

**DIABETES MELLITUS RISK WITH HIV INFECTION TREATED WITH
ANTIRETROVIRAL THERAPY – AN OVERVIEW**

Shaik Mastan^{1,2*}, Kilari Eswar Kumar³

¹Research Scholar, Jawaharlal Nehru Technological University, Hyderabad-500 085, Andhra Pradesh, India; ²Cytel Statistical Software & Services Pvt Ltd, Pune-411029, Maharashtra, India; ³Pharmacology Division, AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530003, Andhra Pradesh, India

*Author for correspondence: shkmastan@gmail.com

Summary

Diabetes mellitus and HIV infection are well known chronic epidemic diseases and resemble in having high morbidity and mortality rates. The availability of potent combined antiretroviral therapy has resulted in a dramatic reduction in HIV-1 associated morbidity and mortality in the developed world. However, this therapy (especially protease inhibitors and nucleoside reverse transcriptase inhibitors) is associated with a range of metabolic complications, including insulin resistance, glucose intolerance, insulin insensitivity, hyperglycemia, dyslipidemia, and lipodystrophy with resultant increased in risk for type 2 diabetes, and subsequently leads to cardiovascular diseases. The antiretroviral drug-induced diabetes mellitus will promote new challenges in the management of HIV infection. This review briefly covers the various aspects of diabetes mellitus risk associated with HIV infection treated with antiretroviral therapy.

Keywords: Diabetes mellitus; HIV infection; antiretroviral therapy; protease inhibitors

Introduction

Among all the months in a year, November and December have been very familiar, challenging, and appraise moment for all the clinicians and researchers who are closely working with 2 well-known epidemic diseases having high mortality and morbidity rates, i.e., World Diabetes Day and World AIDS Day on 14th November and 1st December, respectively. “Diabetes Education and Prevention” and “Universal Access and Human Rights” are the themes for this year’s “World Diabetes Day” and “World AIDS Day,” respectively, which clearly represent a path on how to deal with these epidemic challenges.

The total number of people living with HIV infection was estimated to be 33.4 million [31.1–35.8 million] worldwide and continues to increase.[1] Two-third of all adults and children with HIV live in sub-Saharan Africa, but there is a marked increase in the number of people being diagnosed in central and East Asia, as well as eastern Europe. These facts closely mimic

another global epidemic, that of diabetes mellitus (DM). Estimates from the International Diabetes Federation show 285 million adults (corresponding to 6.4% of the world's adult population) with diabetes in 2010, and this number is expected to increase to 439 million adults (corresponding to 7.8% of the world's adult population) by 2030.[2] The relation between these 2 epidemics is related not only to the above figures but also with the fact that there is an increased risk for type 2 DM with HIV infection [3] as well as its treatment, especially with protease inhibitors (PIs).[4-6] Antiretroviral therapy (ARVT)-induced type 2 diabetes is a challenging global burden and is of much concern due to the recognition of its long-term complications of cardiovascular risk associated with type 2 DM, especially in developing countries

Methods

Literature review was performed using the search criteria of type 2 diabetes and HIV infection, insulin resistance and HIV infection, and metabolic syndrome and HIV infection, on PubMed Database and Google, examining all journal articles published in English. Studies with control populations or longitudinal data were considered for incidence and prevalence data. *In vitro* and *in vivo* studies using cell models and humans were considered for the mechanisms in the pathogenesis of type 2 diabetes. Conference abstracts and articles not written in English were excluded.

Currently available FDA approved antiretroviral drugs

The currently available antiretroviral drugs fall into 6 drug classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), PIs, fusion inhibitors, C-C chemokine receptor type 5 (CCR5) inhibitors, and integrase inhibitors. The complete list of FDA-approved drugs used for the treatment of HIV-1 infection is listed in Table 1.

Risk associated with DM due to ARVT

The microvascular and macrovascular complications of DM are well-known and are reported to be the most prevalent contributors to morbidity and mortality on the global front.[7] Among these complications, cardiovascular disease along with diabetes is well defined, with cardiovascular disease accounting for 65% of deaths among diabetic patients.[6] The elevated risk observed with diabetes is not only due to hyperglycemia but also due to elevated systolic and diastolic blood pressures, low-density lipoprotein cholesterol levels, triglyceride levels, and total cholesterol levels and decreased levels of high-density lipoprotein cholesterol.[8] Due to this risk, the National Cholesterol Education Panel Diabetes recognized diabetes as a cardiovascular disease risk equivalent.[9,10].

Table 1. FDA approved drugs used in the treatment of HIV-infection

Generic Name(s)	Brand Name	Approval Date	Manufacturer Name
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)			
Zidovudine (ZDV or AZT)	Retrovir	19-Mar-87	GlaxoSmithKline
Didanosine (ddI)	Videx	9-Oct-91	Bristol Myers-Squibb
Zalcitabine (ddC)	Hivid	19-Jun-92	Hoffmann-La Roche
Stavudine (d4T)	Zerit	24-Jun-94	Bristol Myers-Squibb
Lamivudine (3TC)	Epivir	17-Nov-95	GlaxoSmithKline
Abacavir sulfate (ABC)	Ziagen	17-Dec-98	GlaxoSmithKline
Enteric coated Didanosine	Videx EC	31-Oct-00	Bristol Myers-Squibb
Abacavir, Zidovudine, and Lamivudine	Trizivir	14-Nov-00	GlaxoSmithKline
Tenofovir disoproxil fumarate (TDF)	Viread	26-Oct-01	Gilead Sciences, Inc.
Emtricitabine (FTC)	Emtriva	02-Jul-03	Gilead Sciences
Abacavir and Lamivudine	Epzicom	02-Aug-04	GlaxoSmithKline
Tenofovir disoproxil fumarate and Emtricitabine	Truvada	02-Aug-04	Gilead Sciences, Inc.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Nevirapine (NVP)	Viramune	21-Jun-96	Boehringer Ingelheim
Delavirdine (DLV)	Rescriptor	4-Apr-97	Pfizer
Efavirenz (EFV)	Sustiva	17-Sep-98	Bristol Myers-Squibb
Etravirine	Intelence	18-Jan-08	Tibotec Therapeutics
Protease Inhibitors (PIs)			
Saquinavir mesylate (SQV)	Invirase	6-Dec-95	Hoffmann-La Roche
Ritonavir (RTV)	Norvir	1-Mar-96	Abbott Laboratories
Indinavir (IDV)	Crixivan	13-Mar-96	Merck
Nelfinavir mesylate (NFV)	Viracept	14-Mar-97	Agouron Pharmaceuticals
Saquinavir	Fortovase	7-Nov-97	Hoffmann-La Roche
Amprenavir (APV)	Agenerase	15-Apr-99	GlaxoSmithKline
Lopinavir and Ritonavir (LPV/RTV)	Kaletra	15-Sep-00	Abbott Laboratories
Fosamprenavir Calcium (FOS-APV)	Lexiva	20-Oct-03	GlaxoSmithKline
Atazanavir sulfate (ATV)	Reyataz	20-Jun-03	Bristol-Myers Squibb
Tipranavir (TPV)	Aptivus	15-Apr-99	GlaxoSmithKline
Darunavir	Prezista	23-Jun-06	Tibotec, Inc.
Fusion Inhibitors			
Enfuvirtide (T-20)	Fuzeon	13-Mar-03	Hoffmann-La Roche & Trimeris
Entry Inhibitors-CCR5 co-receptor antagonist			
Maraviroc	Selzentry	06-August-07	Pfizer
HIV-integrase strand transfer inhibitors			
Raltegravir	Isentress	12-Oct-07	Merck & Co., Inc.

However, several studies have evaluated the incidence of DM and cardiovascular diseases in HIV-infected persons in the era of highly active antiretroviral therapy (HAART) and their impact as causes of death. Further, HIV-infected persons receiving ARVT are at a 4-fold increased risk of developing diabetes compared with HIV-seronegative men.[11]

The same cardiovascular risk factors that are identified in diabetic patients are also found in HIV patients with diabetes, and these risk factors need to be addressed along with the infectious disease issues.[12] These factors clearly indicate the complexity of these issues regarding the provision of rational therapy to patients and minimization of the risk associated with cardiovascular diseases. To say in simple words, therapy for diabetic patients with HIV infection is just like “handling a 2-edged sword.” The risk associated with DM due to ARVT is represented in Figure 1.

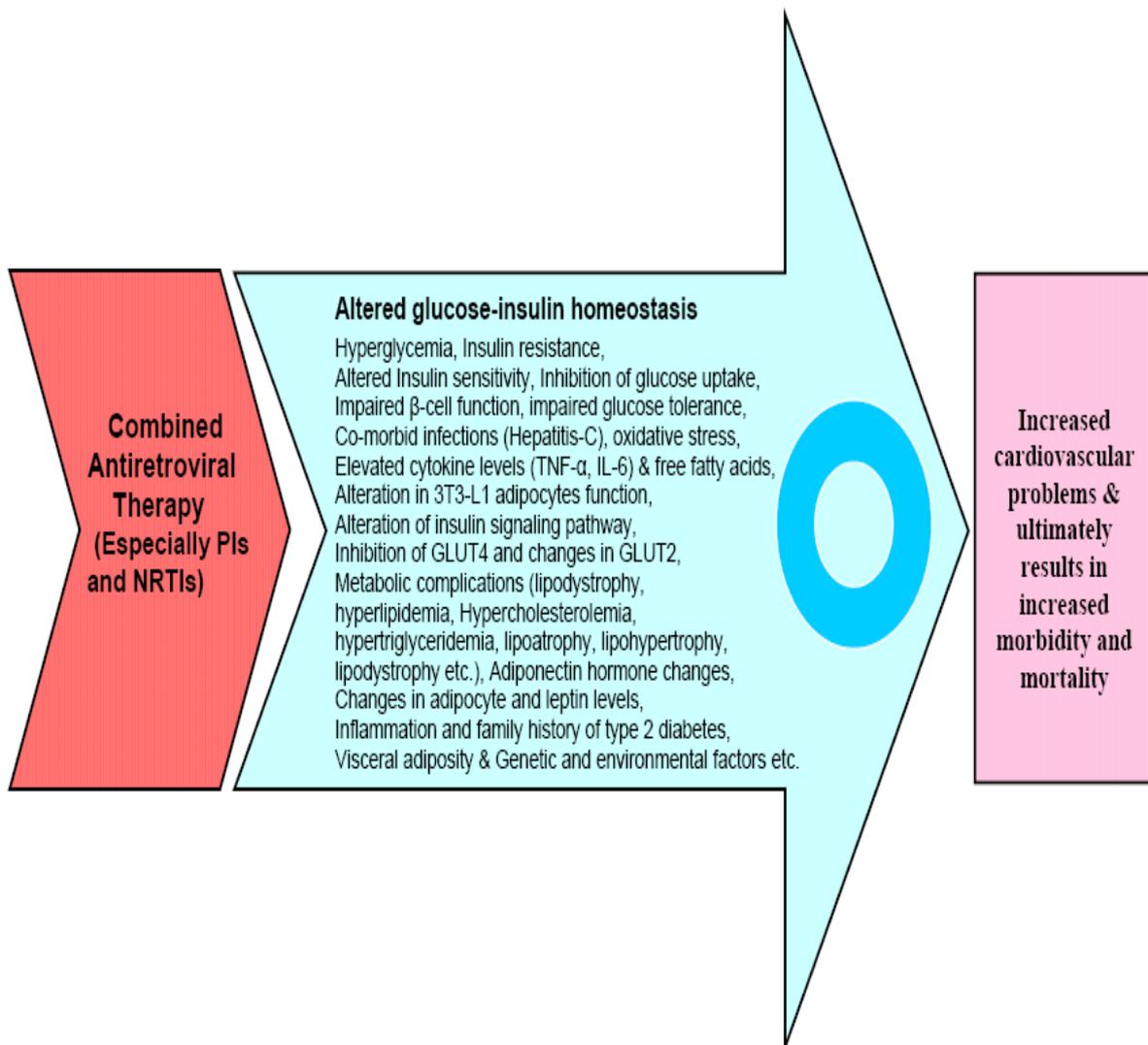


Figure 1. The risk associated with diabetes mellitus due to antiretroviral therapy

First snap about diabetes risk with ARVT

The availability of potent combination antiretroviral regimens, i.e., HAART/combined ARVT, has resulted in a dramatic reduction in HIV-1-associated morbidity and mortality in the developed world,[13] and the lifespan of an HIV patient has steadily increased.[14] However, the optimism generated by such treatment has been tempered by the recognition of an increasing array of adverse metabolic effects. The HIV patients can have a normal lifespan but with that comes an increased risk of death from noninfectious causes like cardiovascular disease and diabetes.[15]

The earliest reported cases of treatment related to DM in HIV infection in the mid-1990's were associated with pentamidine (pancreatic β -cell toxin) use in the setting of treating *Pneumocystis carinii* infection characterized by insulin deficiency, ketoacidosis, and the requirement for insulin therapy.[16] Since the advent of HAART in the mid-1990's, abnormalities in glucose homeostasis have been reported with increasing frequency in persons with HIV.[15,17-20] The FDA issued [21] a public health advisory warning regarding this adverse event in August 1997. By May 1997, it has received 83 reports of exacerbation of diabetes/hyperglycemia or new cases of diabetes in patients taking the drugs. Of these 83 patients, 27 required hospitalization (6 cases were life threatening).[18] The number of cases rose to at least 230 by November 1997.[22] Insulin resistance has been described in 41 (61%) of 67 PI-treated HIV-infected patients,[23] and impaired glucose tolerance was observed in 25 (35%) of 71 HIV-infected patients using HAART.[24] Subsequent studies have confirmed the association of hyperglycemia or DM with PI use.[15,25-29] More recently NRTIs, but not NNRTIs, were found to contribute to the disturbance of glucose metabolism.[30-33] Further, more associations of hyperglycemia and DM with hepatitis C virus (HCV) infection have been reported both in HIV-negative [34-36] and HIV-positive [37-39] populations.

Prevalence of DM and glucose disorders with ARVT

DM and glucose disorders were relatively uncommon in patients with HIV infection before the advent of ARVT, especially with PIs and NRTIs. Within the current treatment pattern, early cases of DM were linked to PI use, with cases of hyperglycemia appearing within 7 months of drug commencement.[40,41] Other metabolic complications associated with ARVT include hyperlipidemia and lipodystrophy, which will remain confounders when attempting to dissect the unique contributors to changes in glucose metabolism. Additional confounders include obesity epidemic, increasing sedentariness, increase in HIV infection rates in ethnic groups with genetic susceptibility to type 2 diabetes, and ARVT composition, as evidence of class-specific and drug-specific adverse effects alters drug regimens over time.[42] With this concept, the metabolic syndrome represents the constellation of the phenotypes of abdominal obesity, hyperlipidemia, elevated fasting glucose, and hypertension, which are closely associated with risk for DM and

cardiovascular disease. The currently accepted international criteria for the diagnosis of DM and glucose disorders and metabolic syndrome are given in Table 2 and Table 3, respectively.

From literature, the incidence of DM and glucose disorders with ARVT is found to be varying with respect to the nature of study, type of population, and parameters measured. Antiretroviral-specific risk factors for glucose abnormalities include exposure to PIs and to certain NRTIs. Of these, use of PIs has emerged as the strongest risk factor, with studies from the early HAART era suggesting a prevalence of 8% to 46% for the spectrum of glucose metabolism abnormalities (e.g., impaired glucose tolerance, insulin resistance, and diabetes) in patients receiving PIs. Some cross-sectional studies have reported a prevalence of diabetes in 2% to 7% of HIV-infected patients receiving PIs and an additional 16% having impaired glucose tolerance. The incidence of DM in HIV-infected patients has been estimated to range from 1% to 10% in various studies.

A study [29] that examined HIV-negative (N = 710) and untreated HIV-infected patients (N = 157) found that fasting glucose levels were similar between treatment-naïve patients and HIV-infected ARVT recipients. Of note, study subjects were overweight by body mass index (BMI), and in this regard, the study cohort is representative of the parallel community problem of obesity and its diabetes-promoting effects. A 7% prevalence of DM was found in HIV-infected treatment-naïve subjects compared with 5% in HIV-negative population. Using the prevalence rates from the HIV-negative population, HIV infection was associated with a 2.2-fold increase in the relative risk of diabetes.

Evidence for increased prevalence of DM and disorders of glucose metabolism was initially derived from patient cohorts with ARVT-associated lipodystrophy. One such study reported the prevalence of DM at 2% in PI recipients with lipodystrophy,[26] with the rate rising to 7% after 14 months of further observation.[28] This study reported the overall prevalence of disorders of glucose metabolism (DM, impaired fasting glucose, and impaired glucose tolerance) at 25%.

Other early studies also report higher rates of disorders of glucose metabolism including DM in 7% compared with 0.5% of otherwise healthy controls, and impaired glucose tolerance in 35% of HIV-infected patients as compared with 5% of controls.[43] Prospective reports show that DM developed in 10% of HIV-infected ARVT recipients during a 4-year follow-up period compared with 3% in HIV-seronegative men.[29] After adjusting for age and BMI, this difference represented a greater than 4-fold increase in relative risk of developing DM. The effect of initiation of ARVT on DM incidence in treatment-naïve patients has been reported recently [44] by the Data Collection on Adverse Events of Anti-HIV Drugs. Incident cases of DM were identified by fasting glucose with an incidence of 5.7 per 1000 person-years follow-up.

The relative risk of developing DM increased 4-fold in those with metabolic syndrome at baseline and 4-fold to 5-fold in incident cases of metabolic syndrome.[45] Further prospective studies of the progression from metabolic syndrome and ARVT-associated lipodystrophy to diabetes and its atherothrombotic complications are awaited.

Prevalence of DM vs. ethnicity, gender, genetic susceptibility and coexistence of HCV infection

The Swiss HIV Cohort Study found that Asian or black ethnicity increased the risk for DM by 4.9-fold and 2.2-fold, respectively.[46] Further the impact of ethnic susceptibility to diabetes (such as South Asians) increasing obesity prevalence and ARVT (particularly older regimens) is unknown. This is a significant issue in resource-poor settings with high rates of HIV infection, where diabetes independently causes substantial morbidity, disability, and premature loss of life.

Only a few studies have specifically examined the prevalence of glucose disorders, specifically in HIV-infected women. One study found a 12% prevalence of DM in HIV-infected female ARVT recipients, compared with 13% in HIV-negative women, using the 75 g oral glucose tolerance test.[47] A cohort from Women's Interagency HIV Study (N = 1785) reported DM incidence at 2.8% in PI recipients vs. 1.2% in those who had never received ARVT and 1.4% in the HIV-negative controls. Significant differences were evident between HIV infected and controls for age, BMI, and hip circumference; nevertheless, exposure to NRTI over 3 years increased the relative risk of incident DM 2.6-fold.[15]

There may be ethnicity-associated genetic susceptibility to the development of DM. A prospective study of HIV-infected patients found a prevalence of DM of 12% among all PI recipients at baseline. After 3 years, the incidence of new cases of diabetes was 7% and all were African Americans.[48]

Coexistent HCV infection with HIV infection seems to increase diabetes risk in some studies. A retrospective study of 1230 HIV-infected ARVT recipients (50% coinfecting with HCV) offers valuable insights. DM prevalence was doubled in those coinfecting with HCV, 5.9% compared with 3.3% in subjects with HIV infection alone. Incident cases of DM were more common in those with HCV co-infection, i.e., 5.8% vs. 2.8%; the incidence of hyperglycemia per 100 person-years was 4.9 in those with HCV co-infection vs. 2.3 in those with treated HIV infection alone.[49]

DM risk associated with NRTI treatment

Several NRTIs and drug combinations were related to the development of DM,[50-52] in particular, lamivudine-stavudine, didanosine-stavudine, and didanosine-tenofovir.[53] Only

limited data are available on the association of DM or hyperglycemia with exposure of NRTIs. Regimens including stavudine,[54] didanosine plus tenofovir,[55] and lamivudine.[11] are considered to be most potent to induce DM risk. Among the currently used NRTIs, the strongest association with mitochondrial toxicity, measured as inhibition of the mitochondrial DNA polymerase- γ , is found for didanosine and stavudine;[56] notably, these 2 drugs are strongly associated with DM.[53] Stavudine, zidovudine, and didanosine were associated with significantly higher risk of DM during long-term follow-up than other NRTIs.[57,58]

DM risk associated with PI treatment

The aggregate of biochemical disturbances observed in many patients on PI-containing therapy resembles those of the metabolic syndrome as defined for the general population (Figure 2). Disturbance in glucose-insulin homeostasis through hyperglycemia, insulin resistance, and impaired β -cell function by PIs was reported in animal models also.[59] The mechanism behind diabetes risk due to ARVT is complex and multifactorial (Figure 3). Various studies on the effects of PIs on glucose disorders have found differing results. Part of the discrepancy is due to different methods used to determine insulin resistance that vary with respect to sensitivity, accuracy, and the specific variable being measured. Overall, the glucose disorders and/or type 2 diabetes risk associated with PIs are distinguished by drug-specific but not class-specific effects. Among all the PIs, indinavir has been reported to be a more potent drug to induce diabetes risk, and atazanavir has been found to have a higher safety profile. Much information is not available to know the potency of DM risk associated with tipranavir and darunavir.

PIs effect on insulin resistance

Insulin resistance occurs when normal insulin levels are inadequate to stimulate glucose uptake in the insulin-signaling pathway in insulin-sensitive tissues such as the liver, muscle, and subcutaneous adipose tissue. The insulin resistance manifests as hyperinsulinemia, hyperglycemia, and hypertriglyceridemia. Insulin resistance is considered central to cardiometabolic disease as it underlies type 2 diabetes as well as it present in atherothrombotic cardiovascular disease. The incidence of insulin resistance in HIV-positive patients is significantly higher in PI-treated patients than in patients treated with NRTIs or NNRTIs,[60] even when one considers related factors such as demography and virology.[61] Today, estimates of the proportion of patients treated with PIs who develop insulin resistance may be as high as 80% compared with ~2% before the advent of HAART. The evidence supporting a direct role for PIs in insulin resistance and type 2 diabetes comes from prospective studies of patients initiating PI-based therapy. More definitive studies in healthy volunteers administered PIs for acute periods suggest that insulin resistance is induced after a relatively short term. Data in patients without AIDS wasting reveals a higher prevalence rate of type 2 diabetes in the HIV-infected population compared to HIV-seronegative cohort independent of HAART, and the highest

prevalence in patients on HAART. The degree to which each individual PI causes insulin resistance varies widely, and it is likely that indinavir has the most potent effect on glucose metabolism, increasing insulin resistance by over 30% as determined by homeostasis model assessment (HOMA) and minimal model.

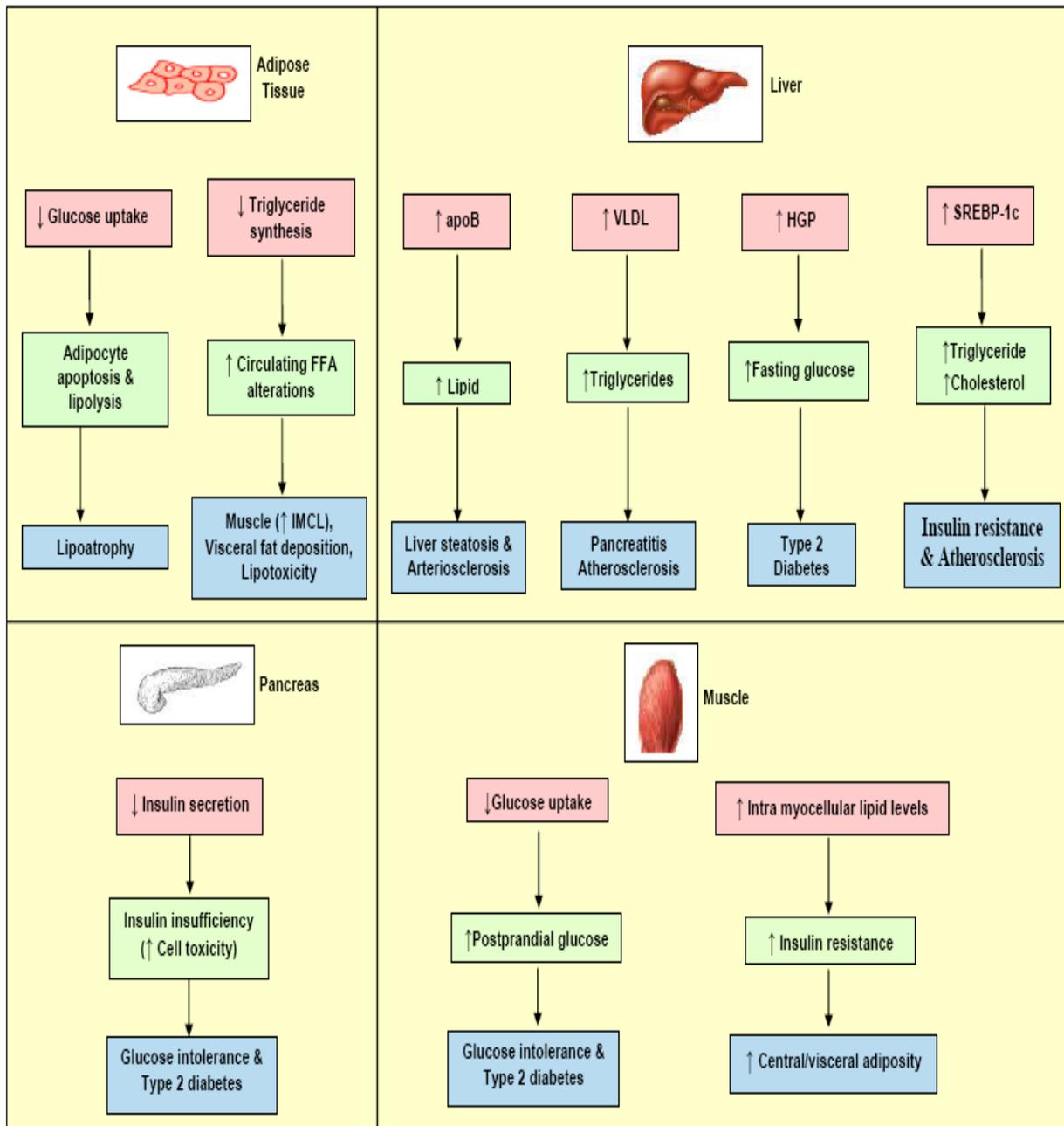


Figure 2. The metabolic effects of protease inhibitors and possible consequences targeting the end organs and disease

Abbreviations: VLDL, very low density lipoproteins; HGP, hepatic glucose production; SREBP, Sterol Regulatory Element-Binding Proteins; FFA, free fatty acid; IMCL, intra myocellular lipid content;

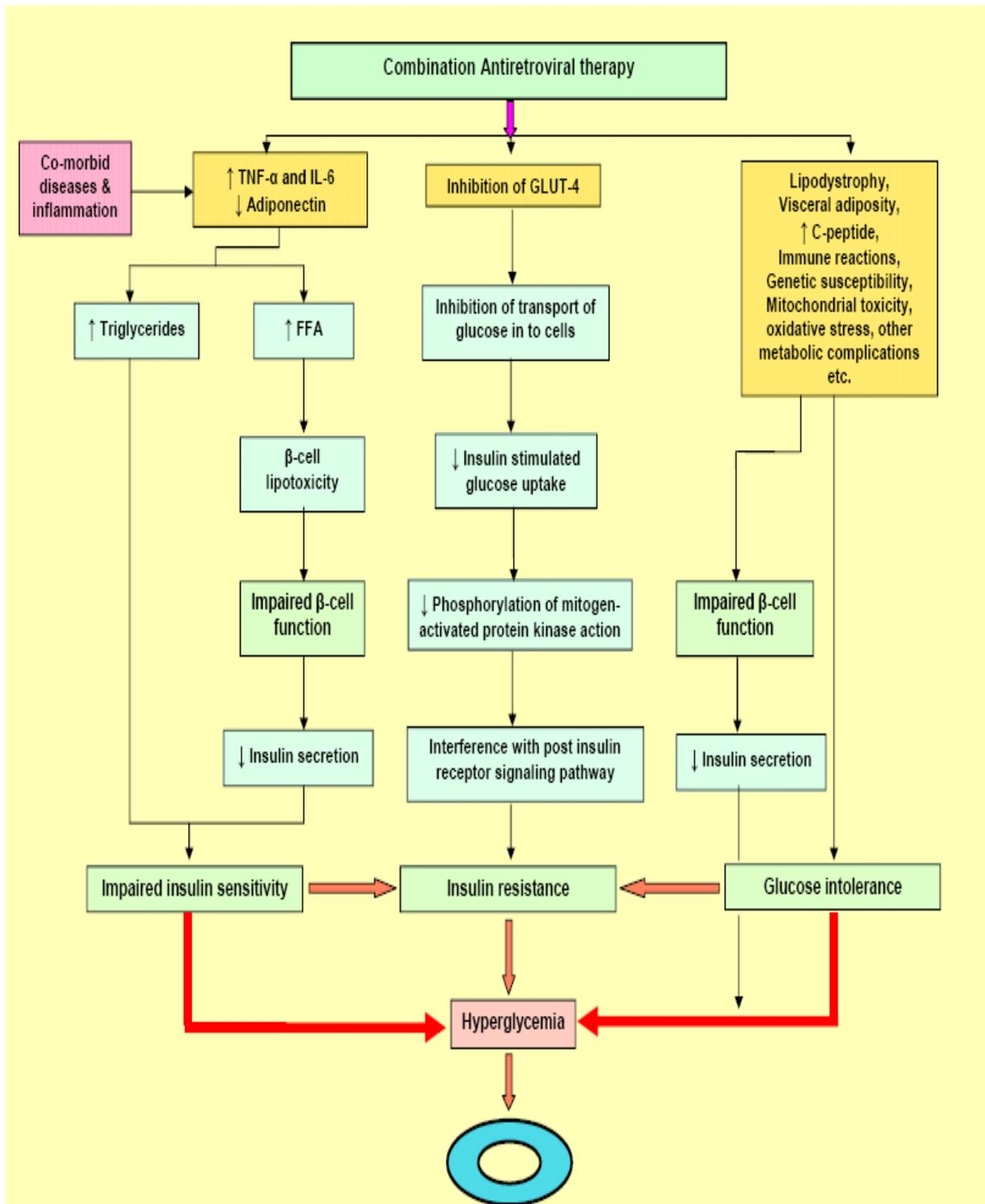


Figure 3. The possible mechanisms behind diabetes risk due to antiretroviral therapy

Abbreviations: TNF, Tumor necrosis factor; IL-6, Interleukin-6; GLUT-4, glucose transporter type 4; FFA, free fatty acid

PIs effect on glucose transport

In pre-clinical as well as in clinical studies of non-HIV-infected human subjects, PIs were shown to acutely inhibit insulin-stimulated glucose disposal.[62-64] The effect on glucose disposal is both rapid and reversible, suggesting a direct blockade of glucose uptake through the glucose transporter isoform 4 (GLUT4, SLC2A4).[65,66] Additional effects on insulin signaling,[67,68] sterol regulatory element binding proteins processing,[69] and adipokine secretion [70] have also been proposed as mechanisms for the inhibition of glucose disposal.

PIs as a class, however, do not equally inhibit glucose disposal. In primary rat adipocytes, amprenavir, ritonavir, or the more therapeutically appropriate combination of lopinavir with ritonavir all inhibited glucose uptake, whereas atazanavir displayed no inhibition compared to controls at therapeutic concentrations under euglycemic, hyperinsulinemic clamp conditions in rats.[71] Therapeutic levels of amprenavir, lopinavir/ritonavir, and ritonavir acutely inhibited both peripheral glucose disposal and glucose uptake in muscles. In the presence of atazanavir, glucose disposal in rats was similar to controls even at higher concentrations.[71]

Table 2. Criteria for diagnosis of diabetes mellitus and disorders of glucose metabolism [42]

Method	Diagnostic category	Fasting glucose	2-Hours glucose
Fasting glucose	Normal	<5.6 mmol/L; <100 mg/dL	-
	Impaired fasting glucose	5.6-6.9 mmol/L; 100-125 mg/dL	-
	Diabetes	≥7.0 mmol/L; ≥126 mg/dL	-
75 g oral glucose	Normal	-	< 7.8 mmol/L; <140 mg/dL
	Impaired fasting glucose	-	7.8-11.1 mmol/L; 140-199 mg/dL
	Diabetes	-	>11.1 mmol/L; >200 mg/dL

Effect of PIs on pancreatic β -cell function

In addition to their effects on peripheral insulin resistance through inhibition of GLUT4, PIs have also been implicated in glucose intolerance through impairment of β -cell function. In vitro as well as in HIV-infected patients, significant decrease in β -cell function and first-phase insulin release are found following exposure to PIs.[72,73] A recent study in which insulin secretion was quantified in MIN-6 murine pancreatic β -cells treated with various PIs at therapeutic levels demonstrated differential effects.[74] Lopinavir and ritonavir dramatically reduced glucose-stimulated insulin secretion, whereas indinavir and atazanavir had little or no effect. PIs also

inhibit amino acid-stimulated insulin secretion in vitro; this effect varied widely among the PIs tested, with a rank order of potency similar to that observed for glucose-stimulated insulin secretion.[74] Other indirect mechanisms such as PI-induced elevation in triglycerides and fatty acids may also adversely affect pancreatic β -cell function in vivo and after extended treatment.[75]

Table 3. Criteria for diagnosis of metabolic syndrome [42,76]

Parameter	International Diabetes Federation Criteria
Waist	>94 cm in men; >80 cm in women
Glucose	>5.6 mmol/L
High density lipoprotein cholesterol	<1.20 mmol/L
Triglycerides	>1.7 mmol/L
Systolic blood pressure	>130 mm Hg
Diastolic blood pressure	>85 mm Hg

Conclusion

Overall, the diabetes risk associated with ARVT seems to be very complex, involving multiple mechanisms and clinical complications, and more attention should be paid for the treatment involving PIs and NRTIs. Even though there is considerable progress addressing the issues around these complications, further research is required to develop diagnostic tests to predict the onset of diabetes, minimize the cardiovascular risk, and rationalize drug design to minimize or eliminate drug-related metabolic complications. Proper diagnosis and monitoring of glucose-insulin homeostasis, selection of appropriate drug regimens, and better understanding of possible drug-drug interactions associated with antiretroviral and antidiabetic drugs are essential requirements to minimize the cardiovascular risk associated with diabetes due to ARVT. Diabetes and HIV need to follow the clinical recommendations given by the 12-member panel of International AIDS Society-USA.[76] Type 2 diabetes will respond to life-style modifications, including regular physical activity, caloric restriction, and modest weight (waist) reduction. Since diabetes related to PI and/or NRTI use has been associated with impairment of glucose uptake by the muscle and hepatic glucose distribution, drug selection for treating hyperglycemia should address these deficits.[76] Metformin has been found to improve insulin sensitivity and reduce abdominal fat in HIV-infected HAART recipients. The thiazolidinediones class of insulin sensitizers in several studies reduced insulin resistance in HIV-associated lipodystrophy and may be considered in those patients with type 2 diabetes and impaired glucose tolerance. From sulphonylurea group, gliclazide may be the preferred drug considering its beneficial effects such as antioxidant, less hypoglycemia, hemobiological, and cardiovascular effects including antidiabetic activity.

A possible solution for improving goal achievement could be to have a pharmacy-run clinic whose staff would meet with HIV patients with diabetes to discuss glucose monitoring and medication regimens and thereby work to attain the International Diabetes Federation and American Diabetes Association goals of therapy. Pharmacist-run diabetes clinics have proven effective in a variety of settings,[77-79] and thus, continuing efforts and coordination of pharmacists, clinicians, and researchers are required for the better understanding of the mechanisms associated with diabetes and ARVT to achieve a better health care of HIV-infected patients.

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