometimes skipped the antiretroviral drugs causing the symptoms(s) or took fewer doses.

These questions referred to symptom(s) experienced for each symptom category rather than each individual symptom reported. Therefore, more than one answer choice could be selected with physicians and patients reporting several actions in response to several different symptoms contained in a symptom group.

A primary outcome of interest was self-medication through proactive and purposeful antiretroviral therapy adjustment. Self-medication was defined as reporting either skipping or altering dosages of selective regimen components or temporary cessation of therapy not recommended by the physician in response to any adverse drug effects in the past year.

Explanatory variables of interest included patient characteristics, specifically; age, gender, educational level and ethnicity. Clinical variables included last plasma viral load and CD4 cell count prior to survey and total duration of antiretroviral therapy. Adverse effect symptom variables included total number of symptoms, number of symptoms reported in each symptom category and the presence of symptoms categorised as severe.

Standard techniques were used for bivariate comparisons. All variables associated with self-medication in bivariate analyses at the $p<0.10$ level were offered for inclusion into multivariate models. Logistic regression was used to identify variables independently associated with the occurrence of proactive self-medication. All reported p-values are two sided.

Table 7.3.1: Categorisation of Common Symptoms Associated With Antiretroviral Therapy Use.

Symptom Category	Action Required	
	No	**Yes**
Subjective	Nightmares	Abdominal pain
	Taste alterations	Depression
	Aches	Nausea
	Malaise	Headache
Objective	Peripheral lipoatrophy	Rash
	Hypertrophy of breasts	Fever
	Central lipohypertrophy	Diarrhea
	Buffalo hump	Bloody urine

7.4 RESULTS

A total of 638 program participants provided completed questionnaires and were eligible for analysis. Overall, subjects reported having experienced an average of 12 antiretroviral-related symptoms in the preceding year. Five hundred and sixty four patients (88.4%) reported subjective symptoms generally not requiring any action. Of these individuals, 279 (49%) reported at least one of these symptoms to be severe. Of the 485 (76%) individuals reporting subjective, action-requiring symptoms 239 (49%) reported one or more severe symptoms. In the objective-no action category, 373 (58.5%) reported such symptoms with 110 (29%) reporting severe symptoms. Lastly, 465 (72.9%) reported objective symptoms requiring action and 144 (31%) of these reported one or more severe symptoms. Of those reporting symptoms in each category, 13% of those with group S symptoms, 11% with group SA symptoms, 15% with group O symptoms and 8% of those with group OA symptoms did not inform their physicians of these symptoms.

Overall, physicians investigated the majority of symptoms and offered treatment. Despite this, patients often reported doing nothing in response to adverse symptoms more frequently than using treatment. Physicians were least likely to recommend treatment and most likely to do nothing in response to group O symptoms.

While the proportion of patients reporting interruptions in therapy was similar to the proportion of physicians recommending this action for each symptom group, patients opted to stop antiretroviral therapy approximately 3% of the time while physicians recommended this course of action in approximately 1% of cases. On the whole, subjective symptoms appear to elicit recommendations for treatment changes (group S=24% and group SA=20% versus group O=11% and group OA=13%) and interruptions (group S=13% and group SA=12% versus group O=7% and group OA=8%) from physicians more often than objective symptoms.

Between 4% and 7.4% of subjects reported proactive self-medicating through skipping doses or certain regimen components depending on symptom type. Overall 70 individuals or 11% reported self-medication for one or more symptom groups over the prior year.

A univariate comparison of those reporting self-medication versus those not reporting such action is shown in Table 7.4.1. No significant differences between groups was noted for CD4 cell count, gender, ethnicity, age or total duration of antiretroviral therapy (all $p>0.05$). Those reporting self-medication were less likely to have plasma viral load below 400 copies/ml with 8% of those with plasma viral load <400 copies/ml versus 22% of those with higher levels reporting self-medication ($p<0.001$). Similarly, 9% of those completing high school reported self-medication as compared to 23% of those with less than a high school education ($p<0.001$). Rates of self-medication among those who were unemployed were double those among employed participants (14% versus 7%, $p=0.005$). In terms of symptoms associated with adverse drug effects, those reporting self-medication reported a greater number of symptoms overall and in each of the symptom groups although this difference did not reach statistical significance for group O symptoms. Moreover, of those reporting at least one severe symptom 15% reported self-medication in comparison to just 5% of those without severe symptoms ($p<0.001$).

Table 7.4.2 summarizes possible predictors of self-medication. Plasma viral load <400 copies/mL and having completed high school were inversely and independently associated with self-medication (AOR 0.35, 95% CI 0.21, 0.61) and (AOR 0.43, 95% CI 0.24, 0.78) respectively. Those reporting at least one severe symptom were more than twice as likely to report self medication (AOR 2.24, 95% CI 1.16, 4.33). Similarly each additional symptom in the objective/action group was associated with a 25% increase in the odds of intentional self-medication (AOR 2.24, 95% CI 1.10, 1.43).

Table 7.4.1: Characteristics of 638 Participants and Comparison of Those Reporting and Not Reporting Self-Medication

Characteristic	Self-medication (n=70) n (%)	No Self-medication (n=568) n (%)	P value
Median baseline CD4 (IQR)	370 215 - 512	395 253 - 590	0.160
Plasma viral load < 400 copies/ml			<0.001
Yes	40 (57)	460 (81)	
No	30 (43)	108 (19)	
Education			<0.001
High	47 (67)	489 (86)	
Low	23 (33)	79 (14)	
Employed			0.005
Yes	20 (28)	263 (46)	
No	50 (72)	305 (54)	
Gender			0.230
Male	64 (91)	537 (95)	
Female	6 (9)	31 (5)	
Ethnicity			0.076
Caucasian	52 (74)	471 (83)	
Other	18 (26)	97 (17)	
Median Age (yrs)	43.0	44.0	0.744
Therapy duration* Median (IQR)	56.5 39.8 – 68.0	57.6 36 – 79	0.226

*** in months**

Table 7.4.1 Continued: Characteristics of 638 Participants and Comparison of Those Reporting and Not Reporting Self-Medication

Characteristic	Self-medication (n=70) n (%)	No Self-medication (n=568) n (%)	P value
Median no. symptoms (IQR)	17.5 11.8 – 23.0	11.0 5.0 – 18.0	<0.001
Type S *	8.5	5.0	<0.001
Type SA[§]	5.0	3.0	<0.001
Type O[¶]	1.0	1.0	0.081
Type OA[∞]	3.0	1.0	<0.001
Severe symptom(s)			<0.001
Yes	56 (80)	312 (55)	
No	14 (20)	256 (45)	

Reported number of symptoms from the group: subjective- no action*, subjective-requires action[§], objective- no action[¶] and objective- requires action[∞].

Table 7.4.2: Multivariate Analysis: Variables Independently Associated With Self-Medication.

Variable	Adjusted Odds Ratio	95% Confidence Interval	P value
Total OA symptoms	1.25	1.10, 1.43	<0.001
Plasma viral load<400 copies/mL	0.35	0.21, 0.61	<0.001
≥ High school education	0.43	0.24, 0.78	0.006
Severe symptom(s)	2.24	1.16, 4.33	0.016

7.5 DISCUSSION

The present study is unique in that it explores self-perceived symptoms associated with antiretroviral use among patients and their subsequent responses in terms of adverse effect management. Rather than broadly defined adherence rates which can be affected by many factors, our study describes purposeful alterations in antiretroviral therapy as a direct response to adverse drug-related symptoms specifically.

In our cohort, adverse symptoms caused by or suspected by patients to be a result of antiretroviral therapy are common with patients reporting an average of 12 symptoms of drug toxicity over the previous year. Moreover, the majority of subjects experienced at least one symptom which they felt to be severe. In a recent study conducted by Ammassari and colleagues, of 358 subjects on triple antiretroviral regimens, 51% of patients reported having at least one moderate or severe symptom related to therapy use in the preceding four weeks[12]. A substantial proportion of patients in our cohort reported that they did not disclose symptoms to their care provider. Although this was slightly less common for symptoms for which physicians would be expected to take action, 11% and 8% respectively did not tell physicians about symptoms for which some treatment and further investigation could have been provided.

For the most part, patterns of physician action or recommendation for each symptom group were mirrored in patient actions. As self-reported by patients, physician recommendations to stop therapy indefinitely were relatively rare, occurring, at most 1.1% of the time for any given symptom group. Two to three times as many patients however, opted to discontinue therapy due specifically to the occurrence of adverse effects. In general, studies of discontinuation due to drug-related toxicities are based on clinical trial data. Reported rates of discontinuation under these circumstances are generally higher than those seen here, ranging from 5 to10% depending on the regimen of interest and duration of follow-up[16,17].

However, these clinical trial data described discontinuation of current therapy rather than indefinite discontinuation of all therapy as in our cohort. Moreover, clinical trials might be expected to have higher rates of discontinuation as therapies under scrutiny are generally of unproven efficacy.

A unique finding of our study is that 11% of subjects admitted to either selectively skipping medications or to taking a drug holiday not recommended by their physicians in order to ameliorate symptoms. One other study that has examined these phenomena based on in-depth data from 99 HIV patients, found that 36 subjects reported altering their medication without medical guidance[5]. Using qualitative techniques the aforementioned study implicated that quality of life and adverse drug effects were two important reasons given for this activity.

It is important to note that the figure of 11% reported here is likely to be an underestimate. The subjects in this cohort, for the most part, are highly experienced as regards antiretroviral treatment. Average CD4 cell counts and viral load measures indicate a population with successful treatment responses. Participants are limited to respondents of a voluntary survey, potentially a more adherent sub-group of individuals. Lastly, the possibility of social desirability bias can not be discounted and may have led to under-reporting of self-medication. In addition, these figures apply to a one year time period. Over a period of several years of treatment a greater proportion of individuals overall may use self-medication strategies at one time or another. A further limitation of the data presented here is that physician and patient responses were aggregated and assessed by group rather than for each individual symptom. Therefore it is not possible to assess agreement between physician and patient responses to specific symptoms.

In multivariate analysis in our cohort, self medication was associated with having a plasma viral load >400 copies/mL. This suggests that individuals with poorer response to

therapy are more likely to adjust their medications. Conversely, higher plasma viral load at study baseline may be a consequence of similar self-medication prior to the study survey. In the above noted study of undisclosed medication altering, those reporting medication "fiddling" were less symptomatic but reported poorer health status than compliant subjects[5]. Studies of regimen modification and discontinuation indicate that poor virologic response is a primary reason for these outcomes[18]. Adherence studies suggest that individuals with higher viral loads and/or lower CD4 counts may be more likely to adjust therapeutic regimens[18-20] and have lower rates of compliance[12,21]. However, these studies do not distinguish between physician and patient mediated decisions to modify or discontinue treatment and do not examine proactive self-medication specifically.

Lower educational status was also associated with self-medication. While some studies have indicated that marginalised individuals may be less adherent to medication regimens overall, research to date indicates no consistent relationship between social class, ethnicity or education and likelihood of non-adherence[22-24]. In the present context this finding may suggest that those with lower educational status have greater difficulty in understanding the importance of strict regimen adherence. Possibly they may also be less able to express their concerns regarding adverse drug effects or feel less disposed to do so.

Having one or more symptoms classified as severe as well as the number of objective action-requiring symptoms reported by patients was associated with increased risk of self-medication. In the study by Ammassori et al, patients reporting non-adherence in the three days prior to interview had higher median side effect scores based on the number and severity of symptoms reported[12]. When taken together, these findings suggest that total symptom burden as a function of symptom severity and number may be of greatest relevance.

That the total number of objective symptoms generally requiring physician action was of importance after adjustment for total number of all symptoms is noteworthy. Symptoms in this class include rash, vomiting, bloody urine, kidney stones, osteoporosis, avascular necrosis, jaundice and diarrhea. These would be clearly apparent to patients and, in most cases, specific symptom report would require diagnosis by the treating physician. Such symptoms should generally prompt investigation and treatment or medication adjustment. However, in nearly 20% of cases patients reported that physicians took no action while specific treatment was offered in only 41% of cases. Theoretically, the blatant nature of these symptoms and attached specific diagnoses in conjunction with the perception that no action or treatment was provided might yield a greater impetus to self-medicate.

Regardless of the factors related to proactive self-medication the high rate of this strategy in our cohort is of great concern. It has been established that patients make personal decisions to manage medications based on their beliefs and information which may take into consideration physical, economic, psychological and social factors[25]. Patients themselves actively attempt to make the best decisions for their health, weighing the advantages and disadvantages of a recommended course of treatment based on a myriad of factors including the limitations that medication may impose[25]. Studies evaluating antiretroviral compliance specifically indicate that patient's experience or fear of possible side effects is an important reason for non-adherence[11,26,27] or for refusal or cessation of therapy[10]. In one recent report, of the 21% who discontinued first antiretroviral therapy 7% did so due to symptoms of side effects and in 5% of subjects the patient's decision was the only reason given for discontinuation[20]. Lastly, patients have been reported to discontinue protease inhibitor inclusive therapy or to desire a switch to protease sparing regimens despite virologic success due to morphological symptoms of HIV-associated lipodsytrophy[6,28].

These studies, in conjunction with the findings reported here suggest that the relevance of subjectively identified symptoms and those not generally considered cause for treatment change or cessation may be greatly underestimated. Our results indicate that self-medication occurs in relation to symptoms regardless of their strict clinical importance. Moreover, the actual presence of symptoms and their true relationship to antiretroviral use may be of less relevance than the patient's perception. The effect on adherence of symptoms which can be clinically validated by laboratory tests or examination and which pose a risk to patient health may be reduced if, as is recommended, medication regimens or doses are adjusted or treatment offered to ameliorate symptoms. With trust and communication in the therapeutic relationship being of paramount importance in maintaining adherence[29,30], physicians can also ill afford to be indifferent to patient identified or clinically benign symptoms, a reaction which has been reported by some HIV-infected individuals[4]. Commitment to, and the success of, long-term antiretroviral therapy requires a fine balance between encouraging patients to maintain efficacious therapy and being alert to the implications of symptoms related to medication use for social and emotional well-being and adherence.

7.6 SUMMARY

In the final chapter we turn to a summary of the main findings of our investigation into the epidemiology of lipodystrophy in British Columbia. The implications and unique contributions of this study and consequent recommendations are discussed.

7.7 REFERENCES

1. Kaul DR, Cinti SK, Carver PL, Kazanjian PH. HIV protease inhibitors: advances in therapy and adverse reactions, including metabolic complications. *Pharmacotherapy* 1999; 19:281298.
2. Lee BL, Safrin S. Interactions and toxicities of drugs used in HIV infection. *Clin Infect Dis* 1992; 14:773-779.
3. Barditch-Crovo P, Chaisson RE. Adverse reactions to therapy for HIV infection. *Em Med Clin N Am* 1995; 13:133-146.
4. Collins E, Wagner C, Walmsley S. Psychosocial impact of the lipodystrophy syndrome in HIV infection. *AIDS Reader* 2000; 10:546-551.
5. Aversa S, Kimberlin C. Psychosocial aspects of antiretroviral medication use among HIV patients. *Patient Educ Couns* 1996; 29:207-19.
6. Martinez E, Garcai-Viejo MA, Blanch L, Gatell JM. Lipodystrophy syndrome in patients with HIV infection: quality of life issues. *Drug Saf* 2001; 24:157-166.
7. Dukersa NHTM, Stoltea IG, Albrechta N, Coutinho RA, de Witac JBF. The impact of experiencing lipodystrophy on the sexual behaviour and well-being among HIV-infected homosexual men. *AIDS* 2001; 15:812-813.
8. Chesney A, Ickvics J, Hecht M, Sikipa G and Rabkin J. Adherence: a necessity for successful HIV combination therapy. *AIDS* 1999; 13 (suppl A):S271-S278.
9. Haubrich RH, Little SJ, Currier JS, Forthal DN, Kemper CA, Beall GN, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. *AIDS* 1999; 13:1099-1107.

10. Bassetti S, Battegay M, Furrer H et al. Why is highly active antiretroviral therapy (HAART) not prescribed or discontinued? Swiss Cohort Study. *J Acquir Immune Defic Syndr* 1999; 21:114-119.

11. Mehta S, Morre RD, Graham NMH. Potential factors affecting adherence with HIV therapy. *AIDS* 1997; 11:1665-1670.

12. Ammassari A, Murri R, Pezzotti P et al. Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. *J Acquir Immune Defic Syndr* 2001; 28:445-449.

13. Eldred L, Wu A, Chaisson RE, Moore RD. Adherence to antiretroviral and Pneumocystis prophylaxis in HIV disease. *J Acquir Immune Defic Syndr* 1998; 18:117-125.

14. Kalichman SC, Ramachandra B, Cath S. Adherence to combination antiretroviral therapies in HIV patients of low health literacy. *J Gen Intern Med* 1999; 14:267-273.

15. Haynes RB, McKibbon KA, Kanani R. Systematic review of randomised trials of intervention to assist patients to follow prescriptions for medications. *Lancet* 1996; 348:383-386.

16. Hammer S, Kathleen ES, Hughes MD et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4+ cell counts of 200 per cubic millimetre or less. *N Engl J Med* 1997; 337:725-733.

17. Gulick RM, Mellors JW, Havlir D et al. Treatment with indinavir , zidovudine and lamivudine n adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med* 1997, 337:734-739.

18. Mocroft A, Youle M, Moore A et al. Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre. *AIDS* 2001; 15:185-194.

19. Van Roon EN, Verzijl JM, Juttmann JR et al. Incidence of discontinuation of highly active antiretroviral therapy (HAART) and its determinants. *J Acquir Immune Defic Syndr* 1999; 20:290-294.

20. d'Arminio Monforte A, Lepri AC, Rezza G et al. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naïve patients. *AIDS* 2000; 14:499-507.

21. Gordillo V, del Amo J, Soriano V, Gonzalez-Lahoz J. Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. *AIDS* 1999; 13:1763-1769.

22. Burgos M, Revsin NS, VilasA, Fontan L. Obstacles in treatment adherence: patient reasons. *International Conference on AIDS.* Geneva, Switzerland 1998 [abstract 32400].

23. Singh N, Berman SM, Swindells S et al. Adherence of human immunodeficiency virus-infected patients to antiretroviral therapy. *Clin Infect Dis* 1999; 29:824-830.

24. Besch CL. Compliance in clinical trials. *AIDS* 1995; 5:1-10.

25. Donovan JL, Blake DR. Patient non-compliance: deviance or reasoned decision-making? *Soc Sci Med* 1992; 34:507-513.

26. Samet J, Libman H, Steger J et al. Compliance with zidovudine therapy in patients infected with human immunodeficiency virus, type 1: a cross sectional study in a municipal hospital clinic. *Am J Med* 1992; 92:495-502.

27. Broers B, Morabia A, Hirschel B. A cohort study of drug users' compliance with zidovudine treatment. *Arch Intern Med* 1994, 154:1121-1127.

28. Silversides A. Protease inhibitors raising quality-of-life issues for HIV patients. *J Am Med College* 1999; 160:894.

29. Altice FL, Mostashari F, Friedland GH. Trust and acceptance of and adherence to antiretroviral therapy. *J Acquir Immune Defic Syndr* 2001; 28:47-58.

30. Roberts KJ, Volberding P. Adherence communication: a qualitative analysis of physician patient dialogue. *AIDS*, 1999; 13: 1771-1778.

CHAPTER 8

GENERAL DISCUSSION

8.1 SUMMARY OF STUDY FINDINGS

Data from the British Columbia HIV/AIDS Drug Treatment Program has provided insight into the epidemiologic parameters of lipodystrophy-related symptoms within the context of a large, unselected population of antiretroviral users under conditions of universal access to HIV-related care and therapy. Preliminary exploration has also indicated that clinically "benign" adverse effects of therapy which include lipodystrophy-associated symptoms may be of importance beyond that of their strict clinical relevance in terms of regimen adherence.

The symptoms of lipodystrophy affect a large proportion of persons using antiretroviral therapy for HIV disease in British Columbia. We have estimated that lipodystrophy, as identified through patient self-report affects approximately one half of persons receiving antiretroviral treatment for HIV disease in British Columbia. Lipoatrophy and lipohypertrophy are more common than lipomatosis or laboratory abnormalities. Others have reported similar or higher rates of prevalent morphological changes[1-3] while most clinical studies indicate a greater rate of triglyceride and cholesterol abnormalities[2,4,5]. It is likely that our estimates are very conservative as under-reporting of dyslipidemia appears to be common. In a sub analysis of treatment program participants with laboratory data concurrent with survey responses we noted that of 107 individuals reporting that they did not have increased cholesterol levels, 40 or 37% actually had higher than normal cholesterol based on laboratory measures. Similarly of 134 reporting normal triglycerides, 60 individuals or 45% actually had elevated triglyceride levels.

Cross sectional analyses implicated older age, unemployment, use of alternative therapies, protease inhibitor exposure and duration of stavudine inclusive therapy in prevalent lipodystrophy. These findings were adjusted for duration of any therapy, use and duration of class specific therapies, adherence and clinical characteristics.

Incident lipodystrophy-associated symptoms in our cohort were also common both within the cohort as a whole and among those recently initiating antiretroviral therapy. Generally, patterns of incidence mirrored prevalence patterns with lipohypertrophy and lipoatrophy being the most commonly reported symptoms, and laboratory abnormalities less common.

Within the cohort as a whole annual incidence of lipohypertrophy was approximately 21% and lipoatrophy approximately 27% while any type of morphologic change was reported among 33% of participants. Among those naïve to therapy and initiating antiretroviral use the cumulative incidence of lipohypertrophy was 29% and of lipoatrophy was 23% while 32% reported any morphologic change after a median of 12 months of therapy. Published studies report similar, if somewhat lower rates of incidence[6-9]. The rates reported here may be greater than previously published estimates as a result of over reporting of morphologic symptoms. In the case of the analysis based on all cohort members, higher rates of symptoms may also be due to more extensive therapy exposure overall as many studies published to date are restricted to individuals with comparatively short therapeutic histories or are limited in terms of the therapeutic regimens explored.

In both studies based on incident symptoms the emergence of lipohypertrophy and lipid abnormalities were associated with the use of protease inhibitor class therapies. The vast majority of published clinical and cohort studies also indicate associations between protease inhibitor use or specific protease inhibitor regimens and the occurrence of morphologic

abnormalities despite wide variation in sample selection and diagnostic criteria[10-16]. The association between dyslipidemia is also consistent with the majority of published data and in all likelihood reflects the known impact of protease inhibitors on lipid profiles[11,15,17,18].

Stavudine use (or duration of use) was associated with both lipoatrophy and lipohypertrophy in an initial analysis including all subjects. In analysis limited to naïve patients initiating therapy, however, female gender, and not stavudine inclusive therapy, appeared to contribute to the emergence of these symptoms. These inconsistencies have several explanations. The association between morphologic changes and stavudine use seen in our cohort is not unique. Others have reported stavudine as contributing to lipoatrophy[14,19,20,21,6] and lipohypertrophy[14] and/or morphologic changes overall[14,19]. For the most part however, subjects in these studies were either highly experienced with nucleoside based regimens or the noted association was related to the duration of stavudine use, similar to results from our cohort. It is possible that stavudine use was not noted as a risk factor in our cohort of recent therapy initiates as pre-exposure and thus duration of stavudine therapy were not extensive enough to result in symptoms. This may indicate a "threshold" effect with nucleoside-related symptom emergence requiring longer term stavudine exposure. Conversely, stavudine may result in symptoms among some individuals due to complex interrelationships with other regimen components and their duration of use which have yet to be delineated. Confounding factors not adequately assessed or biases common to multiple studies are other obvious possible mechanisms.

The indication among naïve subjects that women may be more susceptible to morphologic abnormalities is also of interest. While this may simply be due to reporting bias, this does not explain the absence of any relationship to gender in analyses based on the cohort overall. A recent report may offer some insight. In a study of 42 women undergoing highly

active antiretroviral therapy researchers found that women who developed morphologic changes were most likely to do so within the first year of therapy and, moreover, once recognised, symptoms generally remained stable over long-term follow-up[22]. If relatively early occurrence and future stability is a feature of lipodystrophy symptoms among women then the discrepancy in our result may be explained. Women initiating treatment may indeed be more likely to report incident symptoms in the first year or so of therapy as was seen among our previously naïve subjects. Continued follow-up of this cohort will help to determine whether gender-related patterns of reporting change over additional months of therapy exposure.

In a final study, preliminary data analysis suggested that proactive, intentional regimen adjustment occurs in direct response to adverse drug effects. In terms of lipodystrophy specifically, approximately 5% of subjects reported self-medication as a direct result of these symptoms. In multivariate analysis, proactive self-medication due to known or suspected adverse drug effects was associated with lower educational level, having a plasma viral load of <400 cells/mm^3 and having one or more symptoms categorised as severe. A positive association was also seen with the total number of objectively identifiable symptoms which would generally require action in terms of investigation, treatment or adjustment of antiretroviral therapy. It remains difficult to provide comparisons to the findings of others as there is a paucity of studies regarding proactive self-medication for HIV disease or chronic illness in general. The impact that self-medication activities may have on long-term individual treatment patterns and clinical outcomes is unknown.

In summary, the data presented here do not clarify whether lipoatrophy, lipohypertrophy and dyslipidemia represent distinct syndromes or whether they are connected through a common aetiology. Our data does suggest however, that protease inhibitor use is likely to be

the primary factor related to dyslipidemia, as is suggested by other studies of lipid profiles among those exposed to protease inhibitor class therapies[11,17,18]. It is also clear that treatment variables are of primary relevance to the occurrence of morphologic abnormalities although the data are less consistent.

The data presented here indicate that socio-demographic and clinical characteristics may be irrelevant to the development of lipodystrophy-associated symptoms although patterns of development may be distinct for women. Moreover, they do not suggest that either baseline indicators of disease stage nor progression or treatment success over the course of follow-up play any role in the development of symptoms as has been reported by others[21,23].

When taken together, data from British Columbia Drug Treatment Program participants provides further evidence that, while etiologically complex, symptoms of HIV-associated lipodystrophy are, in all likelihood, true adverse effects of antiretroviral therapy.

8.2 UNIQUE CONTRIBUTIONS, IMPACT AND IMPLICATIONS

The studies comprising this dissertation work have contributed to our understanding of HIV-associated lipodystrophy in several important ways. At the time that these studies were conducted they represented some of the first large-scale investigations of the epidemiologic parameters of lipodystrophy-associated symptoms. They remain some of the few to attempt investigation within a population-based setting under conditions of standard care. Until recently the majority of studies had been based on clinical samples or pre-existing cohorts originally developed to study features of natural history and risk factors for transmission of HIV. The utilisation of self-report data from a large observational treatment cohort while it has important limitations (see Chapter 3) brings a broader perspective to epidemiologic

investigations. Some of these unique aspects were noted in an editorial accompanying the publication of the initial prevalence study included as Chapter 4[24].

Many of these unique contributions are a result of the inherent advantages of large observational databases. Clinical samples can contribute greatly to our understanding of the natural history of symptoms and help to frame etiologic investigation. These samples may also allow for assessment of validity and reliability of outcome measures and extensive data collection through clinical evaluation based on standardised protocol. Clinical samples, however, tend to be highly selective as to study subjects. Subjects are often under the care of a single or few physicians. They are often limited in terms of ethnic, cultural or gender distribution, economic status, treatment regimens, disease stage, and HIV transmission risk group. They can therefore, not be relied upon to provide accurate estimates of prevalence, incidence and range of outcomes which might occur in the general population of antiretroviral users. This also implies that many variables can not be assessed adequately in investigation of possible causal factors and sub-analyses are often hampered by lack of statistical power.

Broad-based observational studies, at their best, include a wide spectrum of individuals without the constraints of age, gender, disease stage and therapeutic regimen often imposed or occurring by chance or selection processes in clinical studies; thereby reducing risk of associated biases. For example, our cohort provided unique insight into the occurrence of lipodystrophy-associated morphologic changes among those initiating antiretroviral treatment. Most prior studies of naïve patients had been conducted in clinical settings with little evaluation of non-nucleoside inclusive regimens and confined to a few select triple regimens.

The salient feature of this comparison is not that one methodological approach is superior but that in the case of lipodystrophy, where large prospective studies with highly controlled and static regimen allocation are virtually impossible, we must rely on a

combination of methodological approaches to build a cogent theory of causation. Findings of observational studies are useful in fulfilling additional criteria for causal inference establishing consistency in comparison to studies of differing design and coherence with results of studies using similar methodologies but based on other populations.

A second unique contribution of this group of studies is that they are the first to report Canadian data. This is important given the unique aspects of medical and HIV-related care in British Columbia and Canada as a whole. Medical care and access to antiretroviral therapy is free to all Canadian citizens. Treatment in British Columbia tends to remain relatively advanced in its application of newly developed therapies and use of multiple drug regimens. Lastly, the population of treatment recipients is comparatively broad- including women, persons of various ethnic background and those infected through homosexual and heterosexual contact, medical procedures and injection drug use.

Findings from cohorts in other countries may not be reflective of the Canadian experience. For example populations receiving treatment in the United States may differ in many respects to Canadian patients. In the United States, those receiving treatment may under-represent marginalised groups and be confined to those with the means and impetus to pay for expensive antiretroviral therapy. Treatment strategies themselves may also differ as cost of treatment is likely to play an important role in regimen selection. In other countries such as Australia, the treated population, or at least those contained in research cohorts is often confined to homosexual men making comparisons difficult.

Lastly, the data presented regarding adverse effects and purposeful or proactive alteration in antiretroviral regimens, while subject to many limitations and preliminary in its scope, are unique. Adherence has become a primary issue in the treatment of HIV disease. Inadequate adherence can result in early treatment failure, lead to a restriction in the future

treatment options, and may pose a public health risk in term of transmission of resistant virus. Unintentional imperfect adherence is common and often due to forgetfulness and difficulty taking doses as scheduled. Therapy tailoring, regimen simplification in terms of number of drugs or doses used and pharmaceutically simplified therapies may help to alleviate some of these problems. However, pro-active self-medication is not amenable to these strategies and has not been well documented or studied. Self-medication has been related to drug toxicities as has inadequate adherence, however, the prevalence of various adverse effects and how they are treated by physicians and patients has also not been examined. In Chapter 7 we sought to provide some preliminary information regarding each of these phenomena in a simple questionnaire. The resulting data is suggestive and provides the impetus for hypothesis formulation and a distinctive line of inquiry.

Considering a more restricted focus, this work has also made a contribution to the Centre for Excellence in HIV/AIDS and HIV research in British Columbia. At the initiation of these studies, adverse effects associated with antiretroviral agents were not an area of investigative priority in British Columbia. This was also true of most large centres dedicated to HIV research as many of the more problematic adverse effects of highly potent antiretroviral regimens were just beginning to emerge and the important consequences of these events had yet to be realised. The work presented here has been part of, and given rise to, the introduction of a new research component to the Centre. The concomitant development of several ongoing projects will allow the Centre to further develop as a premier centre for clinical and epidemiologic investigation in the arena of drug toxicity research.

The Centre is uniquely placed to develop a strong research plan regarding adverse effects of antiviral agents in the context of a broad spectrum of centre mandates and research strategies. The Centres' working structure makes it possible to devise research agendas that

move from the laboratory bench, to small clinical samples and then to population level epidemiology. For instance, the candidate consulted with experts in the areas of clinical care, clinical trials, population health and lipid research in designing and implementing the various studies presented in this document. A prime example of how such collaborative efforts continue to be applied to new investigations is the Centre's current work on mitochondrial toxicity. Within the Centre, laboratory researchers developed a novel polymerase chain reaction assay to assess mitochondrial DNA depletion in peripheral blood cells[25]. The assay was tested by volunteer patients of the HIV/AIDS clinic population to identify other toxicities correlated with differences in mitochondiral DNA levels. Future research plans include the utilisation of data from the drug treatment program participants to identify associations between mitochondrial DNA, reporting of other adverse events and clinical outcomes. This chain of research allows pressing questions to be addressed in a timely and comprehensive fashion, more effectively meeting the needs of clinicians providing HIV-related care and their patients regarding knowledge of adverse drug effects

Furthermore, this research agenda lends itself to greater collaboration with experts in other fields of research in British Columbia. For example, the relationships between dyslipidemia, lipodystrophy and antiretroviral treatments and risk of cardiovascular disease or events are being explored in consultation with local experts in the epidemiology of cardiovascular disease and utilising cardiovascular procedure and event databases. Collaboration with lipid laboratory staff and experts has been initiated to explore possible links between diet and dyslipidemias in the HIV infected population. Meanwhile, studies of the occurrence and impact of adverse drug effects in hard-to-reach populations are being initiated.

The data presented here has also given rise to some specific recommendations that will enable us to expand the nature and scope of future investigations.

8.3 Recommendations

In general, the research described here gives rise to two primary recommendations. The first is improvement in surveillance for known and emerging adverse effects associated with antiretroviral therapy, the second is a call for further research.

8.3.i Surveillance

It has become clear that monitoring for adverse drug effects within the clinical trial process is inadequate to identify emerging health problems associated with antiretroviral therapy. While the reasons for failure to note emerging adverse drug effects in pre-marketing phases of drug development are unclear there are several possible explanations. Firstly, clinical trials are generally relatively small in comparison to the population likely to receive drugs. Secondly, the duration of trials is often limited to one to three years of follow-up. Third, trials are often limited to inclusion of those persons with most advanced disease and those experiencing failure on traditional regimens. This implies a greater rate of mortality during follow-up and participants may die before they experience selected adverse symptoms. Trials are often also restricted in sample selection and drug usage is tightly monitored and controlled. Trials are also limited by their nature in terms of regimens, offering only two or three trial arms. If adverse effects are due to other combinations which include the investigational drug they may not occur in the study population.

Given the inherent limitations of monitoring adverse effects in clinical trials, and the need to provide new drugs expediently, post-marketing surveillance becomes especially

important for anti-HIV medications. Early identification of suspected adverse effects and etiologic investigation are likely to remain complicated. Currently, trials focus on well specified multi-drug regimens while clinical patterns of use generally involve several attempts at initiating therapy and frequent regimen switching and amending making methodologically sound epidemiologic investigations of specific agents using traditional methods challenging.

Currently, identification during post marketing relies on spontaneous physician reporting, generally in the form of case reports or case series and are often confined to serious or life threatening side effects which are clinically overt. Building evidence of causal associations piecemeal through multiple clinical studies may actually delay identification of emerging toxicities. In addition coherence across studies is often extremely limited due to variations in the outcomes assessed, measurement tools, information regarding possible confounders and sample selection which render cogent theoretical development of causation or meta-analytic approaches unfeasible. Continued reliance on this system to capture and investigate emerging adverse drug effects is thus unfeasible, particularly in the current context of increasing prevalence of adverse drug effects.

As long term use of antiretrovirals continues it is likely that new adverse drug effects will continue to emerge at an increasing rate. Etiologic investigation is also likely to become more complex. It may become increasingly difficult to distinguish signs and symptoms that are related directly to the use of a single drug or combination as opposed to those due to long term exposure or long term survival under conditions of severe immunosuppression. Therefore broad scale surveillance of populations using antiretroviral agents in conjunction with focused clinical research is imperative if we are to identify emerging events and investigate underlying mechanisms in a timely fashion.

To be maximally effective surveillance should include a large number of subjects from the population of interest. Subjects should represent the full spectrum of those affected in terms of clinical factors, treatment history, demographic characteristics and risk group. Surveillance tools should be flexible and easily amended to incorporate changes in available regimens and treatment guidelines. Data should be reviewed regularly to evaluate patterns of reporting of known toxicities and for early identification of possible emerging issues.

Data collection may proceed directly through patients, physicians or via pharmacies, laboratories or other health service provider records. Reports of adverse reactions can be systematically monitored through either open-ended questioning or systematic symptom checklists. Each of these approaches has inherent limitations and advantages and a combination of methods is most likely to achieve good compliance with broad-based surveillance.

Reliance on self-reported data by patients is advantageous in that it does not overburden physicians with large HIV-practices and incurs no costs associated with additional paperwork. Self-report of symptoms in the absence of clinical validation can, however, be problematic as standard definitions understood by physicians may be more difficult for patients to report reliably. Self-report may also result in overestimates of the prevalence of some adverse effects and underestimate others. Physician reports may be more reliable, however, detailed individual clinical examination is impracticable for broad scale population-based monitoring. Clinical follow-up is costly and time consuming for both clinicians and subjects making large scale or long-term commitment economically and logistically unfeasible. Moreover, clinical validation can only occur when measurable signs and diagnostic criteria are defined, therefore, more subjective symptoms may be under-reported by physicians. Physician-based reporting does have an advantage in that it may enhance physician-patient communication. Directly

linked laboratory and pharmacy records can ease the burden of reporting for laboratory test data and prescription history and are helpful in cross-validating patient and physician reported data but can initially be costly and time consuming to implement and may require patient consent.

Systematic inquiry, while optimising event capture for known adverse events may be associated with increased risk of false positives while other techniques, such as spontaneous reporting may result in underestimates[26-29]. On the other hand, systematic enquiry, will not identify emerging or unusual adverse events not listed, therefore open ended questions are required in addition to symptom lists.

In addition to simply monitoring the occurrence of adverse drug effects, surveillance systems can add an important component to available research methodology, in effect creating a continuously monitored, open observational cohort. As previously discussed observational data bases can make a unique contribution to our understanding of emerging patterns of adverse events. Simple, regularly scheduled analyses can identify emerging events more rapidly than awaiting a "critical mass" of case reports. Due to the large number of subjects followed issues of sample size are negated and sub-samples are amenable to hypothesis generating analyses.

Given these needs, the candidate, in consultation with a newly convened toxicity committee has implemented a novel program to capture adverse effect data within the Centre's Drug Treatment Program. A toxicity reporting form has been designed (Appendix 7). The form captures data regarding the occurrence of laboratory and clinical adverse effects and whether therapy is being changed or discontinued and the reasons for this. Forms are completed by the physician each time antiretroviral prescriptions are changed for each patient or if they cease treatment. If no medication changes or discontinuations occur, forms are to be

completed on an annual basis. This data will be combined with the DTP participant database such that demographic characteristics, treatment records, laboratory results and toxicity data can be merged for analysis. Data collection has recently commenced and we look forward to reporting preliminary results in the coming year.

8.3.ii Further Research

Given mounting interest in lipodystrophy-associated symptoms, a general requirement for continued research in this area is greater consistency in study methodology allowing for level comparison of studies and meta-analysis. Of particular importance is the specification of the morphologic and laboratory abnormalities which should be considered in a case definition for HIV-associated lipodystrophy. Diagnostic procedures should consider the fiscal and time constraints of physicians and patients. They should be valid, reliable and not dependent on complex procedures which are not readily available. It may however, be necessary to develop a two stage procedure for diagnosis. The first might be highly sensitive but less specific and based on easily obtained information. The second may be more refined, of higher specificity and based on more complex or costly diagnostic procedures and may be better suited to research studies. A multinational study lead by Australian investigators is currently underway. Preliminary reporting from this study indicates that an algorithm including low trunk to peripheral fat ration, abdominal bloating, low leg fat percentage, higher waist/hip ratio and higher anion gap, among other parameters has a sensitivity of 84% and a specificity of 81% in detecting lipodystrophy[30] .

Other aspects of study design should also be considered. For example in our studies univariate analyses often revealed statistically significant associations between patient and treatment characteristics and symptoms that had been featured in prior reports. These findings, for the most part, were not confirmed in multivariate analysis. This exemplifies the

importance of inclusion of and adjustment for possible confounding and collinear variables. Consideration of power issues and attempts to include a more representative sample of study subjects should also be a priority.

Specific epidemiologic research needs are focused on the continued understanding of the aetiology, natural history and long term effects of lipodsytrophy-related symptoms. Firstly treatment effects need to be better delineated. It remains to be determined, under conditions of well defined outcomes assessment, whether protease inhibitor exposure is necessary and sufficient for the occurrence of various symptoms. For example, reports of symptoms among those naïve to protease inhibitors need to be validated. This is likely to prove increasingly difficult as proteases are a mainstay of highly active therapy, many individuals currently using non-nucleoside based therapies are previously protease exposed and the application of mono- and dual-therapies is becoming increasingly rare.

Natural history studies are also needed to determine the pattern of symptom onset, early indications of symptom emergence and the reversibility of morphologic changes. Patterns of symptom evolution among various under-studied patient sub-groups such as women and injection drug users are of great interest. Such studies will be particularly challenging given the relatively small numbers of participants in drug treatment or cohort studies that meet these criteria. Large scale multi-national studies will be required to obtain sufficient numbers of subjects allowing for accurate estimates of symptom incidence and detailed etiologic investigations within these subgroups.

The long-term consequences of symptoms associated with lipodystrophy are clearly of great concern. Whether symptoms are related to increased risk of cardiovascular disease or events are of great importance to patients- particularly in light of the increasing age and the high prevalence of established cardiovascular risk factors in the infected population. Again,

studies will be challenging. Outcomes are likely to be rare and will take many years to accrue in numbers sufficient for analysis. More timely studies will need to use large existing databases such as cardiovascular registries, census data, drug treatment programs and pharmacy records. Selection and merging of data from such a variety of sources and source populations carries many limitations both practical and in terms of data validity.

Finally, in a broader perspective, the impact of various types of adverse drug effects on quality of life and social-emotional well being and functioning should be an area of priority. The complex interrelationship between adverse effects and adherence or other patterns of therapy utilisation and the possible consequences of these on clinical outcomes requires greater exploration. Such research, in conjunction with surveillance data, could provide information to patients and their care providers regarding the possible implications of various treatment strategies allowing for more informed and tailored treatment decision making.

The emergence of novel adverse drug effects as has been evidenced in recent years should also provide the impetus to consider a greater level of collaboration. There is certainly room for collaborative work between companies developing and marketing antiretroviral agents and academic and clinical researchers. More open ended assessment of adverse drug effects within both the clinical trial process and through monitoring compassionate release programs may provide some insight into possible adverse effects prior to wide spread release. Multi-site collaboration between investigators involved in epidemiologic and clinical research could help to ensure that initial investigations are well powered, of adequate design and more inclusive as to study subjects.

8.4 CONCLUSIONS

The work presented here aimed to describe the epidemiologic parameters of HIV-associated lipodsytrophy-related symptoms among persons accessing antiretroviral therapy in British Columbia, Canada. We described a high prevalence and incidence of symptoms among study subjects and identified protease inhibitors as a primary contributing factor in their development based on both cross-sectional and prospective studies.

This work has made many contributions to our understanding of lipodystrophy syndrome. The open observational cohort methodology, use of self-report data, Canadian focus, and description of the impact of adverse effects on self-medication are some of the unique aspects of this research. Moreover, within British Columbia, this research represents part of a continued and expanding initiative at the Centre for Excellence in HIV/AIDS to investigate the role that adverse drug effects play in the future of pharmacologic management of HIV disease.

The studies summarised here and those of others imply a need for improved surveillance and future research of the aetiology, natural history and implications of lipodystrophy symptoms involving collaborative efforts of the pharmaceutical, health care system and academic stakeholders.

Treatment success is function not only of efficacy but patient's willingness to adopt and maintain therapies over many years. Consideration of expected effectiveness, medication burden, and quality of life will become increasingly important in decisions regarding the initiation, alteration and continuation of antiretroviral therapy. In all of our research efforts we would be wise to remain aware of the position of our work in this broader context. A focus should remain on supplying HIV positive individuals with the information and support that they require to make decisions to help them to live with HIV, rather than merely survive it.

8.5 REFERENCES

1. Christeff N, Melchior J, de Truchis P, Perronne C, Nunez EA, Gougeon M. Lipodystrophy defined by a clinical score in HIV-infected men on highly active antiretroviral therapy: correlation between dyslipidaemia and steroid hormone alterations. *AIDS* 1999; 13:2251-2260.
2. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1 protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998; 351:1881-1883.
3. Miller JE, Emery S, French M, Baker D, Cooper DA. The Australian prevalence survey of lipodystrophy syndrome. *7th Conference on Retroviruses and Opportunistic infections*, San Francisco, California 2000 [Abstract 201].
4. Bernasconi E, Carota A, Magenta L, et al. Metabolic changes in HIV infected patients treated with protease inhibitors. *12th World AIDS Conference*. Geneva, Switzerland 1998 [Abstract 12375].
5. Pollner J, Aronson NE, McHugh S et al. Significant increases in serum cholesterol are seen among HIV patients taking protease inhibitors. *12th World AIDS Conference*. Geneva, Switzerland 1998 [Abstract 12269].
6. Martinez E, Morcroft A, Garcia-Viejo MA et al. Risk of lipodystrophy in HIV-1 infected patients treated with protease inhibitors: a prospective cohort study. *Lancet* 2001; 357:592-598.
7. Goujard C, Boufassa F, Deveau C, Laskri D, Meyer L for the Primo Group. Early occurrence of lipodystrophy in HIV-1-infected patients treated during primary infection. *8th Conference on Retroviruses and Opportunistic Infections*. Chicago, Illinois 2001 [Abstract 403].

8. van der Valk M, Gisolf EH, Reiss P et al on behalf of the Prometheus study group. Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. *AIDS* 2000; 15:847-855.

9. Rakotoambinina B, Medioni J, Rabian C, Jubault V, Jais JP, Viard JP. Lipodystrophic syndromes and hyperlipidemia in a cohort of HIV-1-infected patients receiving triple combination antiretroviral therapy with a protease inhibitor. *J Acquir Immune Defic Syndr* 2001; 27:443-449.

10. Carr A, Samaras K Burton S et al. A syndrome of peripheral lipodystrophy, hyperlipidemia and insulin resistance due to HIV protease inhibitors. *AIDS* 1998; 12:F51-F58.

11. Carr A, Samaras K, Thorisdottir A et al. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidemia, and diabetes mellitus: a cohort study. *Lancet* 1999; 353:2093-2099.

12. Bogner RJ, Vielhauer V, Beckmann RA, Michl G, Wille L, Salzberger B, Goebel FD. Stavudine versus zidovudine and the development of lipodystrophy. *J Acquir Immune Defic Syndr* 2001; 27:237-244.

13. Striker R, Conlin D, Marz M, Wiviott L. Localized adipose tissue hypertrophy in patients receiving immunodeficiency virus protease inhibitors. *CID* 1998; 27:218-220.

14. Carr A, Miller J, Law M, Cooper DA. A syndrome of lipoatrophy, lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS* 2000; 14:F25-F32.

15. Tsiodras S, Mantzoros C, Hammer S, Samore M. Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: a 5-year cohort study. *Arch Intern Med* 2000; 160:2050-2056.

16. Schindler JT, Sponer KM, Deker CF. Buffalo humps associated with protease inhibitors [Letter]. *Ann Intern Med* 1998; 129:164.

17. Sullivan AK, Feher MD, Nelson MR, Gazzard BG. Marked hypertriglyceridemia associated with ritonavir therapy [Letter]. *AIDS* 1998; 12:1395-6.

18. Behrens G, Dejam A, Schmidt H et al. Impaired glucose tolerance, beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors. *AIDS* 1999; 13:F36-F70.

19. Saint-Marc T, Partisani M, Poizot-Martin I et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study. *AIDS* 2000; 14:37-49.

20. Mallal SA, John M, Moore C, James IR, McKinnon EJ. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS* 2000; 14:1309-1316.

21. Lichtenstein KA, Ward DJ, Moorman AC et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS* 2001; 15:1389-1398.

22. Carpenter CCJ, J *Acquir Immune Defic Syndr* 2001; 28:332-335.

23. Boufassa F, Dulioust A, Lascaux AS et al. Lipodystrophy in 685 HIV-1-treated patients: influence of antiretroviral treatment and immunovirological response. *HIV Clin Trials* 2001; 2:339-345.

24. Gharakhanian S. The HIV-associated lipodystrophy syndrome: research, results, yet more questions. *AIDS* 2001; 15:271-273.

25. Cote H, Brumme ZL, Craib JP et al. Changes in peripheral blood mitochondrial DNA among HIV-infected patients experiencing nucleoside toxicity. *New Engl J Med* 2002 (in press).

26. Keith MR, Bellanger-McCleery RA, Fuchs JE. Multidisciplinary program for detecting and evaluating adverse drug reactions. *Am J Hosp Pharm* 1989; 46:101-110.

27. Brewer T, Colditz GA. Postmarketing surveillance and adverse drug reactions: Current perspectives and future needs. *JAMA* 1999; 281:824-829.

28. Fisher S, Bryant SG, Kluge RM. Detecting adverse drug reactions in postmarketing surveillance: interview validity. *Drug Info J* 1987; 21:173-183.

29. Wallin J, Sjovall J. Detection of adverse drug reactions in a clinical trial using two types of questioning. *Clin Ther* 1981; 3:450-452.

30. Carr A for the HIV Lipodystrophy Case Definition Study Group. An objective case definition of HIV lipodystrophy. Abstract submitted to the *9th Conference on Retroviruses and Opportunistic Infections*. Seattle, Washington 2002.

APPENDIX 1

Drug Treatment Programme Survey; 1998-1999

The HIV/AIDS Drug Treatment Program

Annual Participant Survey 1998/99

This annual survey is for **participants in the HIV/AIDS Drug Treatment Program.** If you are HIV-positive and a treatment program participant, the BC Centre for Excellence in HIV/AIDS (the Centre) would like to find out more about your living conditions, health status, and needs for treatment and care. Participants' responses to this survey will be used by the Centre to inform and educate British Columbians about the health and living conditions of persons living with HIV/AIDS.

To participants

Completion of this annual survey is voluntary. If you want to participate, please read it over carefully and answer it as best you can. The survey will take about 35 minutes to complete; because of participants' comments, some questions have been changed. The completed survey can be mailed to us in the enclosed self-addressed stamped envelope. **Any information you provide to us will remain strictly confidential.** Thank you in advance for your participation and co-operation.

To physicians

Please ensure the participant noted on the inside page receives this questionnaire. If this individual is no longer your patient please inform the Centre at (604) 806-8515. Thank you for your assistance.

Questions?

If you have specific questions or are interested in obtaining more information about the Centre's research activities, please contact the program co-ordinator, **Bonnie Devlin,** at (604) 806-8306. You can also refer to the *forecast*, the Centre's quarterly newsletter, and published research articles for information on the HIV/AIDS Drug Treatment program and other research activities. Subscriptions for our newsletter and other information material can be requested by writing to the following address: BC Centre for Excellence in HIV/AIDS, 608-1081 Burrard Street, Vancouver, BC, V6Z 1Y6. You can phone in your request to (604) 806-8515. Visit our website at http://cfeweb.hivnet.ubc.ca/

1. Personal Information

NOTE: In this section we would like you to read and complete some general background questions about your current education and employment status and the place you live.

1. What is the highest grade (or year) of secondary (high school) or elementary school you attended?

   Years of schooling: ..... _____
   Never attended school .....❑
   Unsure .....❑

2. How many years of education have you completed at university or another post-secondary institution (College, institutes of technology, CEGEPs, trade schools)?

   Years of schooling: ..... _____
   Less than 1 year .....❑
   Unsure/Never attended .....❑

3. What certificates, diplomas, or degrees have you obtained **(check one or more)**?

   High school diploma.....❑
   Trades certificate .....❑
   Undergraduate university degree .....❑
   Post-graduate university degree .....❑
   CEGEP, College, institute of technology certificate .....❑
   Never received a degree, diploma or certificate .....❑
   Other (specify): _____

4. What kind of housing are you currently living in?

   House .....❑
   Hotel, rooming-house, etc.....❑
   Jail or prison.....❑
   Hospital.....❑
   Other(specify):_____
   Condominium/Apartment .....❑
   Shelter, hostel.....❑
   No fixed address.....❑

NOTE: **If you are currently living in an institution (like a jail or prison or hospital) then go to question 14.**

5 How many adults and children, including yourself, currently reside in your home?

Number of adults: _____ Number of children: _____

6. Do you currently share your housing arrangements with another person(s)? **(check one or more)**

No one	❑	Roommate	❑
Friend(s)	❑	Partner/lover	❑
Spouse	❑	Child(ren)	❑
Family	❑	Other	

(specify):_____

7. Is your home in need of any repairs?

No, only regular maintenance ..... ❑

Yes, minor repairs (missing or loose floor tiles, needs paint, new counters, defective steps or railing, broken appliances, etc.) ..... ❑

Yes, major repairs (defective plumbing or electrical wiring, structural repairs to walls, floors or ceilings, etc.) ..... ❑

8. Will you be able to remain in your present housing throughout your illness?

Yes	❑	No	❑
Unsure	❑		

9. Are you **currently** employed in a job that pays money?

Full time	❑	Part-time	❑
Self-employed	❑	Not at all	❑

NOTE: If you are not employed please go to question 12.

10. **IF EMPLOYED (paid employment)**, please describe your **current** occupation:
Specify: _____

11. **IF EMPLOYED (paid employment)**, please indicate how many hours you normally work at your **current** job(s) per week:
_____ hours per week

12. **IF NOT EMPLOYED,** check the box or boxes which show your **current** status:

Unemployed but available for work ..... ❑
Temporarily unavailable for work (sick leave) _____ ❑
Permanently unable to work ..... ❑
Home duties ..... ❑
Student ..... ❑
Retired from job ..... ❑
Other (specify): _____

13. What other **current** sources of support do you have: **(check one or more)**

Unemployment insurance (UIC) ..... ❑
Canadian Pension Plan (CPP) ..... ❑
Provincial income assistance (GAIN, Handicapped, Welfare) ..... ❑
Savings or borrowing ..... ❑
Long-term disability insurance ..... ❑
Not applicable (in jail or prison)..... ❑
Other forms of income(specify): _____

14. Check the box which shows your **current** gross annual earnings (wages, salaries and net self employment, and any other income) before deductions:

Under $5,000	❑	$30,000-$34,999	❑
$5,000-$9,999	❑	$35,000-$39,999	❑
$10,000-$14,999	❑	$40,000-$44,999	❑
$15,000-$19,999	❑	$45,000-$49,999	❑
$20,000-$24,999	❑	$50,000 and over	❑
$25,000-$29,999	❑	Unsure of income	❑

15. Check one or more ethnic/cultural group that applies to you:

Aboriginal/First Nations	❑	Jewish.....	❑
Asian (Chinese, Vietnamese, etc.)	❑	Metis.....	❑
Black	❑	Middle Eastern	❑
Caucasian/White	❑	South Asian (Indian, Pakistani etc.)	❑
Hispanic/Latino	❑	Prefer not to answer	...❑
Inuit	❑	Other(s): (specify) _____	

16. What languages can you speak well enough to conduct a conversation:
(check one or more)

English	❑	Hindi	❑
French	❑	Punjabi.....	❑
Spanish	❑	Prefer not to answer_____	❑
Cantonese.....	❑	Other(s): (specify) _____	
Mandarin	❑		

17. Are you a status or registered Indian (**as defined by the Indian Act**) ?

Yes ..... ❑
No, I am Metis, Inuit, or non-status ..... ❑
No ..... ❑

18. Were you born in Canada?

Yes ..... ❑ **(Go to question 20)**
No ..... ❑

19. **IF NO**, what country were you born in?

Specify country of birth: _____

20. How long have you been living in British Columbia?

Less than 1 year ..... ❑ 1 to 2 years ..... ❑
3 to 4 years ..... ❑ 5 or more years ..... ❑
Unsure ..... ❑

2. Health Status

NOTE: In this section we would like you to read and complete some basic questions about your current health status.

21. In general, would you say that your current health is:

Excellent ..... ❑ Fair ..... ❑
Very good ..... ❑ Poor ..... ❑
Good ..... ❑

22. **Compared to one year ago**, how would you rate your health in general now?

Much better now ..... ❑ Somewhat worse now ..... ❑
Somewhat better now ..... ❑ Much worse now ..... ❑
About the same ..... ❑

23. How much pain or discomfort do you have from illness at present?

None ..... ❑ Moderate ..... ❑
Mild or infrequent ..... ❑ Severe or persistent ..... ❑

24. In the past month, have you had any bodily pain?

Yes ..... ❑ No ..... ❑

25. **IF YES**, was the pain:

Very mild ..... ❑ Moderate ..... ❑

Mild ..... ❑ Severe ..... ❑

26. Please circle the number that best describes whether each of the following statements is true or false for you.

Responses:

1. Definitely true
2. Mostly true
3. Not sure
4. Mostly false
5. Definitely false

Circle the appropriate number

- I am somewhat ill ..... 1 ..... 2 ..... 3 ..... 4 5
- I am as healthy as anybody I know ..... 1 ..... 2 ..... 3 ..... 4 5
- My health is excellent ..... 1 ..... 2 ..... 3 ..... 4 5
- I have been feeling bad lately ..... 1 ..... 2 ..... 3 ..... 4 5

27. This set of questions concerns some problems you may have to deal with because of your illness. **Please circle one number per item.**

Responses:

1. A problem for more than 3 months
2. A problem for 3 months or less
3. Not a problem at all

Circle the appropriate number

- Does your health keep you from working at a job, doing work around the house or going to school? ..... 1 ..... 2 3

- Have you been unable to do certain kinds or amounts or work, house work or school work because of your health? ..... 1 ..... 2 3

- The kinds or amounts of vigorous activities you can do, like lifting heavy objects, running or participating in strenuous sports? ..... 1 ..... 2 3

- The kinds or amounts of moderate activities you can do, like moving a table, carrying two full bags of groceries? ..... 1 ..... 2 3
- Walking uphill or climbing 10 steps without resting? ..... 1 ..... 2 3
- Bending, lifting or stooping? ..... 1 ..... 2 3
- Walking one block? ..... 1 ..... 2 3
- Eating, dressing, bathing or using the toilet?..... 1 ..... 2 3

28. For each of the following questions, please circle the number for the one answer that comes closest to the way you have been feeling **during the past month**.

Responses:

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

How much time during the past month: **Circle** the appropriate number

- has your health limited your social activities (like visiting with friends or close relatives)? 1 ..... 2 ..... 3 ..... 4 ..... 5 6
- have you been a very nervous person? 1 ..... 2 ..... 3 ..... 4 ..... 5 6
- have you felt calm and peaceful? 1 ..... 2 ..... 3 ..... 4 ..... 5 6
- have you felt downhearted and blue? 1 ..... 2 ..... 3 ..... 4 ..... 5 6
- have you been a happy person? 1 ..... 2 ..... 3 ..... 4 ..... 5 6
- have you felt so down in the dumps that nothing could cheer you up? 1 ..... 2 ..... 3 ..... 4 ..... 5 6

29. How tall are you without shoes on?

____ Feet ___ Inches **or** ___ Centimetres

30. How much do you weigh?

___ Kilograms**or** ___ Pounds

31. Have you gained or lost ten pounds or more within the past year?

Yes ..... ❑ No ..... ❑

If Yes, do you know why? (specify): _____

32. Do you have insurance that covers all or part of the cost of the following items:

	Yes	No	Unsure
• Dental expenses	❑	❑	❑
• Eye glasses or contact lenses	❑	❑	❑
• Extended hospital coverage	❑	❑	❑
• Life insurance	❑	❑	❑
• Long term health care benefits	❑	❑	❑
• Prescription medications	❑	❑	❑

33. Do you get any insurance benefits, such as those mentioned in the above question, as part of your current employment?

Yes ..... ❑ No ..... ❑

I am not currently employed .... ❑ Unsure ..... ❑

34. Do you pay for any of these insurance benefits privately?

Yes ..... ❑ No ..... ❑

35. What is the name(s) of the insurance company that provides these benefits? **(check one or more)**

MSA ..... ❑ Manufacturer's Life ..... ❑

CU and C ..... ❑ Great West Life ..... ❑

Mutual Life ..... ❑ Aetna ..... ❑

Pacific Blue Cross ..... ❑ Don't Know ..... ❑

Other (specify): _____

3. Clinical Status

NOTE: In this section we would like to you read and complete some basic questions about your lifestyle and clinical history. Participants' comments on last year's questionnaire indicated that side effects of drugs were important to them, so this year we have added a question about them.

36. In what year and month **do you think** you were infected with HIV?
Year: 19___ Month: _____ Unsure ❑

37. How do you think you got HIV? **(check one or more boxes)**
Sex with a man ..... ❑
Sex with a woman ..... ❑
Injection drug use ..... ❑
Blood product ..... ❑
Blood transfusion ..... ❑
Unsure/prefer not to answer ..... ❑
Other(specify)_____

38. Have you ever donated blood?
Yes ..... ❑
No ..... ❑ **(go to question 42)**
Unsure/prefer not to answer ..... ❑ **(go to question 42)**

39. **If you have donated blood**, how many donations have you ever made?
1 donation ..... ❑
2 to 4 donations ..... ❑
5 to 9 donations ..... ❑
10 or more donations..... ❑

40. What year did you **first** donate blood?
Year of **first** blood donation: **19**___

41. What year did you **last** donate blood?
Year of **last** blood donation: **19**___

42. **Have you been vaccinated for or received the following: (Check one box per item)**

	Yes	No	Unsure	
• Hepatitis B (Hep B) vaccine	❑	..... ❑	..... ❑	IF YES, # of doses:
• *Haemophilus influenza* type B vaccine.....	❑	..... ❑	..... ❑	IF YES, #of doses:
• Pneumococcal vaccine (Pneumovax).....	❑	..... ❑	..... ❑	
• "Flu" (Influenza) vaccine (in the last year).....	❑	..... ❑	..... ❑	
• Tetanus immunization (in the last 10 years)...	❑	..... ❑	..... ❑	
• TB skin test (PPD)	❑	..... ❑	..... ❑	**IF YES**, was it:

Positive ❑ Negative ❑

43. Please indicate whether you have experienced any of the following side effects from your current HIV therapy: **(check all that apply)**

Side Effect	Ever had	Currently have	
	Yes	Yes	Never
• **Cardiovascular Problems**			
High blood pressure	❑	❑	❑
Chest pain diagnosed by doctor as heart attack or similar	❑	❑	❑
• **Eye Problems**			
Blurred vision, painful eye that your doctor thinks is the result of inflammation of one of the layers of the eye	❑	❑	❑
• **Female-Specific Problems**			
Menstrual changes (changes in your period)	❑	❑	❑
• **Gastrointestinal Problems**			
Abdominal pain/discomfort	❑	❑	❑
Diarrhea	❑	❑	❑
Difficult digestion	❑	❑	❑
Presence of gas in stomach/bloating	❑	❑	❑
Nausea (feeling like you need to vomit)	❑	❑	❑
Vomiting	❑	❑	❑
Taste alterations (food and drink taste funny)	❑	❑	❑
• **Liver Function Test**			
Jaundice (skin/eyes turning yellow)	❑	❑	❑
Pain/discomfort over the liver (under rib cage on right)	❑	❑	❑
Doctor told you your liver is sick	❑	❑	❑
• **General Problems.**			
Decreased concentration	❑	❑	❑
Depression/suicidal feelings	❑	❑	❑
Dizziness	❑	❑	❑
Difficult breathing	❑	❑	❑
Fatigue/feeling tired	❑	❑	❑
Fever	❑	❑	❑
Headache	❑	❑	❑
Insomnia/problems sleeping	❑	❑	❑
Malaise (generally unwell)	❑	❑	❑
Hives; itchy welts	❑	❑	❑
Weakness	❑	❑	❑
Loss of appetite	❑	❑	❑

- **Skin Problems**
  - Rash ..... ❑ ..... ❑ ..... ❑
  - Dryer skin ..... ❑ ..... ❑ ..... ❑

- **Muscle and Skeletal Problems**
  - Blood in joints ..... ❑ ..... ❑ ..... ❑
  - Haematomas (large bruises without remembering hurting yourself) ..... ❑ ..... ❑ ..... ❑
  - Aches in joints and/or muscles ..... ❑ ..... ❑ ..... ❑

- **Peripheral Nervous System Problems**
  - Numbness or pins and needles around mouth ..... ❑ ..... ❑ ..... ❑
  - Numbess or pins and needles in hands/feet ..... ❑ ..... ❑ ..... ❑

- **Metabolic Problems**
  - Diabetes mellitus (high blood sugar) ..... ❑ ..... ❑ ..... ❑
  - Elevated cholesterol levels ..... ❑ ..... ❑ ..... ❑
  - Changes in body shape with any of the following:
    - Weight gain around abdomen ..... ❑ ..... ❑ ..... ❑
    - Thinner arms, legs and/or face ..... ❑ ..... ❑ ..... ❑
    - Pad of tissue on back of neck ..... ❑ ..... ❑ ..... ❑
  - Enlargement of breasts ..... ❑ ..... ❑ ..... ❑
  - Lactation/"leaky breasts" ..... ❑ ..... ❑ ..... ❑
  - Elevated triglyceride levels ..... ❑ ..... ❑ ..... ❑

- **Sexual Problems**
  - Sexual dysfunction (unable to obtain/maintain erection) ..... ❑ ..... ❑ ..... ❑
  - Decreased interest in sex ..... ❑ ..... ❑ ..... ❑

- **Urinary Problems**
  - Painful/difficult urination ..... ❑ ..... ❑ ..... ❑
  - Discharge of bloody urine ..... ❑ ..... ❑ ..... ❑
  - Kidney stones ..... ❑ ..... ❑ ..... ❑
  - Told by doctor that kidneys are not functioning properly ..... ❑ ..... ❑ ..... ❑
  - Abdominal pain due to kidney spasms (very intense pain that starts next to lower back and can move to the genitals and/or inner thigh ..... ❑ ..... ❑ ..... ❑

- **Other Problems**
  - Loss of hair ..... ❑ ..... ❑ ..... ❑
  - Ingrown toenail ..... ❑ ..... ❑ ..... ❑
  - Perianal abcesses/"tails" ..... ❑ ..... ❑ ..... ❑
  - Other (please specify): _____ ❑ ..... ❑ ..... ❑

44. **In the last year,** have you ever been admitted to hospital overnight or longer?

Yes ..... ❑ No ..... ❑
Unsure ..... ❑

45. **If yes,** how many times did you go to hospital?

Only once	❑	2 to 4 times	❑
5 or more times	❑	None	❑
Unsure	❑		

46. **In the last year**, how many times did you receive medical attention or care from the following health care providers or services?

	1 time	2 - 4 times	5 or more times	Never	Unsure
Family/regular doctor	❑	❑	❑	❑	❑
Other medical doctor (such as surgeon, allergist, specialist)	❑	❑	❑	❑	❑
Nurse/street nurse	❑	❑	❑	❑	❑
Dentists or orthodontist	❑	❑	❑	❑	❑
Chiropractor	❑	❑	❑	❑	❑
Physiotherapist	❑	❑	❑	❑	❑
A drop-in clinic	❑	❑	❑	❑	❑
Hospital/emergency	❑	❑	❑	❑	❑
Detox	❑	❑	❑	❑	❑
Other (specify: _____)	❑	❑	❑	❑	❑

47. Do you or have you had any of the following conditions: **(Confirmed by your doctor)**

	Yes	No	Unsure
• **Hepatitis**			
• Type A	❑	❑	❑
• Type B	❑	❑	❑
• Type C	❑	❑	❑
• Non-A, Non-B	❑	❑	❑
• Non-A, Non-B, Non-C	❑	❑	❑
• Hepatitis due to other causes (such as medications or alcohol)	❑	❑	❑
• **Diabetes**	❑	❑	❑
• **Heart Disease** (if Yes, please specify)	❑	❑	❑
• High blood pressure	❑	❑	❑
• Heart Attack	❑	❑	❑
• Leaky Valve	❑	❑	❑
• Other: _____			
• **High cholesterol**	❑	❑	❑
• **Hemophilia**	❑	❑	❑
• **Alterations of blood lipids**	❑	❑	❑

4. Food and Hunger Issues

NOTE: Participants' comments on last year's questionnaires indicated that financial and food problems were important to them, so this question has been added.

48. Below is a series of statements that people have made about their food situation. Please indicate whether the statement is often true, sometimes true or never true for your household or the individuals in your household. **Please circle one number per item.**

Responses:
1. Often true
2. Sometimes true
3. Never true

Circle the appropriate number

- I worry whether my food will run out before I get money to buy more. ..... 1 ..... 2 3
- I worry about whether the food that I can afford to buy for my household will be enough. ..... 1 ..... 2 3
- The food that I bought just didn't last, and I didn't have money to get more. ..... 1 ..... 2 3
- I ran out of the foods that I needed to put together a meal and I didn't have money to get more food. ..... 1 ..... 2 3
- We eat the same thing for several days in a row because we only have a few different kinds of food on hand and don't have money to buy more. ..... 1 ..... 2 3
- I am often hungry, but I don't eat because I can't afford enough food. ..... 1 ..... 2 3
- I eat less than I think I should because I don't have enough money for food. ..... 1 ..... 2 3
- I can't afford to eat properly..... 1 ..... 2 3
- **IF YOU HAVE CHILDREN** - My child(ren) is (are) not eating enough because I just can't afford enough food. ..... 1 ..... 2 3

49. Sometimes people lose weight because they don't have enough to eat. In the past year, did you lose weight because there wasn't enough food?

Yes ..... ❑ No ..... ❑
Don't know ..... ❑

50. In the past year, have you had hunger pangs but couldn't eat because you couldn't afford food?

Yes ..... ❑ No ..... ❑
Don't know ..... ❑

5. Social Support and Coping

51. Below is a list of the ways you might have felt or behaved. Please indicate how often you have felt this way **during the past week** by circling the appropriate number.

Responses:

1. Rarely or none of the time (Less than 1 day)
2. Some or a little of the time (1-2 days)
3. Occasionally or a moderate amount of time (3-4 days)
4. Most or all of the time (5-7 days)

During the past week: **Circle** the appropriate number

- I was bothered by things that usually don't bother me..... 1 ..... 2 .....3 4
- I did not feel like eating; my appetite was poor..... 1 ..... 2 .....3 4
- I felt that I could not shake off the blues even with help from my family or friends ..... 1 ..... 2 .....3 4
- I felt that I was just as good as other people..... 1 ..... 2 .....3 4

- I had trouble keeping my mind on what I was doing ..... 1 ..... 2 .....3 4
- I felt depressed..... 1 ..... 2 .....3 4
- I felt that everything I did was an effort ..... 1 ..... 2 .....3 4
- I felt hopeful about the future ..... 1 ..... 2 .....3 4

- I thought my life had been a failure..... 1 ..... 2 .....3 4
- I felt fearful ..... 1 ..... 2 .....3 4

- My sleep was restless ..... 1 ..... 2 ..... 3 4
- I was happy ..... 1 ..... 2 ..... 3 4

- I talked less than usual ..... 1 ..... 2 ..... 3 4
- I felt lonely ..... 1 ..... 2 ..... 3 4
- People were unfriendly ..... 1 ..... 2 ..... 3 4
- I enjoyed life ..... 1 ..... 2 ..... 3 4

- I had crying spells ..... 1 ..... 2 ..... 3 4
- I felt sad ..... 1 ..... 2 ..... 3 4
- I felt that people disliked me ..... 1 ..... 2 ..... 3 4
- I could not get "going" ..... 1 ..... 2 ..... 3 4

6. Alternative Therapies

NOTE: We recognize that alternative therapies may now play an integral role in an individual's therapeutic regimen. In the interest of furthering our knowledge of these therapies, we would appreciate full disclosure of therapies you use, or have used in the past.

52. Have you ever used any **alternative** (non-prescription) therapies for your HIV disease?

Yes ..... ❑
No ..... ❑ **(go to question 58)**
Unsure/ prefer not to answer ❑ **(go to question 58)**

53. **IF YES**, what are **your reasons** for taking HIV-related **alternative** therapies? **(choose all that apply)**

To enhance your immune response ..... ❑
To supplement your dietary intake ..... ❑
To prevent infection ..... ❑
To improve your energy level ..... ❑
You feel good about taking alternative therapies ..... ❑
Alternative therapies won't do any harm ..... ❑
Other(s) (specify): _____

54. Have you ever consulted any of the following alternative practitioners for HIV/AIDS related conditions? **(choose all that apply)**

Acupuncturist	❑	Doctor of Chinese medicine	❑
Herbalist	❑	Homeopath	❑
Holistic medicine specialist	❑	Naturopath	❑
Osteopath	❑	Traditional Aboriginal healer	❑

Other(s) (specify): _____

55. What is your major source of information regarding **alternative** therapies? **(choose all that apply)**

Alternative practitioner	❑	Family	❑
Physician (MD)	❑	Health food stores	❑
Magazines	❑	Newspapers	❑
Friend(s)	❑	Scientific journals	❑
Support groups, other persons with HIV	❑	Television	❑
Internet	❑	Other(s)(specify): _____	

56. Approximately how much do you spend on **alternative** therapies per month?

< $50 per month	❑	$200 to $400 per month	❑
$50 to $99 per month	❑	Over $400 per month	❑
$100 to $199 per month	❑	Unsure	❑

58. Please indicate whether you have used any of the following **alternative** therapies: **(check all that apply)**

Alternative Therapy	**Ever used Yes**	**Currently Yes**	If you stopped please provide a reason **Ineffective**	**Cost**	**Other reason**
• **Acupuncture**	❑	❑	❑	❑	_____
• **Compound Q** (Coenzyme Q10)	❑	❑	❑	❑	_____
• **Dietary Supplements** (*Macrobiotic diet, Blue-green algae, Boost)*	❑	❑	❑	❑	_____
• **DNCB**	❑	❑	❑	❑	_____
• **Herbs** (*Chinese herbs, St. John's Wort, etc.*)	❑	❑	❑	❑	_____
• **Homeopathy**	❑	❑	❑	❑	_____
• **Marijuana**	❑	❑	❑	❑	_____
• **Massage** (*Reiki, Shiatsu*)	❑	❑	❑	❑	_____
• **Meditation**	❑	❑	❑	❑	_____
• **Naturopathy**	❑	❑	❑	❑	_____
• **N-Acetyl-cysteine**	❑	❑	❑	❑	_____
• **Stress Reduction** (Support groups, Relaxation	❑	❑	❑	❑	_____
• **Tactile therapies** (Therapeutic touch, Reflexology)	❑	❑	❑	❑	_____
• **Vitamins and minerals**	❑	❑	❑	❑	_____

Other alternative (non-prescription) treatments

• _____	❑	❑	❑	❑	_____
• _____	❑	❑	❑	❑	_____
• _____	❑	❑	❑	❑	_____

7. Lifestyle

NOTE:	In this section we would like to you read and complete some basic questions about your lifestyle.

58. **In the last six months**, have you **ever had trouble** taking your antiretroviral medications (like AZT, ddI, ddC, 3TC, d4T, Saquinavir, Ritonavir, and Indinavir)?

All of the time ..... ❑ Most of the time ..... ❑

Half of the time..... ❑ Some of the time ..... ❑

Never ..... ❑ Unsure ..... ❑

I was not on antiretroviral therapy during the last six months ..... ❑

NOTE: If you never had any problems with taking your medications please go to question 60.

59. **If you had problems in the last six months**, how long did you stop taking your antiretroviral medications for?

Less than one day ..... ❑ Less than one week ..... ❑

Less than one month ..... ❑ Less than three months ..... ❑

Did not stop taking them ..... ❑ Unsure ..... ❑

60. Have you ever injected drugs?

Yes ..... ❑

No ..... ❑ **(go to question 63)**

Unsure/prefer not to answer ..... ❑ **(go to question 63)**

61. **Over the last 6 months,** did you inject any drugs?

Yes ..... ❑

No ..... ❑ **(go to question 63)**

Unsure/prefer not to answer ..... ❑ **(go to question 63)**

62. **Over the last 6 months**, what is the **longest** period of time you were drug-free **(i.e. not using injection drugs) ?**

Less than one day..... ❑ Less than one week ..... ❑

Less than one month ..... ❑ Less than three months..... ❑

Less than six months..... ❑ Unsure/prefer not to answer..... ❑

63. Have you ever attended any kind of alcohol or other drug treatment program?

Yes ..... ❑ No ..... ❑

Unsure/prefer not to answer ..... ❑

8. Feedback

NOTE: This section is intended for your feedback. Your suggestions help us to improve the questionnaire from year to year. Please take a few minutes and complete these few questions.

64. Please rate this questionnaire according to the following categories **(check one box per row)**:

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
• The questionnaire was easy to read	❑	❑	❑	❑	❑
• The questions were easy to understand	❑	❑	❑	❑	❑
• The choices for responses were adequate	❑	❑	❑	❑	❑

65. Was this questionnaire

Too short in length ..... ❑ Too long in length ..... ❑

About the right length ..... ❑ Unsure ..... ❑

66. How long did it take you to answer this questionnaire? _____

67. Please write any further information that you think is relevant. You may add additional pages to this questionnaire if necessary.

_____

_____

_____

_____

_____

Thank you very much for taking the time to answer these questions. Please put the completed questionnaire in the enclosed self-addressed and stamped envelope and drop it in the mail.

APPENDIX 2

Drug Treatment Programme Survey; 1999-2000

The HIV/AIDS Drug Treatment Program

Annual Participant Survey 1999/2000

This annual survey is for **participants in the HIV/AIDS Drug Treatment Program.** If you are HIV-positive and a treatment program participant, the BC Centre for Excellence in HIV/AIDS (the Centre) would like to find out more about your living conditions, health status, and needs for treatment and care. Participants' responses to this survey will be used by the Centre to inform and educate British Columbians about the health and living conditions of persons living with HIV/AIDS.

To participants

Completion of this annual survey is voluntary. If you want to participate, please read it over carefully and answer it as best you can. The survey will take about 35 minutes to complete; because of participants' comments, some questions have been changed. The completed survey can be mailed to us in the enclosed self-addressed stamped envelope. **Any information you provide to us will remain strictly confidential.** Thank you in advance for your participation and co-operation.

To physicians

Please ensure the participant noted on the inside page receives this questionnaire. If this individual is no longer your patient please inform the Centre at (604) 806-8515. Thank you for your assistance.

Questions?

If you have specific questions or are interested in obtaining more information about the Centre's research activities, please contact the program co-ordinator, **Bonnie Devlin,** at (604) 806-8306. You can also refer to the *forecast*, the Centre's quarterly newsletter, and published research articles for information on the HIV/AIDS Drug Treatment program and other research activities. Subscriptions for our newsletter and other information material can be requested by writing to the following address: BC Centre for Excellence in HIV/AIDS, 608-1081 Burrard Street, Vancouver, BC, V6Z 1Y6. You can phone in your request to (604) 806-8515. Visit our website at http://cfeweb.hivnet.ubc.ca/

1. Personal Information

NOTE: In this section we would like you to read and complete some general background questions about your current education and employment status and the place you live.

1. What is the highest grade (or year) of secondary (high school) or elementary school you attended?

   Years of schooling: ..... _____
   Never attended school ..... ❑
   Unsure ..... ❑

2. How many years of education have you completed at university or another post-secondary institution (College, institutes of technology, CEGEPs, trade schools)?

   Years of schooling: ..... _____
   Less than 1 year ..... ❑
   Unsure/Never attended ..... ❑

3. What certificates, diplomas, or degrees have you obtained **(check all that apply).**

   High school diploma ..... ❑
   Trades certificate ..... ❑
   Undergraduate university degree ..... ❑
   Post-graduate university degree ..... ❑
   CEGEP, College, institute of technology certificate ..... ❑
   Never received a degree, diploma or certificate ..... ❑
   Other (specify): _____

4. What kind of housing are you currently living in?

   House ..... ❑
   Hotel, rooming-house, etc. ..... ❑
   Jail or prison ..... ❑
   Hospital ..... ❑
   Condominium/Apartment ..... ❑
   Shelter, hostel ..... ❑
   No fixed address ..... ❑
   Other(specify): _____

   NOTE: If you are currently living in an institution (like a jail or prison or hospital) then go to question 14.

5 How many adults and children, including yourself, currently reside in your home?

   Number of adults: _____ Number of children: _____

6. Do you currently share your housing arrangements with another person(s)? **(check one or more)**

No one.....❑ Roommate.....❑
Friend(s).....❑ Partner/lover .....❑
Spouse.....❑ Child(ren).....❑
Family.....❑
Other(specify):_____

7. Is your home in need of any repairs?

No, only regular maintenance .....❑

Yes, minor repairs (missing or loose floor tiles, needs paint, new counters, defective steps or railing, broken appliances, etc.).....❑

Yes, major repairs (defective plumbing or electrical wiring, structural repairs to walls, floors or ceilings, etc.).....❑

8. Will you be able to remain in your present housing throughout your illness?

Yes .....❑ No.....❑
Unsure.....❑

9. Are you **currently** employed in a job that pays money?

Full time .....❑ Self-employed .....❑
Part-time .....❑ Disability pay .....❑
Not at all .....❑

NOTE: If you are not employed please go to question 12.

10. **IF EMPLOYED (paid employment or currently on disability pay)**, please describe your **current** occupation or occupation providing disability pay:
Specify: _____

11. **IF EMPLOYED (paid employment)**, please indicate how many hours you Normally work at your **current** job(s) per week: _____hours per week.

12. **IF NOT EMPLOYED,** check the box or boxes which show your **current** status:

Unemployed but available for work .....❑
Temporarily unavailable for work (sick leave) _____❑
Permanently unable to work .....❑
Currently unable to work – Long-term disability .....❑
Home duties .....❑
Student .....❑
Retired from job.....❑
Other (specify): _____

13. What other **current** sources of support do you have: **(check one or more)**

Unemployment insurance (UIC) ..... ❑
Canadian Pension Plan (CPP) ..... ❑
Provincial income assistance (GAIN, Handicapped, Welfare) ..... ❑
Savings or borrowing ..... ❑
Long-term disability insurance ..... ❑
Not applicable (in jail or prison)..... ❑
Other forms of income(specify): ..... _____

14. Check the box which shows your **current** gross annual earnings (wages, salaries and net self employment, and any other income) before deductions:

Under $5,000	❑	$30,000-$34,999	❑
$5,000-$9,999	❑	$35,000-$39,999	❑
$10,000-$14,999	❑	$40,000-$44,999	❑
$15,000-$19,999	❑	$45,000-$49,999	❑
$20,000-$24,999	❑	$50,000 and over	❑
$25,000-$29,999	❑	Unsure of income	❑

15. Check one or more ethnic/cultural group that applies to you:

Aboriginal/First Nations	❑	Jewish.....	❑
Asian (Chinese, Vietnamese, etc.)	❑	Metis.....	❑
Black	❑	Middle Eastern	❑
Caucasian/White	❑	South Asian (Indian, Pakistani etc.)	❑
Hispanic/Latino	❑	Prefer not to answer	❑
Inuit	❑	Other(s): (specify) _____	

16. What languages can you speak well enough to conduct a conversation:
(check one or more)

English	❑	Hindi	❑
French	❑	Punjabi.....	❑
Spanish	❑	Prefer not to answer_____	❑
Cantonese.....	❑	Other(s): (specify) _____	
Mandarin	❑		

17. Are you a status or registered Indian (**as defined by the Indian Act**) ?

Yes ..... ❑
No, I am Metis, Inuit, or non-status ..... ❑
No ..... ❑

18. Were you born in Canada?

Yes ..... ❑ **(Go to question 20)**
No ..... ❑

19. **IF NO**, what country were you born in?

Specify country of birth: _____

20. How long have you been living in British Columbia?

Less than 1 year ..... ❑ 1 to 2 years ..... ❑
3 to 5 years ..... ❑ More than 5 years ..... ❑
Unsure ..... ❑

2. Health Status

NOTE: In this section we would like you to read and complete some basic questions about your current health status.

21. In general, would you say that your current health is:

Excellent ..... ❑ Fair ..... ❑
Very good ..... ❑ Poor ..... ❑
Good ..... ❑

22. **Compared to one year ago**, how would you rate your health in general now?

Much better now ..... ❑ Somewhat worse now ..... ❑
Somewhat better now ..... ❑ Much worse now ..... ❑
About the same ..... ❑

23. How much pain or discomfort do you have from illness at present?

None ..... ❑ Moderate ..... ❑
Mild or infrequent ..... ❑ Severe or persistent ..... ❑

24. In the past month, have you had any bodily pain?

Yes ..... ❑ No ..... ❑

25. **IF YES**, was the pain:

Very mild ..... ❑ Moderate ..... ❑

Mild ..... ❑ Severe ..... ❑

26. Please circle the number that best describes whether each of the following statements is true or false for you.

Responses:

1. Definitely true
2. Mostly true
3. Not sure
4. Mostly false
5. Definitely false

Circle the appropriate number

- I am somewhat ill ..... 1 ..... 2 ..... 3 ..... 4 5
- I am as healthy as anybody I know ..... 1 ..... 2 ..... 3 ..... 4 5
- My health is excellent ..... 1 ..... 2 ..... 3 ..... 4 5
- I have been feeling bad lately ..... 1 ..... 2 ..... 3 ..... 4 5

27. This set of questions concerns some problems you may have to deal with because of your illness. **Please circle one number per item.**

Responses:

1. A problem for more than 3 months
2. A problem for 3 months or less
3. Not a problem at all

Circle the appropriate number

- Does your health keep you from working at a job, doing work around the house or going to school? ..... 1 ... 2 3

- Have you been unable to do certain kinds or amounts or work, house work or school work because of your health? ..... 1 ... 2 3

- The kinds or amounts of vigorous activities you can do, like lifting heavy objects, running or participating in strenuous sports? ..... 1 ..... 2 3

- The kinds or amounts of moderate activities you can do, like moving a table, carrying two full bags of groceries? ..... 1 ... 2 3
- Walking uphill or climbing 10 steps without resting? ..... 1 ... 2 3
- Bending, lifting or stooping? ..... 1 ... 2 3
- Walking one block? ..... 1 ... 2 3
- Eating, dressing, bathing or using the toilet?..... 1 ... 2 3

28. For each of the following questions, please circle the number for the one answer that comes closest to the way you have been feeling **during the past month**.

Responses:

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

How much time during the past month: **Circle** the appropriate number

- has your health limited your social activities (like visiting with friends or close relatives)? ..... 1 ..... 2 ..... 3 .... 4 ..... 5 6
- have you been a very nervous person? .....1 ..... 2 ..... 3 .... 4 ..... 5 6
- have you felt calm and peaceful? .....1 ..... 2 ..... 3 .... 4 ..... 5 6
- have you felt downhearted and blue? .....1 ..... 2 ..... 3 .... 4 ..... 5 6
- have you been a happy person? .....1 ..... 2 ..... 3 .... 4 ..... 5 6
- have you felt so down in the dumps that nothing could cheer you up? .....1 ..... 2 ..... 3 .... 4 ..... 5 6

29. How tall are you without shoes on?

____ Feet ___ Inches **or** ___ Centimetres

30. How much do you weigh?

___ Kilograms **or** ___ Pounds

31. Have you gained or lost ten pounds or more within the past year?

Yes **Gained**..... ❑ No ..... ❑

Yes **Lost**..... ❑

If Yes, do you know why? (specify): _____

32. Do you have private insurance (i.e., insurance other than B.C. Medical Services, MSSH, First Nations Band, DIA or federal/provincial government coverage) that covers all or part of the cost of the following items:

	Yes	**No**	**Unsure**
• Dental expenses	❑	❑	❑
• Eye glasses or contact lenses	❑	❑	❑
• Extended hospital coverage	❑	❑	❑
• Life insurance	❑	❑	❑
• Long term health care benefits	❑	❑	❑
• Prescription medications	❑	❑	❑

33. Do you get any insurance benefits, such as those mentioned in the above question, as part of your current employment?

Yes ..... ❑ No ..... ❑

I am not currently employed .... ❑ Unsure ..... ❑

34. Do you pay for any of these insurance benefits (other than MSP) on your own?

Yes ..... ❑ No ..... ❑

35. What is the name(s) of the insurance company that provides these benefits? **(check one or more)**

North West Life ..... ❑ Manufacturer's Life ..... ❑

London and C ..... ❑ Great West Life ..... ❑

Sun Life ..... ❑ Aetna ..... ❑

Pacific Blue Cross ..... ❑ Don't Know ..... ❑

Other (specify): _____

3. Clinical Status

NOTE: In this section we would like to you read and complete some basic questions about your lifestyle and clinical history. Participants' comments on last year's questionnaire indicated that side effects of drugs were important to them, so this year we have added another question about them.

36. In what year and month **do you think** you were infected with HIV?
Year: 19___ Month: _____ Unsure ❑

37. How do you think you got HIV? **(check one or more boxes)**

Sex with a man	❑	Blood transfusion	❑
Sex with a woman	❑	Unsure/prefer not to answer	❑
Injection drug use	❑	Other (specify) : _____	
Blood product	❑		

38. Have you ever donated blood?

Yes	❑	
No	❑	**(go to question 42)**
Unsure/prefer not to answer	❑	**(go to question 42)**

39. **If you have donated blood**, how many donations have you ever made?

1 donation	❑	2 to 4 donations	❑
5 to 9 donations	❑	10 or more donations	❑

40. What year did you **first** donate blood?
Year of **first** blood donation: **19**___

41. What year did you **last** donate blood?
Year of **last** blood donation: **19**___

42. Have you been vaccinated for or received the following: **(Check one box per item)**

	Yes	No	Unsure	
• Hepatitis B (Hep B) vaccine	❑	❑	❑	IF YES, # of doses:
• *Haemophilus influenza* type B vaccine	❑	❑	❑	IF YES, #of doses:
• Pneumococcal vaccine (Pneumovax)	❑	❑	❑	
• "Flu" (Influenza) vaccine (in the last year)	❑	❑	❑	
• Tetanus immunization (in the last 10 years)	❑	❑	❑	
• TB skin test (PPD)	❑	❑	❑	**IF YES**, was it: Positive ❑ Negative ❑

43. Please indicate whether you have experienced any of the following side effects from your current HIV therapy: **(check all that apply)**

Side Effect	Ever had	Currently have	Never had
	Yes	Yes	Never
• **Cardiovascular Problems**			
High blood pressure	❑	❑	❑
Chest pain diagnosed by doctor as heart attack or similar	❑	❑	❑
• **Eye Problems**			
Blurred vision, painful eye that your doctor thinks is the result of inflammation of one of the layers of the eye	❑	❑	❑
• **Female-Specific Problems**			
Menstrual changes (changes in your period)	❑	❑	❑
• **Gastrointestinal Problems**			
Abdominal pain/discomfort	❑	❑	❑
Diarrhea	❑	❑	❑
Difficult digestion	❑	❑	❑
Presence of gas in stomach/bloating	❑	❑	❑
Nausea (feeling like you need to vomit)	❑	❑	❑
Vomiting	❑	❑	❑
Taste alterations (food and drink taste funny)	❑	❑	❑
• **Liver Function Test**			
Jaundice (skin/eyes turning yellow)	❑	❑	❑
Pain/discomfort over the liver (under rib cage on right)	❑	❑	❑
Doctor told you your liver is sick	❑	❑	❑
• **General Problems.**			
Decreased concentration	❑	❑	❑
Depression/suicidal feelings	❑	❑	❑
Dizziness	❑	❑	❑
Difficult breathing	❑	❑	❑
Fatigue/feeling tired	❑	❑	❑
Fever	❑	❑	❑
Headache	❑	❑	❑
Insomnia/problems sleeping	❑	❑	❑
Malaise (generally unwell)	❑	❑	❑
Hives; itchy welts	❑	❑	❑
Weakness	❑	❑	❑
Loss of appetite	❑	❑	❑

- **Skin Problems**
  - Rash ❑ ❑ ❑
  - Dryer skin ❑ ❑ ❑

- **Muscle and Skeletal Problems**
  - Blood in joints ❑ ❑ ❑
  - Haematomas (large bruises without remembering hurting yourself) ❑ ❑ ❑
  - Aches in joints and/or muscles ❑ ❑ ❑

- **Peripheral Nervous System Problems**
  - Numbness or pins and needles around mouth ❑ ❑ ❑
  - Numbess or pins and needles in hands/feet ❑ ❑ ❑

- **Metabolic Problems**
  - Diabetes mellitus (high blood sugar) ❑ ❑ ❑
  - Elevated cholesterol levels ❑ ❑ ❑
  - Changes in body shape with any of the following:
    - Weight gain around abdomen ❑ ❑ ❑
    - Thinner arms, legs and/or face ❑ ❑ ❑
    - Pad of tissue on back of neck ❑ ❑ ❑
  - Enlargement of breasts ❑ ❑ ❑
  - Lactation/"leaky breasts" ❑ ❑ ❑
  - Elevated triglyceride levels ❑ ❑ ❑

- **Sexual Problems**
  - Sexual dysfunction (unable to obtain/maintain erection) ❑ ❑ ❑
  - Decreased interest in sex ❑ ❑ ❑

- **Urinary Problems**
  - Painful/difficult urination ❑ ❑ ❑
  - Discharge of bloody urine ❑ ❑ ❑
  - Kidney stones ❑ ❑ ❑
  - Told by doctor that kidneys are not functioning properly ❑ ❑ ❑
  - Abdominal pain due to kidney spasms (very intense pain that starts next to lower back and can move to the genitals and/or inner thigh ❑ ❑ ❑

- **Other Problems**
  - Loss of hair ❑ ❑ ❑
  - Ingrown toenail ❑ ❑ ❑
  - Perianal abcesses/"tails" ❑ ❑ ❑
  - Other (please specify): _____

44. **In the last year,** have you changed the antiretroviral medications you are taking because of any of these side effects?

Yes ..... ❑ No ..... ❑

If **Yes,** specify the side effect: _____

45. **In the last year,** have you ever been admitted to hospital overnight or longer?

Yes ..... ❑ No ..... ❑

Unsure ..... ❑

46. **If yes,** how many times were you admitted to hospital?

Only once ..... ❑ 2 to 4 times ..... ❑

5 or more times ..... ❑ Unsure ..... ❑

47. **In the last year**, how many times did you receive medical attention or care from the following health care providers or services?

	1 time	2 - 4 times	5 or more times	Never	Unsure
Family/regular doctor	❑	❑	❑	❑	❑
Other medical doctor (such as surgeon, allergist, specialist)	❑	❑	❑	❑	❑
Nurse/street nurse	❑	❑	❑	❑	❑
Dentists or orthodontist	❑	❑	❑	❑	❑
Chiropractor	❑	❑	❑	❑	❑
Physiotherapist	❑	❑	❑	❑	❑
A drop-in clinic	❑	❑	❑	❑	❑
Hospital/emergency	❑	❑	❑	❑	❑
Detox/recovery house	❑	❑	❑	❑	❑
Other (specify: _____)	❑	❑	❑	❑	❑

48. Do you or have you had any of the following conditions: **(Confirmed by your doctor)**

	Yes	No	Unsure
• **Hepatitis**			
• Type A	❑	❑	❑
• Type B	❑	❑	❑
• Type C	❑	❑	❑
• Non-A, Non-B	❑	❑	❑
• Non-A, Non-B, Non-C	❑	❑	❑
• Hepatitis due to other causes (such as medications or alcohol)	❑	❑	❑
• **Diabetes**	❑	❑	❑
• **Heart Disease** (if Yes, please specify)	❑	❑	❑
• High blood pressure	❑	❑	❑
• Heart Attack	❑	❑	❑

- Leaky Valve ..... ❑ ..... ❑ ..... ❑
- Other: _____
- **High cholesterol** ..... ❑ ..... ❑ ..... ❑
- **Hemophilia** ..... ❑ ..... ❑ ..... ❑
- **Alterations of blood lipids** ..... ❑ ..... ❑ ..... ❑

4. Social Support and Coping

49. Below is a list of the ways you might have felt or behaved. Please indicate how often you have felt this way **during the past week** by circling the appropriate number.

Responses:
1. Rarely or none of the time (Less than 1 day)
2. Some or a little of the time (1-2 days)
3. Occasionally or a moderate amount of time (3-4 days)
4. Most or all of the time (5-7 days)

During the past week: **Circle** the appropriate number

- I was bothered by things that usually don't bother me ..... 1 .....2 ..... 3 4
- I did not feel like eating; my appetite was poor ..... 1 .....2 ..... 3 4
- I felt that I could not shake off the blues even with help from my family or friends ..... 1 .....2 ..... 3 4
- I felt that I was just as good as other people ..... 1 .....2 ..... 3 4

- I had trouble keeping my mind on what I was doing ..... 1 .....2 ..... 3 4
- I felt depressed ..... 1 .....2 ..... 3 4
- I felt that everything I did was an effort ..... 1 .....2 ..... 3 4
- I felt hopeful about the future ..... 1 .....2 ..... 3 4

- I thought my life had been a failure ..... 1 .....2 ..... 3 4
- I felt fearful ..... 1 .....2 ..... 3 4
- My sleep was restless ..... 1 .....2 ..... 3 4
- I was happy ..... 1 .....2 ..... 3 4

- I talked less than usual ..... 1 .....2 ..... 3 4
- I felt lonely ..... 1 .....2 ..... 3 4
- People were unfriendly ..... 1 .....2 ..... 3 4
- I enjoyed life ..... 1 .....2 ..... 3 4

- I had crying spells ..... 1 .....2 ..... 3 4
- I felt sad ..... 1 .....2 ..... 3 4
- I felt that people disliked me ..... 1 .....2 ..... 3 4
- I could not get "going" ..... 1 .....2 ..... 3 4

5. Fatigue

NOTE:	The next several questions deal with your sleeping habits and your general level of fatigue.

50. On average, how many hours of sleep do you get each night?
    Hours: _____ Unsure/Don't know ..... ❑

51. Do you usually take one or more naps during the day?
    Yes ..... ❑ No ..... ❑ Go to question 53

52. If yes, how long do you usually **nap** for each day in total (including all naps):
    Hours: _____ Unsure/Don't know ..... ❑

53. Do you regularly have trouble going to sleep or staying asleep when you go to bed at night?
    Yes ..... ❑ No ..... ❑

54. How often do you find sleep refreshing?
    Most of the time ..... ❑ Sometimes ..... ❑
    Never ..... ❑ Unsure/Don't know ..... ❑

55. How often do you find it difficult to stay awake when you want to?
    Most of the time ..... ❑ Sometimes ..... ❑
    Never ..... ❑ Unsure/Don't know ..... ❑

6. Complementary / Alternative Therapies (CAT)

NOTE:	We recognize that alternative therapies may now play an integral role in an individual's therapeutic regimen. In the interest of furthering our knowledge of these therapies, we would appreciate full disclosure of therapies you use, or have used in the past.

56. Have you ever used any **alternative** (non-prescription) therapies for your HIV disease?

Yes ..... ❑
No ..... ❑ **(go to question 66)**
Unsure/ prefer not to answer ❑ **(go to question 66)**

57. Approximately how much do you spend on **CAT** therapies per month?

< $50 per month..... ❑
$50 to $99 per month ..... ❑
$100 to $199 per month ..... ❑
$200 to $400 per month.... ❑
Over $400 per month..... ❑
Unsure ..... ❑

58. **IF YES**, what are **your reasons** for taking HIV-related **CAT**? **(choose all that apply)**

To enhance your immune response ..... ❑
To lower your viral load ..... ❑
To manage side effects of other therapies ..... ❑
To supplement your dietary intake ..... ❑
To have greater control over your health ..... ❑
To prevent infections ..... ❑
To improve your energy level ..... ❑
You feel good about taking CAT .... ❑
CAT won't do any harm ..... ❑
Other(s) (specify):

_____

59. **In the last year**, have you consulted any of the following alternative practitioners for HIV/AIDS related conditions? **(choose all that apply)**

Acupuncturist..... ❑
Herbalist ..... ❑
Holistic medicine specialist ..... ❑
Osteopath..... ❑
Doctor of Chinese medicine. ❑
Homeopath ..... ❑
Naturopath ..... ❑
Traditional Aboriginal healer ❑
Other(s) (specify): _____

60. What is your major source of information regarding **alternative** therapies? **(choose all that apply)**

Alternative practitioner	❑	Family/friend(s)	❑
Physician (MD)	❑	Health food stores	❑
Magazines/papers/TV	❑	Local AIDS organizations	❑
Support groups, other persons with HIV	❑	Scientific journals	❑
Internet	❑	Other(s) (specify): _____	

61. Do you tell your medical doctor that you are using these therapies?

Always	❑	Often	❑	Never	❑
Sometimes	❑	Rarely	❑		

62. If you **ever** tell your doctor, how supportive of your CAT use have they been?

Very supportive	❑	Somewhat supportive	❑
Neutral	❑	Not very supportive	❑
Not at all supportive	❑		

63. Do you ever feel that you put your health at risk by using CATs?

Always	❑	Often	❑
Sometimes	❑	Rarely	❑
Never	❑	**(Go to question 65)**	

64. If you ever feel that using CATs puts you at risk, why is this?

Not enough information available about effects of CAT	❑
Not enough HIV-specific information about effects	❑
I spend too much money on CATs	❑
Not enough professional guidance to help me use them	❑
Lack of physician's support	❑
Other (specify): _____	

65. Please indicate whether you have used any of the following **alternative** therapies: **(check all that apply)**

Alternative therapy	**Ever used Yes**	Currently **Yes**	If you stopped please provide a reason **Ineffective**	**Cost**	**Other reason**
Diet/Nutrition/Lifestyle changes					
• Dietary Supplements (*Macrobiotic diet, Blue-green algae, Boost)*	❑	❑	❑	❑	_____
• Exercise	❑	❑	❑	❑	_____
• Vitamins/minerals	❑	❑	❑	❑	_____
• Other (Specify) _____	❑	❑	❑	❑	_____
Bioelectromagnetics	❑	❑	❑	❑	_____
Alternative practice systems					
• Homeopathy	❑	❑	❑	❑	_____
• Acupuncture	❑	❑	❑	❑	_____
• Naturopathy	❑	❑	❑	❑	_____
• Chinese medicine	❑	❑	❑	❑	_____
• Other(Specify) _____	❑	❑	❑	❑	_____
Herbal medicine (Please specify exact herbs used - for example, St Johns wort)					
• Specify _____	❑	❑	❑	❑	_____
• Specify _____	❑	❑	❑	❑	_____
• Specify _____	❑	❑	❑	❑	_____
Manual healing					
• Massage (*Reiki, Shiatsu*)	❑	❑	❑	❑	_____
• Therapeutic touch	❑	❑	❑	❑	_____
• Reflexology)	❑	❑	❑	❑	_____
• Other (Specify) _____	❑	❑	❑	❑	_____
Mind-body control					
• Meditation	❑	❑	❑	❑	_____
• Yoga	❑	❑	❑	❑	_____
• Other (Specify) _____	❑	❑	❑	❑	_____
Pharmacological/Biological treatment					
• Compound Q (Coenzyme Q10)	❑	❑	❑	❑	_____
• DNCB	❑	❑	❑	❑	_____
• N-Acetyl-cysteine (NAC)	❑	❑	❑	❑	_____
• Marijuana	❑	❑	❑	❑	_____
• Ozone therapy	❑	❑	❑	❑	_____
• Other (Specify) _____	❑	❑	❑	❑	_____

Alternative therapy	Ever used Yes	Currently Yes	If you stopped please provide a reason Ineffective	Cost	Other reason

Other alternative (non-prescription) treatments

- _____ .... ❑ ..... ❑ ..... ❑ ..... ❑ ..... _____
- _____ .... ❑ ..... ❑ ..... ❑ ..... ❑ ..... _____
- _____ .... ❑ ..... ❑ ..... ❑ ..... ❑ ..... _____

7. Lifestyle

NOTE: In this section we would like to you read and complete some basic questions about your lifestyle.

66. **In the last six months**, have you **ever had trouble** taking your antiretroviral medications (like AZT, ddI, ddC, 3TC, d4T, Saquinavir, Ritonavir, and Indinavir)?

All of the time ..... ❑ Most of the time ..... ❑
Half of the time..... ❑ Some of the time ..... ❑
Never ..... ❑ Unsure ..... ❑
I was not on antiretroviral therapy during the last six months ..... ❑

NOTE: If you never had any problems with taking your medications please go to question 68.

67. **If you had problems in the last six months**, how long did you stop taking your antiretroviral medications for?

Less than one day ..... ❑ Less than one week ..... ❑
Less than one month ..... ❑ Less than three months ..... ❑
Did not stop taking them ..... ❑ Unsure ..... ❑

68. Have you ever injected drugs?

Yes ..... ❑
No ..... ❑ **(go to question 71)**
Unsure/prefer not to answer ..... ❑ **(go to question 71)**

69. **Over the last 6 months,** did you inject any drugs?

Yes ..... ❑
No ..... ❑ **(go to question 71)**
Unsure/prefer not to answer ..... ❑ **(go to question 71)**

70. **Over the last 6 months**, what is the **longest** period of time you went without **injecting** drugs ?

Less than one day..... ❑ Less than one week ..... ❑
Less than one month ..... ❑ Less than three months..... ❑
Less than six months..... ❑ Unsure/prefer not to answer..... ❑

71. Have you ever attended any kind of alcohol or other drug treatment program?

Yes ..... ❑ No ..... ❑
Unsure/prefer not to answer ❑

8. Feedback

NOTE:	This section is intended for your feedback. Your suggestions help us to improve the questionnaire from year to year. Please take a few minutes and complete these few questions.

72. Please rate this questionnaire according to the following categories **(check one box per row)**:

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
• The questionnaire was easy to read	❑	❑	❑	❑	❑
• The questions were easy to understand	❑	❑	❑	❑	❑
• The choices for responses were adequate	❑	❑	❑	❑	❑

73. Was this questionnaire

Too short in length ❑ Too long in length ❑
About the right length ❑ Unsure ❑

74. How long did it take you to answer this questionnaire? _____

75. Please write any further information that you think is relevant. You may add additional pages to this questionnaire if necessary.

_____

_____

_____

_____

_____

_____

Thank you very much for taking the time to answer these questions. Please put the completed questionnaire in the enclosed self-addressed and stamped envelope and drop it in the mail.

APPENDIX 3

Drug Treatment Programme Survey; 2000-2001

The HIV/AIDS Drug Treatment Program Annual Participant Survey 2000/2001

This annual survey is for **participants in the HIV/AIDS Drug Treatment Program.** If you are HIV-positive and a treatment program participant, the BC Centre for Excellence in HIV/AIDS (the Centre) would like to find out more about your living conditions, health status, and needs for treatment and care. Participants' responses to this survey will be used by the Centre to inform and educate British Columbians about the health and living conditions of persons living with HIV/AIDS.

To participants

Completion of this annual survey is voluntary. If you want to participate, please read it over carefully and answer it as best you can. The survey will take about 35 minutes to complete; because of participants' comments, some questions have been changed. The completed survey can be mailed to us in the enclosed self-addressed stamped envelope. **Any information you provide to us will remain strictly confidential.** Thank you in advance for your participation and co-operation.

To physicians

Please ensure the participant noted on the inside page receives this questionnaire. If this individual is no longer your patient please inform the Centre at (604) 806-8515. Thank you for your assistance.

Questions?

If you have specific questions or are interested in obtaining more information about the Centre's research activities, please contact the program co-ordinator, **Bonnie Devlin,** at (604) 806-8306. You can also refer to the *forecast*, the Centre's quarterly newsletter, and published research articles for information on the HIV/AIDS Drug Treatment program and other research activities. Subscriptions for our newsletter and other information material can be requested by writing to the following address: BC Centre for Excellence in HIV/AIDS, 608-1081 Burrard Street, Vancouver, BC, V6Z 1Y6. You can phone in your request to (604) 806-8515. Visit our website at http://cfeweb.hivnet.ubc.ca/

1. Personal Information

NOTE: In this section we would like you to read and complete some general background questions about your current education and employment status and the place you live.

1. What is the highest grade (or year) of secondary (high school) or elementary school you attended?

   Years of schooling: ..... _____
   Never attended school ..... ❑
   Unsure ..... ❑

2. How many years of education have you completed at university or another post-secondary institution (College, institutes of technology, CEGEPs, trade schools)?

   Years of schooling: ..... _____
   Less than 1 year ..... ❑
   Unsure/Never attended ..... ❑

3. What certificates, diplomas, or degrees have you obtained **(check all that apply).**

   High school diploma ..... ❑
   Trades certificate ..... ❑
   Undergraduate university degree ..... ❑
   Post-graduate university degree ..... ❑
   CEGEP, College, institute of technology certificate ..... ❑
   Never received a degree, diploma or certificate ..... ❑
   Other (specify): _____

4. What kind of housing are you currently living in?

   House ..... ❑
   Hotel, rooming-house, etc. ..... ❑
   Jail or prison ..... ❑
   Hospital ..... ❑
   Other(specify):_____
   Condominium/Apartment ..... ❑
   Shelter, hostel ..... ❑
   No fixed address ..... ❑

   NOTE: **If you are currently living in an institution (like a jail or prison or hospital) then go to question 14.**

5 How many adults and children, **including yourself**, currently reside in your home?

   Number of adults: _____ Number of children: _____

6. Do you currently share your housing arrangements with another person(s)? **(check one or more)**

No one ..... ❑
Friend(s) ..... ❑
Spouse ..... ❑
Family ..... ❑
Other(specify):_____

Roommate ..... ❑
Partner/lover ..... ❑
Child(ren) ..... ❑

7. Will you be able to remain in your present housing throughout your illness?

Yes ..... ❑
Unsure ..... ❑
No ..... ❑

8. Are you **currently** employed in a job that pays money or on disability pay (check all that apply)?

Full time ..... ❑
Part-time ..... ❑
Not at all ..... ❑

Self-employed ..... ❑
Disability pay ..... ❑

NOTE: If you are not employed please go to question 11.

9. **IF EMPLOYED (paid employment or currently on disability pay)**, please describe your **current** occupation or occupation providing disability pay:
Specify: _____

10. **IF EMPLOYED (paid employment)**, please indicate how many hours you Normally work at your **current** job(s) per week: _____hours per week.

11. **IF NOT EMPLOYED,** check the box or boxes which show your **current** status:

Unemployed but available for work ..... ❑
Temporarily unavailable for work/sick leave ..... ❑
Permanently unable to work ..... ❑
Currently unable to work – Long-term disability ..... ❑
Home duties ..... ❑
Student ..... ❑
Retired from job ..... ❑
Other (specify): ..... _____

12. What other **current** sources of support do you have: **(check one or more)**

- Unemployment insurance (UIC) ❑
- Canadian Pension Plan (CPP) ❑
- Provincial income assistance (GAIN, Handicapped, Welfare) ❑
- Savings or borrowing ❑
- Long-term disability insurance ❑
- Not applicable (in jail or prison) ❑
- Other forms of income(specify): _____

13. Check the box which shows your **current** gross annual earnings (wages, salaries and net self employment, and any other income) before deductions:

Under $5,000	❑	$30,000-$34,999	❑
$5,000-$9,999	❑	$35,000-$39,999	❑
$10,000-$14,999	❑	$40,000-$44,999	❑
$15,000-$19,999	❑	$45,000-$49,999	❑
$20,000-$24,999	❑	$50,000 and over	❑
$25,000-$29,999	❑	Unsure of income	❑

14. Check one or more ethnic/cultural group that applies to you:

Status Indian/Aboriginal /First Nations	❑	Jewish	❑
Non-status Indian/Aboriginal /First Nations	❑	Asian (Chinese, Vietnamese, etc.)	❑
Inuit/ Métis	❑	South Asian (Indian, Pakistani etc.)	❑
Black	❑	Middle Eastern	❑
Caucasian/White	❑	Prefer not to answer	❑
Hispanic/Latino	❑	Other(s): (specify) _____	

15. Were you born in Canada?

- Yes ❑ **(Go to question 17)**
- No ❑

16. **IF NO**, what country were you born in?

Specify country of birth: _____

2. Health Status and Clinical History

NOTE: In this section we would like you to read and complete some basic questions about your current health status.

17. How tall are you without shoes on?

____ Feet ___ Inches **or** ___ Centimetres

18. How much do you weigh?

___ Kilograms **or** ___ Pounds

19. Have you gained or lost ten pounds or more within the past year?

Yes **Gained**..... ❑ No ..... ❑

Yes **Lost**..... ❑

If Yes, do you know why? (specify): _____

20. In general, would you say that your current health is:

Excellent ..... ❑ Fair ..... ❑

Very good..... ❑ Poor ..... ❑

Good ..... ❑

21. **Compared to one year ago**, how would you rate your health in general now?

Much better now..... ❑ Somewhat worse now ..... ❑

Somewhat better now ..... ❑ Much worse now ..... ❑

About the same ..... ❑

22. How much pain or discomfort do you have from illness at present?

None ..... ❑ Moderate ..... ❑

Mild or infrequent ..... ❑ Severe or persistent ..... ❑

23. In the past month, have you had any bodily pain?

Yes ..... ❑ No ..... ❑

24. **IF YES**, was the pain:

Very mild ..... ❑		Moderate ..... ❑	
Mild ..... ❑		Severe ..... ❑	

25. Please circle the number that best describes whether each of the following statements is true or false for you.

Responses:
1. Definitely true
2. Mostly true
3. Not sure
4. Mostly false
5. Definitely false

Circle the appropriate number

- I am somewhat ill ..... 1 ..... 2 ..... 3 ..... 4 5
- I am as healthy as anybody I know ..... 1 ..... 2 ..... 3 ..... 4 5
- My health is excellent ..... 1 ..... 2 ..... 3 ..... 4 5
- I have been feeling bad lately ..... 1 ..... 2 ..... 3 ..... 4 5

26. This set of questions concerns some problems you may have to deal with because of your illness. **Please circle one number per item.**

Responses:
1. A problem for more than 3 months
2. A problem for 3 months or less
3. Not a problem at all

Circle the appropriate number

- Does your health keep you from working at a job, doing work around the house or going to school? ..... 1 ... 2 3
- Have you been unable to do certain kinds or amounts or work, house work or school work because of your health? ..... 1 ... 2 3
- The kinds or amounts of vigorous activities you can do, like lifting heavy objects, running or participating in strenuous sports? ..... 1 ..... 2 3
- The kinds or amounts of moderate activities you can do, like moving a table, carrying two full bags of groceries? ..... 1 ... 2 3
- Walking uphill or climbing 10 steps without resting? ..... 1 ... 2 3

- Bending, lifting or stooping? ..... 1 ... 2 3
- Walking one block? ..... 1 ... 2 3
- Eating, dressing, bathing or using the toilet?..... 1 ... 2 3

27. For each of the following questions, please circle the number for the one answer that comes closest to the way you have been feeling **during the past month**.

Responses:

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

How much time during the past month: **Circle** the appropriate number

- has your health limited your social activities (like visiting with friends or close relatives)? ..... 1 ..... 2 ..... 3 ... 4 ..... 5 6
- have you been a very nervous person? ..... 1 ..... 2 ..... 3 ... 4 ..... 5 6
- have you felt calm and peaceful? ..... 1 ..... 2 ..... 3 ... 4 ..... 5 6
- have you felt downhearted and blue? ..... 1 ..... 2 ..... 3 ... 4 ..... 5 6
- have you been a happy person? ..... 1 ..... 2 ..... 3 ... 4 ..... 5 6
- have you felt so down in the dumps that nothing could cheer you up? ..... 1 ..... 2 ..... 3 ... 4 ..... 5 6

28. In what year and month **do you think** you were infected with HIV?
Year: 19 ___ Month: _____ Unsure ❑

29. How do you think you got HIV? **(check one or more boxes)**

Sex with a man ..... ❑
Sex with a woman ..... ❑
Injection drug use ..... ❑
Blood product ..... ❑
Blood transfusion ..... ❑
Unsure/prefer not to answer ..... ❑
Other (specify) : _____

30. Have you ever injected drugs (non prescription)?

Yes ..... ❑
No ..... ❑ **(go to question 32)**
Unsure/prefer not to answer ..... ❑ **(go to question 32)**

31. **Over the last 6 months,** did you inject any drugs?

Yes ..... ❑
No ..... ❑
Unsure/prefer not to answer ..... ❑

32. **In the last year,** have you ever been admitted to hospital overnight or longer?

Yes ..... ❑ No ..... ❑
Unsure ..... ❑

33. **If yes,** how many times were you admitted to hospital?

Only once ..... ❑ 2 to 4 times ..... ❑
5 or more times ..... ❑ Unsure ..... ❑

34. **In the last year**, how many times did you receive medical attention or care from the following health care providers or services?

	1 time	2 - 4 times	5 or more times	Never	Unsure
Family/regular doctor	❑	❑	❑	❑	❑
Other medical doctor (such as surgeon, allergist, specialist)	❑	❑	❑	❑	❑
Nurse/street nurse	❑	❑	❑	❑	❑
Dentists or orthodontist	❑	❑	❑	❑	❑
Chiropractor	❑	❑	❑	❑	❑
Physiotherapist	❑	❑	❑	❑	❑
A drop-in clinic	❑	❑	❑	❑	❑
Hospital/emergency	❑	❑	❑	❑	❑
Detox/recovery house	❑	❑	❑	❑	❑
Other (specify: _____)	❑	❑	❑	❑	❑

3. Health Insurance

NOTE:	In this section we would like you to complete some basic questions about any health insurance you may have.

35. Do you have **private** insurance (i.e., insurance other than B.C. Medical Services, MSSH, First Nations Band, DIA or federal/provincial government coverage) that covers all or part of the cost of the following items:

	Yes	No	Unsure
• Dental expenses	❑	❑	❑
• Eye glasses or contact lenses	❑	❑	❑
• Extended hospital coverage	❑	❑	❑
• Life insurance	❑	❑	❑
• Long term health care benefits	❑	❑	❑
• Prescription medications	❑	❑	❑

36. Do you get any insurance benefits, such as those mentioned in the above question, as part of your current employment?

Yes ..... ❑ No ..... ❑
I am not currently employed .... ❑ Unsure ..... ❑

37. Do you pay for any of these insurance benefits (other than MSP) on your own?

Yes ..... ❑ No ..... ❑

38. What is the name(s) of the insurance company that provides these benefits? **(check one or more)**

North West Life ..... ❑ Manufacturer's Life ..... ❑
London and C ..... ❑ Great West Life ..... ❑
Sun Life ..... ❑ Aetna ..... ❑
Pacific Blue Cross ..... ❑ Don't Know ..... ❑
Other (specify): _____

4. Medication-Related Issues

NOTE: Participants' comments on last year's survey indicate that side effects that may be caused by antiretroviral medicines (AZT, ddI, 3TC, d4T, Indinavir, Ritonavir, Saquinavir) are an important issue. We are very interested in finding out more about how these symptoms affect you and how doctors can help you to cope with them.

39. For **each** of the possible side effects listed below indicate whether you have had each symptom **in the past year,** and whether you are **still** experiencing the symptom(s). For each symptom that you have now or have had, please indicate the severity on the 3 point scale with:
    1. mild
    2. moderate
    3. severe

A. Symptoms	**Yes -Past year**	**Yes - Still**	**Severity**
Vivid dreams/nightmares	❑	❑	1 2 3
Hallucinations	❑	❑	1 2 3
Taste alterations	❑	❑	1 2 3
Decreased concentration	❑	❑	1 2 3
Dryer skin	❑	❑	1 2 3
Difficulty breathing	❑	❑	1 2 3
Insomnia/problems sleeping	❑	❑	1 2 3
Malaise (generally unwell)	❑	❑	1 2 3
Weakness	❑	❑	1 2 3
Loss of appetite	❑	❑	1 2 3
Haematomas (large bruises without remembering hurting yourself	❑	❑	1 2 3
Aches in joints and/or muscles	❑	❑	1 2 3
Numbness or pins and needles around mouth	❑	❑	1 2 3
Decreased interest in sex	❑	❑	1 2 3

If you have had any of these symptoms during the past year, what did **<u>your</u> <u>doctor</u>** do or say you should do about them? **(Select ALL that apply)**

- Did not tell doctor ❑
- Investigated cause of symptoms and will observe/wait ❑
- Doctor did not think the symptoms were caused by my antiretrovirals ❑
- Changed my antiretroviral therapy (changed some drugs or doses) ❑
- Interrupted antiretroviral therapy for a while (drug holiday) ❑
- Stopped all antiretroviral therapy indefinitely ... ❑
- Prescribed or recommended medications or action to treat symptoms ❑
- Nothing ❑
- Unsure/do not remember ❑

If you have had any of these symptoms during the past year, what did/do **you** **actually do** about them? **(Select ALL that apply)**

Followed my doctor's instructions ❑
Treated symptoms (natural, prescribed or over the counter therapies) ❑
Took a break from all my antiviral drugs for a while (drug holiday, pulse therapy) ❑
Sometimes skipped the antiviral drugs causing the symptom, or took fewer doses ❑
Stopped all antiretroviral therapy ❑
Nothing, I just live(d) with the symptoms/waited ❑
Unsure/do not remember ❑

B. Symptoms	Yes -Past year	Yes - Still	Severity
Abdominal pain/discomfort	❑	❑	1 2 3
Nausea (feeling like you need to vomit)	❑	❑	1 2 3
Pain/discomfort over the liver (under ribs)	❑	❑	1 2 3
Depression/suicidal feelings	❑	❑	1 2 3
Dizziness	❑	❑	1 2 3
Numbness or pins and needles in hands/feet	❑	❑	1 2 3
Fatigue/feeling tired	❑	❑	1 2 3
Headache	❑	❑	1 2 3
Sexual dysfunction (unable to get /maintain erection)	❑	❑	1 2 3
Painful/difficult urination	❑	❑	1 2 3

If you have had any of these symptoms during the past year, what did **your** **doctor** do or say you should do about them? **(Select ALL that apply)**

Did not tell doctor ❑
Investigated cause of symptoms and will observe/wait ❑
Doctor did not think the symptoms were caused by my antiretrovirals ❑
Changed my antiretroviral therapy (changed some drugs or doses) ❑
Interrupted antiretroviral therapy for a while (drug holiday) ❑
Stopped all antiretroviral therapy indefinitely ❑
Prescribed or recommended medications or action to treat symptoms ❑
Nothing ❑
Unsure/do not remember ❑

If you have had any of these symptoms during the past year, what did/do **you actually do** about them? **(Select ALL that apply)**

Followed my doctor's instructions ❑
Treated symptoms (natural, prescribed or over the counter therapies) ❑
Took a break from all my antiviral drugs for a while (drug holiday, pulse therapy) ❑
Sometimes skipped the antiviral drugs causing the symptom, or took fewer doses ❑
Stopped all antiretroviral therapy ❑
Nothing, I just live(d) with the symptoms/waited ❑
Unsure/do not remember ❑

C. Symptoms

	Yes -Past year	Yes - Still	Severity
Weight gain around abdomen	❑	❑	1 2 3
Thinner arms, legs and/or face	❑	❑	1 2 3
Pad of tissue on back of neck	❑	❑	1 2 3
Enlargement of breast/chest	❑	❑	1 2 3
Loss of hair	❑	❑	1 2 3

If you have had any of these symptoms during the past year, what did **your doctor** do or say you should do about them? **(Select ALL that apply)**

Did not tell doctor ❑
Investigated cause of symptoms and will observe/wait ❑
Doctor did not think the symptoms were caused by my antiretrovirals ❑
Changed my antiretroviral therapy (changed some drugs or doses) ❑
Interrupted antiretroviral therapy for a while (drug holiday) ❑
Stopped all antiretroviral therapy indefinitely ❑
Prescribed or recommended medications or action to treat symptoms ❑
Nothing ❑
Unsure/do not remember ❑

If you have had any of these symptoms during the past year, what did/do **you actually do** about them? **(Select ALL that apply)**

Followed my doctor's instructions ❑
Treated symptoms (natural, prescribed or over the counter therapies) ❑
Took a break from all my antiviral drugs for a while (drug holiday, pulse therapy) ❑
Sometimes skipped the antiviral drugs causing the symptom, or took fewer doses ❑
Stopped all antiretroviral therapy ❑
Nothing, I just live(d) with the symptoms/waited ❑
Unsure/do not remember ❑

D. Symptoms	Yes -Past year	Yes - Still	Severity
Hives/itchy welts	❑	❑	1 2 3
Blood in joints	❑	❑	1 2 3
Diarrhea	❑	❑	1 2 3
Jaundice (skin/eyes turning yellow)	❑	❑	1 2 3
Rash	❑	❑	1 2 3
Osteoporosis (brittle, weak bones)	❑	❑	1 2 3
Avascular necrosis of the hip	❑	❑	1 2 3
Doctor told you your liver is sick	❑	❑	1 2 3
Vomiting	❑	❑	1 2 3
Fever	❑	❑	1 2 3
Discharge of bloody urine	❑	❑	1 2 3
Kidney stones	❑	❑	1 2 3
Told by doctor that kidneys aren't functioning properly	❑	❑	1 2 3
Abdominal pain due to liver spasms (very intense pain that starts next to lower back and can move to the genitals and/or inner thigh)	❑	❑	1 2 3

If you have had any of these symptoms during the past year, what did **<u>your</u> <u>doctor</u>** do or say you should do about them? **(Select ALL that apply)**

- Did not tell doctor ❑
- Investigated cause of symptoms and will observe/wait ❑
- Doctor did not think the symptoms were caused by my antiretrovirals ❑
- Changed my antiretroviral therapy (changed some drugs or doses) ❑
- Interrupted antiretroviral therapy for a while (drug holiday) ❑
- Stopped all antiretroviral therapy indefinitely ❑
- Prescribed or recommended medications or action to treat symptoms ❑
- Nothing ❑
- Unsure/do not remember ❑

If you have had any of these symptoms during the past year, what did/do **<u>you</u> actually do** about them? **(Select ALL that apply)**

- Followed my doctor's instructions ❑
- Treated symptoms (natural, prescribed or over the counter therapies) ❑
- Took a break from all my antiviral drugs for a while (drug holiday, pulse therapy) ❑
- Sometimes skipped the antiviral drugs causing the symptom, or took fewer doses ❑
- Stopped all antiretroviral therapy ❑
- Nothing, I just live(d) with the symptoms/waited ❑
- Unsure/do not remember ❑

40. Has a **doctor** told you that you have the following problems? Were any of these problems diagnosed for the **first time in the past year**?

	No Never	Yes Ever	Past year 1st time
High blood pressure	❑	❑	❑
Chest pain diagnosed by doctor as heart attack or similar	❑	❑	❑
Leaky valve	❑	❑	❑
Diabetes mellitus (high blood sugar)	❑	❑	❑
Increased or high cholesterol	❑	❑	❑
Increased or high triglyceride levels or lipid abnormalities	❑	❑	❑
High homocystene levels	❑	❑	❑
Family history of heart disease (father or brother had a heart attack/stroke before the age of 55)	❑	❑	❑
Hep B/Hep C	❑	❑	❑
Other (specify) _____	❑	❑	❑

41. Have you EVER smoked tobacco - cigarettes, cigars, or a pipe - regularly?

Yes ..... ❑ No ..... ❑ **(go to question 44)**

42. At what age did you start smoking regularly?

_____ years old

43. How much do or did you smoke?

How many manufactured cigarettes **a day**? _____

How many grams of "hand-rolled" cigarette tobacco* **per week**? _____ g

How many cigars **per week**? _____

How many grams of pipe tobacco* **per week**? _____ g

*Note: a 1.75 ounce pouch of tobacco equals 50 grams

5. Social Support and Coping

44. Below is a list of the ways you might have felt or behaved. Please indicate how often you have felt this way **during the past week** by circling the appropriate number.

Responses:

1. Rarely or none of the time (Less than 1 day)
2. Some or a little of the time (1-2 days)
3. Occasionally or a moderate amount of time (3-4 days)
4. Most or all of the time (5-7 days)

During the past week:	**Circle** the appropriate number
• I was bothered by things that usually don't bother me	1 .....2 ..... 3 4
• I did not feel like eating; my appetite was poor	1 .....2 ..... 3 4
• I felt that I could not shake off the blues even with help from my family or friends	1 .....2 ..... 3 4
• I felt that I was just as good as other people	1 .....2 ..... 3 4
• I had trouble keeping my mind on what I was doing	1 .....2 ..... 3 4
• I felt depressed	1 .....2 ..... 3 4
• I felt that everything I did was an effort	1 .....2 ..... 3 4
• I felt hopeful about the future	1 .....2 ..... 3 4
• I thought my life had been a failure	1 .....2 ..... 3 4
• I felt fearful	1 .....2 ..... 3 4
• My sleep was restless	1 .....2 ..... 3 4
• I was happy	1 .....2 ..... 3 4
• I talked less than usual	1 .....2 ..... 3 4
• I felt lonely	1 .....2 ..... 3 4
• People were unfriendly	1 .....2 ..... 3 4
• I enjoyed life	1 .....2 ..... 3 4
• I had crying spells	1 .....2 ..... 3 4
• I felt sad	1 .....2 ..... 3 4

6. Fatigue

NOTE: The next several questions deal with your sleeping habits and your general level of fatigue.

45. On average, how many hours of sleep do you get each night?
Hours: _____ Unsure/Don't know ..... ❑

46. Do you usually take one or more naps during the day?
Yes ..... ❑ No ..... ❑ Go to question 48

47. If yes, how long do you usually **nap** for each day in total (including all naps):
Hours: _____ Unsure/Don't know ..... ❑

48. Do you regularly have trouble going to sleep or staying asleep when you go to bed at night?
Yes ..... ❑ No ..... ❑

49. How often do you find sleep refreshing?
Most of the time ..... ❑ Sometimes ..... ❑
Never..... ❑ Unsure/Don't know ..... ❑

50. How often do you find it difficult to stay awake when you want to?
Most of the time ..... ❑ Sometimes ..... ❑
Never..... ❑ Unsure/Don't know ..... ❑

7. Complementary / Alternative Therapies (CAT)

NOTE: We recognize that alternative therapies may now play an integral role in an individual's therapeutic regimen. In the interest of furthering our knowledge of these therapies, we would appreciate full disclosure of therapies you use, or have used in the past.

51. Have you ever used any **complementary** or **alternative (CAT)** (non-prescription) therapies for your HIV disease?
Yes ..... ❑
No ..... ❑ **(go to question 61)**
Unsure/ prefer not to answer ❑ **(go to question 61)**

52. Approximately how much do you spend on **CAT** therapies per month?

< $50 per month	❑	$200 to $400 per month	❑
$50 to $99 per month	❑	Over $400 per month	❑
$100 to $199 per month	❑	Unsure	❑

53. **IF YES**, what are **your reasons** for taking HIV-related **CAT**? **(choose all that apply)**

To enhance your immune response	❑	To prevent infections	❑
To lower your viral load	❑	To improve your energy level	❑
To manage side effects of other therapies	❑	You feel good about taking CAT	❑
To supplement your dietary intake	❑	CAT won't do any harm	❑
To have greater control over your health	❑	Other(s) (specify):	

_____

54. **In the last year**, have you consulted any of the following alternative practitioners for HIV/AIDS related conditions? **(choose all that apply)**

Acupuncturist	❑	Doctor of Chinese medicine	❑
Herbalist	❑	Homeopath	❑
Holistic medicine specialist	❑	Naturopath	❑
Osteopath	❑	Traditional Aboriginal healer	❑

Other(s) (specify): _____

55. What is your major source of information regarding **alternative** therapies? **(choose all that apply)**

Alternative practitioner	❑	Family/friend(s)	❑
Physician (MD)	❑	Health food stores	❑
Magazines/papers/TV	❑	Local AIDS organizations	❑
Support groups, other persons with HIV	❑	Scientific journals	❑
Internet	❑	Other(s) (specify): _____	

56. Do you tell your medical doctor that you are using these therapies?

Always	❑	Often	❑	Never	❑
Sometimes	❑	Rarely	❑		

57. If you **ever** tell your doctor, how supportive of your CAT use have they been?

Very supportive	❑	Somewhat supportive	❑
Neutral	❑	Not very supportive	❑
Not at all supportive	❑		

58. Do you ever feel that you put your health at risk by using CATs?

Always ..... ❑ Often ..... ❑
Sometimes ..... ❑ Rarely ..... ❑
Never ..... ❑ **(Go to question 60)**

59. If you ever feel that using CATs puts you at risk, why is this?

Not enough information available about effects of CAT ..... ❑
Not enough HIV-specific information about effects ..... ❑
I spend too much money on CATs ..... ❑
Not enough professional guidance to help me use them ..... ❑
Lack of physician's support ..... ❑
Other (specify): _____

60. Please indicate whether you have used any of the following CATs: **(check all that apply)**

Alternative therapy	**Ever used Yes**	**Currently Yes**	If you stopped please provide a reason **Ineffective**	**Cost**	**Other reason**
Diet/Nutrition/Lifestyle changes					
• Dietary Supplements (*Macrobiotic diet, Blue-green algae, Boost)*	❑	❑	❑	❑	_____
• Exercise	❑	❑	❑	❑	_____
• Vitamins/minerals	❑	❑	❑	❑	_____
• Other (Specify) _____	❑	❑	❑	❑	_____
Bioelectromagnetics	❑	❑	❑	❑	_____
Alternative practice systems					
• Homeopathy	❑	❑	❑	❑	_____
• Acupuncture	❑	❑	❑	❑	_____
• Naturopathy	❑	❑	❑	❑	_____
• Chinese medicine	❑	❑	❑	❑	_____
• Other(Specify) _____	❑	❑	❑	❑	_____
Herbal medicine (Please specify exact herbs used - for example, St Johns wort)					
• Specify _____	❑	❑	❑	❑	_____
• Specify _____	❑	❑	❑	❑	_____
• Specify _____	❑	❑	❑	❑	_____
Manual healing					
• Massage (*Reiki, Shiatsu*)	❑	❑	❑	❑	_____
• Therapeutic touch	❑	❑	❑	❑	_____
• Reflexology)	❑	❑	❑	❑	_____
• Other (Specify) _____	❑	❑	❑	❑	_____

Alternative therapy	**Ever used Yes**	**Currently Yes**	If you stopped please provide a reason **Ineffective**	**Cost**	**Other reason**
Mind-body control					
• Meditation	❑	❑	❑	❑	_____
• Yoga	❑	❑	❑	❑	_____
• Other (Specify) _____		❑	❑	❑	_____
Pharmacological/Biological treatment					
• Compound Q (Coenzyme Q10)	❑	❑	❑	❑	_____
• DNCB	❑	❑	❑	❑	_____
• N-Acetyl-cysteine (NAC)	❑	❑	❑	❑	_____
• Marijuana	❑	❑	❑	❑	_____
• Ozone therapy	❑	❑	❑	❑	_____
• Other (Specify) _____		❑	❑	❑	_____
Other alternative (non-prescription) treatments					
• _____		❑	❑	❑	❑ _____
• _____		❑	❑	❑	❑ _____

8. Feedback

NOTE: This section is intended for your feedback. Your suggestions help us to improve the questionnaire from year to year. Please take a few minutes and complete these few questions.

61. Please rate this questionnaire according to the following categories **(check one box per row)**:

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
• The questionnaire was easy to read	❑	❑	❑	❑	❑
• The questions were easy to understand	❑	❑	❑	❑	❑
• The choices for responses were adequate	❑	❑	❑	❑	❑

62. Was this questionnaire

Too short in length	❑	Too long in length	❑
About the right length	❑	Unsure	❑

63. How long did it take you to answer this questionnaire? _____

64. Please write any further information that you think is relevant. You may add additional pages to this questionnaire if necessary.

_____

_____

_____

_____

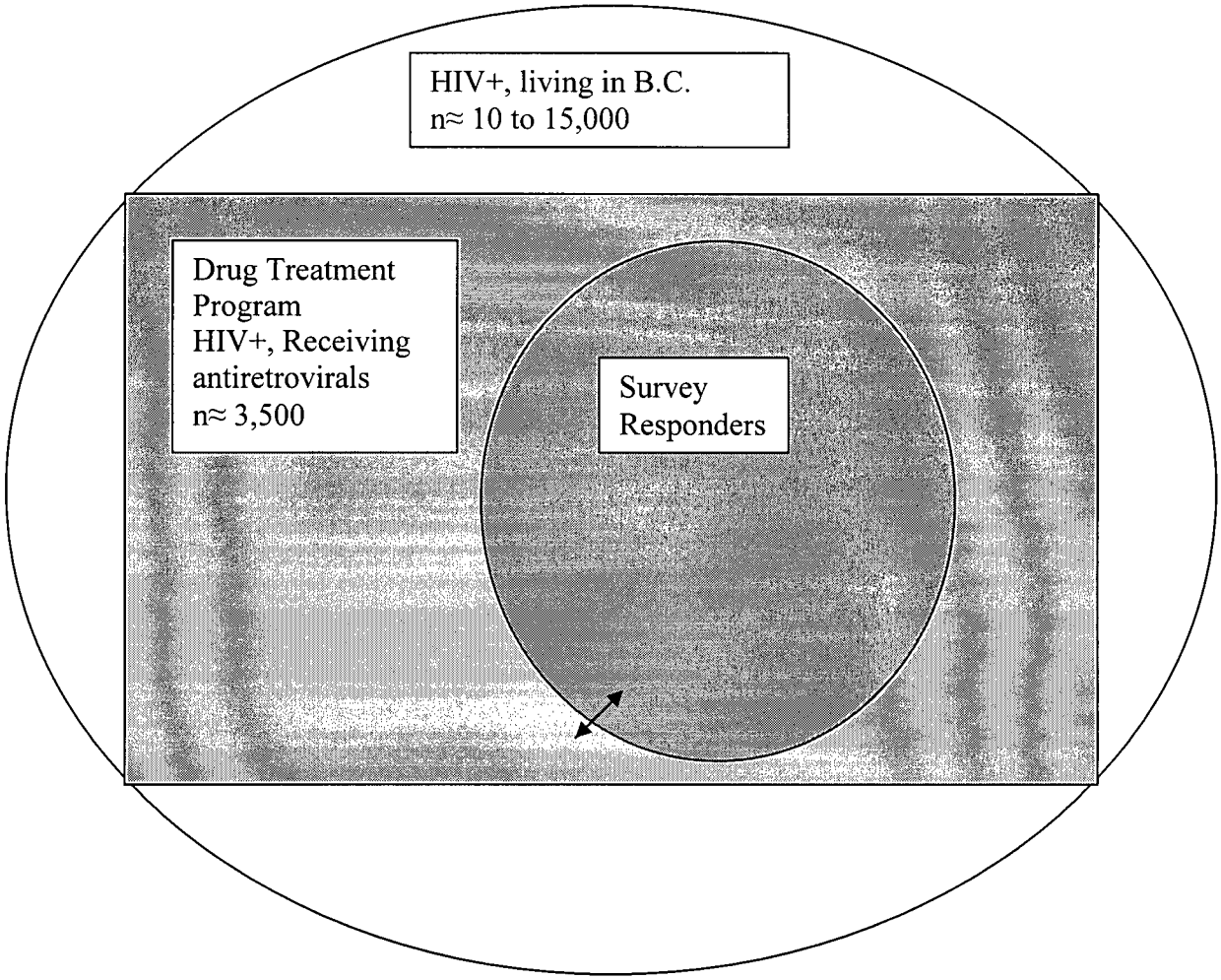
_____

_____

Thank you very much for taking the time to answer these questions. Please put the completed questionnaire in the enclosed self-addressed and stamped envelope and drop it in the mail.

APPENDIX 4

Overview of Sampling Strategies



Study 1 Prevalence: All individuals that responded to the annual blanket survey of all drug treatment program enrolees over the period 10/1998 and 09/1999. n=1035

Study 2 Incidence: All individuals who responded to the annual blanket survey between 09/1998 and 11/1999 and then to a second successive survey between 11/1999 and 12/2000. n=745.

Study 3 Naïve Incidence: All antiretroviral naïve individuals who initiated treatment between 10/1998 and 05/2001 and returned a participant survey no less than 3 and no more than 24 months after therapy start. n=366

Study 4 Adherence: All individuals responding to the annual blanket survey between 01/2001 and 11/2001. n=638

APPENDIX 5

Statement of Authorship Contribution

APPENDIX 6

Copyright Release Form

O'Brien, David

From: Brown, Tanya
Sent: Tuesday, April 23, 2002 5:37 AM
To: O'Brien, David
Subject: FW: copyright for manuscript

Dear Mr O'Brian,

I received this email from someone who is desperate for permission to reproduce an article from AIDS. I'm not totally sure if you are the right person to pass this on to. I'd appreciate it if you would please let me know.

Thanks for your help.

Regards,

Tanya Brown
Editorial Coordinator, AIDS

****
Tel +44 20 7940 7517
Fax +44 20 7940 7520
email tbrown@lww.co.uk
www.aidsonline.com
****

-----Original Message-----
From: kheath@hivnet.ubc.ca [mailto:kheath@hivnet.ubc.ca]
Sent: 22 April 2002 22:49
To: tbrown@lww.co.uk
Subject: copyright for manuscript

--
Hi,
Sorry for this desperate message. I am due to turn in my PhD dissertation to our university library this Thursday. One of the chapters of the thesis is a paper that I published in AIDS- 2001, volume 15. Katherine Heath et al. entitled "Lipodystrophy-associated morphologic, cholesterol and triglyceride abnormalites in a population-based HIV/AIDS treatment database"

The library will not award me my PhD until I have permission from AIDS to reprint this article in the dissertation.
Could you fax me some sort of permission form or copyright release for this purpose by this Thursday?

Fax Number: 001 604-806-9044

Thank you so very very much!
Dr. (Almost) Kate Heath

APPENDIX 7

Toxicity Reporting Form

This form is to be completed by the physician when a patient's ART therapy changes, or annually if there is no change. Additional assistance can be requested by calling toll-free: 1-800-665-7677.	CFE#:

PATIENT INFORMATION

First name _____ Family name _____ Date form completed Day _____ Month_____ Year _

Please check below any adverse effects or symptoms that the patient is currently experiencing

LABORATORY

- ☐ Triglycerides > 8.48 mmol/l
- ☐ Cholesterol > 7.77 mmol/l
- ☐ AST or ALT > 5 x ULN
- ☐ Amylase > 2 x ULN
- ☐ Lipase > 2 x ULN
- ☐ Lactic acid >3 mmol/l, or >2.1 mmol/l with symptoms
- ☐ Hyperglycemia (significant)
- ☐ Anemia / cytopenia (significant)

CLINICAL

- ☐ GI intolerance
- ☐ Kidney stones/hematuria/renal colic
- ☐ Vascular disease (MI, stroke, angina, etc.)
- ☐ Retinoid toxicities (nail deformation, dry skin, hair loss, ulcers)
- ☐ Rash
- ☐ Peripheral neuropathy
- ☐ Osteoporosis
- ☐ Osteonecrosis
- ☐ Fat accumulation
- ☐ Fat loss
- ☐ CNS / psychiatric (depression, hallucinations, etc.)

If you have noted any signs or symptoms in this patient which you feel may be related to ART use, please describe below:

(Specify) _____

Are you **changing or discontinuing** antiretroviral treatment at this time?

☐Yes- **changing** ☐Yes-**discontinuing** ☐No, neither

If **changing or discontinuing**, why is this?

- ☐ Patient is experiencing **new** or **worsening** side effects **listed above**
- ☐ Patient is experiencing **new** or **worsening** side effects **not included above**

(Specify) _____

(Specify) _____

- ☐ Pill fatigue / patient request
- ☐ Treatment failure
- ☐ Adherence issues
- ☐ Drug interaction (Specify) _____
- ☐ Other (Specify) _____