WEST AFRICAN JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Serum Lipids and Glucose Abnormalities in HIV/AIDS Patients on Antiretroviral Therapies

Lipides sériques et de glucose anomalies dans le domaine du VIH / sida patients sur les thérapies antirétrovirales

A. K. Salami*, A. A. Akande†, A. B. Olokoba*

ABSTRACT

BACKGROUND: **With the introduction of highly active antiretroviral therapy (HAART) the outlook of HIV/AIDS has changed from a killer disease to a treatable chronic infectious one. However HAART is associated with some metabolic disorders some of which are now being seen in people living with HIV/AIDS (PLWHA) accessing care from our centre.**

OBJECTIVE: **To determine the prevalence and pattern of dyslipidaemia and dysglycaemia amongst Nigerian HIV/AIDS patients on HAART.**

METHODS: **PLWHA who were regular on ART for at least three months and had pre-treatment CD4⁺ count, fasting lipid and glucose profiles were grouped into two treatment regimens: protease inhibitor, (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI). Pre and post-exposure metabolic and non-metabolic variables were compared for each regimen as well as within regimen comparison of the differences between post exposure metabolic variables.**

RESULTS: **Three hundred and twenty-seven patients; [male=134 (41%), female=193 (59%)] met the study criteria in the two groups: PI = 94(29%) and NNRTI= 233(71%). The pretreatment metabolic changes in both groups (PI vs. NNRTI) were low HDL-C; 29(31%) vs.77 (33%), followed by hypertriglyceridaemia; 16(17%) vs.38 (16%) and hypercholesterolaemia; 6(6%) vs.10 (4%). After exposure to two different HAART regimens hypertriglyceridaemia and hypercholesterolaemia became more prevalent especially with Pi based therapy than NNRTI; 74(79%) vs. 108(54%) and 58(51%) vs.72(31%) respectively. These relative higher risks of a PI containing regimen to induce hyper-triglyceridaemia and hypercholesterolaemia were about three times more than that of NNRTI, both risks were statistically significant; p = 0.0003 and p = 0.0001.**

CONCLUSION: **Low HDL-C, hypertriglyceridaemia and hypercholesterolaemia are common in untreated HIV/AIDS patients. HAART especially those including protease inhibitors worsens this dyslipidaemia. WAJM 2009; 28(1): 300–305.**

Keywords: **AIDS, Antiretroviral therapy, Dyslipidaemia, Dysglycaemia, HIV, Nigeria.**

RÉSUMÉ

CONTEXTE: *Avec l'introduction du traitement antirétroviral hautement actif (HAART) l'évolution du VIH / sida est passé d'un tueur à une maladie infectieuse chronique traitable. Toutefois HAART est associée à certains troubles métaboliques dont certaines sont en train d'être vu chez les personnes vivant avec le VIH / sida (PVVIH) d'accès aux soins de notre centre.*

OBJECTIF: *Pour déterminer la prévalence et la structure de la dyslipidémie et dysglycaemia nigériane entre le VIH / sida sur le traitement HAART.*

MÉTHODES: *les PVVIH qui ont été régulièrement sous ARV pendant au moins trois mois et a pré-traitement CD4 + count, le jeûne de lipides et de glucose profils ont été regroupés en deux régimes de traitement: inhibiteur de protéase (IP) ou non-nucléosidiques de la transcriptase inverse inhibiteur (INNTI). Pré et post-exposition métaboliques et non-métaboliques variables ont été comparés pour chaque régime, ainsi que dans le régime comparaison des différences entre post-exposition métaboliques variables.*

RÉSULTATS: *Trois cent vingt-sept patients, [les hommes = 134 (41%), les femmes = 193 (59%)] a rencontré l'étude des critères dans les deux groupes: PI = 94 (29%) et INNTI = 233 (71%). Le prétraitement des changements métaboliques dans les deux groupes (c. INNTI IP) sont faibles HDL-C, 29 (31%) vs.77 (33%), suivie par l'hypertriglycéridémie, 16 (17%) vs.38 (16%) et l'hypercholestérolémie , 6 (6%) vs.10 (4%). Après exposition à deux régimes différents HAART hypertriglycéridémie et l'hypercholestérolémie est devenue plus fréquente en particulier avec Pi de thérapie que INNTI, 74 (79%) versus 108 (54%) et 58 (51%) vs.72 (31%) respectivement. Ces relative des risques plus élevés d'un régime contenant des IP pour inciter hyper-triglyceridaemia et hypercholestérolémie étaient environ trois fois plus que celui des INNTI, les deux risques étaient statistiquement significative, p = 0.0003 et p = 0.0001.*

CONCLUSION: *Basse HDL-C, l'hypertriglycéridémie et l'hypercholestérolémie sont communs non traitées dans le VIH / sida. HAART en particulier ceux comprenant des inhibiteurs de protéase aggrave cette dyslipidémie.* ***WAJM 2009, 28(1): 300–305.***

Mots-clés: *sida, les ARV, une dyslipidémie, Dysglycaemia et du Nigéria.*

Department of Medicine* And Chemical Pathology†, College of Health Sciences, University of Ilorin, PMB 1515, Ilorin, Nigeria
Correspondence: **Dr. A. K. Salami, P.O. Box 4470, Ilorin, Nigeria. E-mail: salkaz2000@yahoo.com 08033856580.**

Abbreviations: **AIDS**, acquired immune deficiency syndrome; **ARV**, antiretroviral; **DM**, diabetes mellitus; **D4T**, stavudine; **EFV**, efavirenz; **FPG**, fasting plasma glucose. **HAART**, highly active antiretroviral therapy; **HDL-C**, high density lipoprotein cholesterol; **HIV**, human immune deficiency virus; **IDV**, indinavir; **IFG**, impaired fasting glycaemia; **LDL-C**, low density lipoprotein cholesterol; **NNRTI**, non-nucleoside reverse transcriptase inhibitor; **NVP**, nevirapine**; PI**, protease inhibitor; **PLWHA**, people living with HIV/AIDS**; RTV**, ritonavir**; T-C**, total cholesterol; **3TC**, lamivudine.

INTRODUCTION

The clinical benefit of Antiretroviral (ARV) drugs in ameliorating symptoms of AIDS and improving survival of HIV/AIDS patients has been documented in our centre along with some short term side effects of these drugs.[1] Although we monitored only the $CD4^+$ lymphocytes rise in response to Highly Active Antiretroviral Therapy (HAART), our experience of improved quality of life of PLWHA was similar to that of those[2,3] that monitored both viral load decline and rising levels of $CD4^+$ cells count in response to HAART. Nigerian. Persons Living with HIV/AIDS (PLWHA) are now leaving long enough for some of the longer term side effects of ARV to manifest in them. The medical literature is full of reports of some of these side effects; such as lipodystrophy[4], dyslipidaemia,[5] IFG and frank diabetes mellitus[6] and lately increasing risks of cardiovascular diseases.[7] We have started to observe some of these metabolic derangements especially that of lipid profiles and blood sugar in some PLWHA on HAART during their follow-up assessment. This was what informed our aim of determining the prevalence and pattern of dyslipidaemia and glucose disorders amongst PLWHA accessing ARV drugs from the University of Ilorin teaching hospital; a tertiary care centre in Nigeria.

SUBJECTS, MATERIALS AND METHODS

The study site was the Infectious Diseases clinics of the Department of Medicine at the University of Ilorin Teaching Hospital, Ilorin. The subjects were all the PLWHA who were on ARV drugs since commencement of HAART programme in 2002. However, for the purpose of this study the inclusion criteria were records of pretreatment $CD4^+$ count, lipid profile: [total cholesterol (T-C), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride] and fasting plasma glucose (FPG) and at least 12 weeks of regular ARV therapy. Patients who satisfied these criteria were placed in either of two treatment groups; Pi based: ritonavir or indinavir {RTV or IDV} + stavudine {D4T} + lamivudine {3TC} and NNRTI based; nevirapine or efavirenz {NVP or EFV} + D4T + 3TC ARV therapy.

All ARV drugs were accessed from the national ARV programme and therefore what determined ARV drugs combination of a patient were partly drugs availability and toxicities and intolerance to any of the drugs. Choice of suitable alternatives was sometimes also limited by availability. All the patients received 2 NRTI (D4T + 3TC) as the backbone of the 2 regimens.

Patients that satisfied the study criteria were informed about the proposed study and their consent was obtained. PLWHA who had co-morbidities like DM, chronic liver or renal diseases or medications that could influence serum lipids were excluded. Thereafter their age, sex, weight at the time of commencement of ARV drugs as well as the duration and type of the ARV drug combinations were obtained from their respective hospital files. On the morning of follow-up clinics, each patient had his/her venous blood drawn for serum lipids and glucose measurement after a 12-hour overnight fast. Fasting serum lipids and lipoproteins were assayed by enzymatic technique (QCA kit, Spain).[8] Serum HDL-C was also determined by enzymatic method after precipitation of low density and very low density lipoproteins with dextran sulfate MgCl2 (QCA kit, Spain).[9] FPG was determined by the glucose oxidase method.[10] Disordered levels were defined according to the WHO guidelines[11] as T-C (>5.2mmol/l), triglyceride (1.8mmol/l), HDL-C (<0.8mmol/l), LDL-C (>4.65mmol/l) and elevated FPG was as defined by the expert committee on the diagnosis and classification of DM[6] as FPG $\geq$ 6.1 mmol/L but <7.0 mmol/L was defined as impaired fasting glycaemia (IFG) and FPG, $\geq$7.0 mmol/L was diagnostic of DM. A minimum of 12 weeks of regular ARV therapy was chosen because this was the

Table 1: Distribution of Patients by Sex and Treatment Regimen

Sex	Number (%)			
	Pi-based*		NNRTI-based*	
	RTV	3TCIDV	EFV	NVP
Both	5.5(56)	39(41)	156(67)	77(33)
Male	22(40)	17(44)	64(41)	31(40)
Female	33(60)	22(56)	92(59)	46(60)

*Both PI- and NNRTI-based regimens all contain D4T and 3TC

Table 2: Pre- and Post- ARV Exposure Characteristics of the Patients

Variable	Mean ± SD (Range)			
	Pre-exposure		Post-exposure	
	Pi Group	NNRTI Group	Pi Group	NNRTI Group
Age (years)	34.5 ± 8.3 (17–58)	31.3 ± 5.7 (23–64)	34.5 ± 8.3 (17–58)	31.3 ± 5.7 (23–64)
Weight (kg)				
Mean	45.4 ± 7.7	48.8 ± 7.9	68.8 ± 11.7	65.4 ± 14.7
Range	(28–72)	(33–68)	(47–81)	(45–95)
$CD4^+$ (cells/ul)				
Mean	126.4 ± 17.6	122.4 ± 17.8	181.2 ± 24.5	200.4 ± 29.3
Range	(6–430)	(20–354)	(190–580)	(260–760)
Length of ARV exposure (wks)				
Mean	–	–	77.2 ± 22.3	108.5±38.6
Range	–	–	(4–96)	(4–192)

Table 3: Metabolic Variables Before and After Antiretroviral Therapy

Metabolite (mmol/l)	Mean (SD)			
	Pi-based ARVT		NNRTI-based ARVT	
	Pre exposure	Post -exposure	Pre-exposure	Post-exposure
TC	4.5(1.12)	5.9(1.5)	4.3(1.1)	5.2(1.5)
HDL-C	0.9(0.4)	1.4(0.5)	0.9(0.3)	1.4(0.4)
LDL-C	2.8(1.0)	3.4(1.1)	2.8(1.0)	3.2(1.1)
TG	1.2(0.6)	1.8(0.5)	1.2(0.6)	1.5(0.7)
FPG	4.5(1.0)	4.5(1.2)	1.0(4.8)	1.2(0.3)

TC, total cholesterol; HDLC, high density lipoprotein cholesterol; LDLC, low density lipoprotein cholesterol; TG, triglycerides; and FPG, fasting plasma glucose. P-value of difference between mean value of metabolites, pre-exposure v post exposure; * p < 001, +, p > 0.05.

Table 4. Lipid Profile of Patients Before and After ARV Exposure

Variable (mmol/L)		Number (%)			
		Pi-based n=94		NNRTI-based n=233	
		Pre exposure	Post exposure	Pre exposure	Post exposure
TC	<5.2	16(17)	9(20)	33(14)	45(19)
	5.2–6.5	72(77)	27(29)	193(82)	116(50)
	>6.5	6(6)	58(51)	10(4)	72(31)
HDLC	<0.9	29(31)	5(5)	77(33)	28(11)
	0.9–1.55	58(62)	57(61)	134(57)	127(56)
	>1.55	7(7)	32(34)	22(10)	78(33)
LDLC	<3.37	17(18)	13(14)	52(22)	25(11)
	3.37–4.14	73(78)	44(47)	175(74)	139(59)
	>4.14	4(4)	37(39)	7(3)	69(30)
TG	<0.6	13(14)	0(0)	40(17)	0(0)
	0.6–1.8	65(69)	20(21)	157(67)	128(46)
	>1.8	16(17)	74(79)	38(16)	108(54)
FPG	<0.6	89(95)	81(86)	225(96)	183(79)
	<6.16.1–6.9	5(5)	13(14)	8(4)	43(18)
	≥7.0	0(0)	0(0)	0(0)	7(3)

TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; FPG, fasting plasma glucose.

Table 5: Comparison of Post-exposure Metabolic Values to both Pi and NNRTI-based Regimens

Variable (mmol/L)	Pi	NNRTI	χ^2	RR	95% confidence interval	p-value
TC >6.5	58	72	26.4	2.44	1.72-3.47	0.0001*
HDLC >1.55	32	78	0.01	1.02	0.71-1.46	0.92+
LDLC >4.14	37	69	2.9	0.88	0.75-1.03	0.8
TG >1.8	74	108	28.4	2.95	1.89-4.59	0.0003
FPG 6.1-6.9	13	43	1.01	1.10	0.93-1.29	0.32

TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; FPG, fasting plasma glucose.

time when repeat assessments of metabolic parameters were done in all our patients on HAART.

Data were analysed using Statistical Package for Social Sciences, "SPSS/PC+, version 11.0, SPSS Inc, Chicago, USA. 2002". Frequencies and percentages of all the variables were generated and the means of paired variables, i.e. the pre- and post-ARV exposures means of weight, $CD4^+$ cells count, lipid profiles and FPG were compared for differences by the paired sample t-test. Proportions of patients that developed changes in one metabolic variable or the other after exposure to any of the two treatment regimens were compared by chi-square tests after adjusting for number of patients that had similar changes at baseline. The relative risk (RR= an indicator of the degree of association between observed metabolic changes and a predictor ARV regimen) was estimated with a 95% confident limit. Possible gender association with metabolic variables was also determined by cross tabulation test. P-value value of less 0.05 was upheld as statistically significant.

RESULTS

Three hundred and twenty-seven patients; [males = 134 (41%) and females = 193, (59%)] met the study inclusion criteria in the two groups: Pi= 94(29%) and NNRTI= 233(71%), (Table 1). The mean age in both groups; Pi vs. NNRTI was about the same 34.5 ± 8.3 vs. 31.3 ± 5.7years, p- = 0.96, as was the pre-exposure mean weight; 45.4 ± 7.7 vs. 48.8 ± 7.9kg and $CD4^+$ cell count; 126.4 ± 17.6 vs.122.4 ± 17.8cells/ul, Table 2. The average lengths of exposure to either of these two regimens were 77.2 ± 22.3 weeks and 108.5 ± 38.6 weeks respectively. The commonest pre ARV exposure metabolic abnormality in both Pi vs. NRTI groups was low HDL-C;29(31%) vs.77(33%),followed by hypertriglyceridaemia;16(17%) vs. 38(16%) and hypercholesterolaemia; 6(6%) vs.10(4%). IFG was seen in both Pi and NNRTI groups; 5(5%) vs. 8(4%) of the cases.

Post ARV exposure (Pi vs. NNRTI) mean weight improved by 23.4kg

Table 6: Sex Distribution of Post Exposure Metabolic changes by Individual ARV Drug

Metabolic Variables	Specific ARV drug by sex											
	PI						NNRTI					
	RTV			IDV			EFV			NVP		
	M	F	Total	M	F	Total	M	F	Total	M	F	Total
TC > 6.5	10	24	34	7	17	24	19	29	48	9	15	24
HDLC > 1.55	8	11	19	5	6	13	20	31	51	11	16	27
LDLC > 4.14	6	15	21	2	14	16	18	28	46	11	12	23
TG > 1.8	15	28	43	8	23	31	29	43	72	14	22	36
FPG > 7.0	–	–	–	–	–	–	4	1	5	2	–	2

TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; FPG, fasting plasma glucose.

vs.16.6kg over the pre exposure values (p- <0.0001), and mean $CD4^+$ increased by 54.8 vs. 78 cells/ul, p = 0.038, (Table 2). There were further increments in level of all the metabolic variables after ARV exposures, but to varying degrees, Table 3. The number of PLWHA that developed hypertriglyceridaemia was higher under a Pi based HAART compared to NNRTI; 74(79%) vs.108(54%) and it was similar for hypercholesterolaemia; 58(51%) vs.72(31%), Table 4. The risk of hypertriglyceridaemia under a Pi based ARV was about three times higher than that of NNRTI; RR=2.95,(95%CI=1.89–4.59), χ^2=28.4, and the risk of hypercholesterolaemia was about 2.5 times higher; RR=2.44, (95%CI=1.72–3.47), χ^2=26.4, both were statistically significant; p-0.0003 and p-0.0001, Table 5. Occurrence of post-ARV elevated LDL-C was slightly higher in the Pi group than the NNRTI; 39% vs. 30%, however, there was no associated increased risk [RR = 0.88 (95%CI = 0.75–1.03), χ^2=2.9, p 0.8]. HDL-C was elevated to about the same frequency in both groups; 32(34%) vs. 78(33%) without any risk difference. There was also no differential risk of IFG between Pi and NNRTI; RR = 1.10(95%CI = 0.93–1.29),χ^2=1.01, p-= 0.32, even though it occurred more frequently in the NNRTI than Pi group: 43(18%) vs. 13(14%).

There was a gender difference in the occurrence of these post exposure metabolic changes being commoner in females than males, Table 6. Hypertriglyceridaemia remained the commonest abnormality followed by hypercholesterolaemia and elevated LDL-C. These occurred in both Pi- and NNRTI-based therapies but, more frequent in ARV drug regimens containing EFV, RTV and IDV in that descending order. DM occurred in seven (3%) cases, six males and a female; all were in NNRTI group; five patients in EFV containing regimen and one in NVP containing NNRTI.

DISCUSSION

Majority of the patients seen in this study had advanced HIV/AIDS and presented late for care as shown by their low mean pretreatment weight and $CD4^+$ cells count. Fear of stigmatization which we have reported in one of our series could be responsible for this[12]. Both Pi and NNRTI regimens prevented progression of diseases in their recipients as evidenced by improvement in their weight and $CD4^+$ cell counts after ARV exposure. This has indirectly confirmed the effectiveness of Pi therapy in our patients as that of NNRTI had earlier been reported.[1] Possibly because of the severity of the disease, a number of lipid and glycaemic abnormalities were observed at baseline; these included in order of decreasing frequency low HDL-C, hypertriglyceridaemia, hypercholesterolaemia, and IFG. All these except low HDL-C were seen in patients with very severe disease, their $CD4^+$ count ranged between 3-48cells/ul. It might therefore mean that very low $CD4^+$ count was a predictor of dyslipidaemia in ARV naïve AIDS patients. Some researcher[4] have attributed pre exposure dyslipidaemia to the enhanced lipogenesis and impaired postprandial triglyceride clearance that often result from increased generation of tumor necrosis factor-á (TNFá) and interferon-ã (IFNã) cytokines at an advanced stage of HIV/AIDS spectrum.

The post exposure metabolic abnormalities in order of prevalence were hypertriglyceridaemia, hypercholesterolaemia and IFG as well as DM. These occurred in both Pi and NNRTI treatment groups to a varying degree, the Pi group induced more of hypertryglyceridaemia, hypercholesterolaemia and LDL-C while NNRTI induced more of high HDL-C and IFG. In fact patients that received Pi-based therapy had a threefold increased risk of developing hypertriglyceridaemia and about two and a halve time higher risk of developing hypercholesterolaemia over the NNRTI recipients. These risks were evident in the percentage distribution of cases of dyslipidaemia that met the National Cholesterol Education Program guidelines intervention criteria[13] where 79% and 51% of all Pi recipients developed hypertriglyceridaemia and hypercholesterolaemia compared to 54% and 31% on NNRTI therapy.

Dyslipidaemia was commoner in females while dysglycaemia occurred more in males. However, because of the small number of diabetic cases, seven (3%) in all, it is difficult to rationalize on this observation. Furthermore, this relative high rate of DM in the NNRTI group was at variance with widely cited studies[14,15] that reported high level of dysglycaemia from Pi based therapy. This was ascribed to Pi induced insulin resistance. Our experience, however, was similar to some other reports[16,17] that had observed more cases of dysglycaemia from NNRTI based therapy. Reasons for this may have to be further investigated. The Pi- associated dyslipidaemia on the other hand could partly be due to the use of plain ritonavir and indinavir which are known to be prone to inducing dyslipidaemia[18,19]. These two unboosted drugs are the commonly prescribed Pi for our patients because the boosted varieties are not readily available on the national programme. Stavudine on its own could have contributed to the

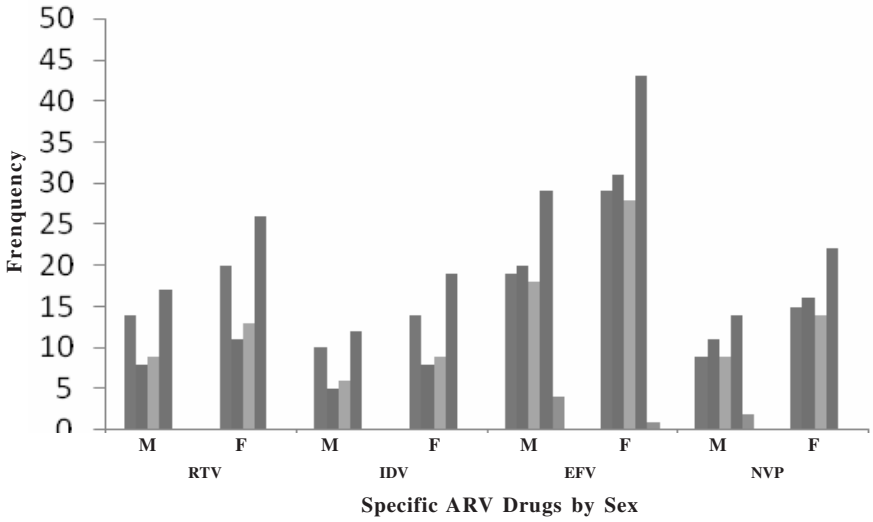

Figure 1: **Distribution of patients by sex against post-exposure abnormalities according to regimen. Pi-based, RTV and IDV; NNRTI-based, EFV and NVP.**

TC>6.5 **HDLC>1.55** **LDLC>4.14** **TG>1.8** **FPG>70**

development of dyslipidaemia in both Pi and NNRTI-based regimens as the drug has been associated with elevated TC, LDLC and triglyceride.[20] Same could be said of efavirenz[21] out of the other NNRTI drugs and this might led credence to why EFV was the most lipid inducing ARV drug in this report. Nevirapine however, is a lipid friendly ARV drug and could be responsible for the observed raised HDLC[22] in this same group of patients.

HAART-induced metabolic changes in this report resulted from the combined effects of NRTIs with Pi or NNRTI the pathogenesis of which though could be different but overall effect could be synergistic to some extent. Therefore, to reduce the risk of cardiovascular complications[7,23] that could develop from this ARV induced dyslipidaemia it is quite expedient on the planners of national ART programme to start implementing the new WHO guidelines[24] for ARV therapy in adults that recommend gradual withdrawal of stavudine containing regimens so as to avoid or minimize some of its predictable toxicities and replace it with a more lipid friendly substitute such as tenoforvir.[21,25] It is also time for replacement of plain or unboosted Pi with boosted varieties.

REFERENCES

1. Salami AK, Olatunji PO, Fawibe EA. Influence of highly active anti-retroviral therapy (HAART) on the survival of HIV-infected patients: Part report of the Ilorin trial center. *African Journal Clinical Experi-mental Microbiology* 2005; **6:** 34–39.
2. Hammer SM, Squires KE, Hughes MD, Grimmes JM, Demeter LM, Gurrier JS, *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 millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Engl J Med* 1997; **337:** 725–733.
3. Marschner IC, Collier AC, Coombs RW, D'Aquilla RT, De Gruttola V, Fischl MA. Use of changes in plasma levels of Human immunodeficiency virus type 1 RNA to assess the clinical benefit of antiretroviral therapy. *J Infect Dis* 1998; **177:** 40–47.
4. Georg B, Reinhold ES. Lipodystrophy Syndrome. HIV Medicine, 14th edition, flying publisher 2006, pages 1–3. Available at http://www.hivmedicine.com/textbook/cr.htm
5. Dube MP, Stein JH, Aberg JA, Fitchtenbaum CJ, Gerber JG, Tashiman KT, *et al.* Guidelines for the evaluation and management of hyperlipidaemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003; **37:** 613–27.
6. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997; **20:** 1183–1197.
7. Friis-Moller N, Sabin CA, Weber R, D'arminio Monforte A, EL- Sadr WM, Reiss P. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003; **349:** 1993–2003.
8. Siedel J, Hagele EO, Ziegenhorn J. Reagent for the enzymatic determination of serum total cholesterol with improved lipolytic efficiency. *Clin Chem* 1983; **29:** 1075–1080.
9. Mcgowan MW, Artiss JD, Stranbargh DR. Perioxidase coupled method for the colorimetric determination of serum triglyceride. *Clin Chem* 1983; **29:** 538–542.
10. Trinder P. Determination of blood glucose using 4-aminophenazone as oxygen acceptor. *J Clin Path* 1969; **22:** 246.
11. Alberti KG, Zimmet PZ. Definition of diagnosis and classification of diabetes mellitus and its complications. PART 1. Definition and classification of diabetes mellitus, provisional report of a WHO consultation. *Diabet Med* 1998; **15:** 539–553.
12. Salami AK, Olatunji PO, Oluboyo PO. Spectrum and prognostic significance of opportunistic diseases in HIV/AIDS patients in Ilorin, Nigeria. *West Afr J Med* 2006; **25:** 52–56.
13. Second Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol (Adult Treatment Panel II). *Circulation.* 1994; **89:** 1333–1445.
14. Vigouroux C, Gharakhanian S, Salhi Y, Nguyen TH, Adda N, Rozenbaum W. Diabetes, insulin resistance and hyperlipidaemia in lipodystrophic HIV-infected patients on highly active anti-retroviral therapy (HAART). *Diabetes Metab* 1999; **25:** 225–232.
15. Hertel J, Struthers H, Horj CB, Hruz PW. A structural basis for the acute effects of HIV protease inhibitors on GLUT4 intrinsic activity. *J Biol Chem* 2004; **279:** 55147–52.
16. Ledergerber B, Furrer H, Rickenbach M, Lehmann R, Elzi L, Hirschel B. Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. Clin Infect Dis. 2007; **45:** 111–119.
17. WHOPAR pARV4, summary of product characteristics; Stavudine Capsules 30mg/40mg (Ranbaxy) HA296/297. *Uncommon:* Development of diabetes mellitus. 2007, version 1.0

pages 5-9. Available at: http://www.who.int/prequal/WHOPAR/WHOPARPRODUCTS/HA296PARV4v1.pdf

18. Sullivan AK, Nelson MR. Marked hyperlipidaemia on ritonavir therapy. AIDS. 1997;11: 938–939.
19. Roberts AD, Muesing RA, Parenti DM, Hsia J, Wasserman AG, Simon GL. Alterations in serum levels of lipid and lipoproteins with indinavir therapy for human immunodeficiency virus-infected patients. *Clin Infect Dis* 1999; **29:** 441–443.
20. Gallant JE, Staszewski S, Pozniak AL, Dejesus E, Sulleiman JM, Miller MD *et al.* Efficacy and safety of tenofovir vs. stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA* 2004; **292:** 191–201.
21. Núñez M, Soriano V, Martín-Carbonero L, Barios A, Barrerio P, Blanco F, *et al.* (Spanish Efavirenz vs. Nevirapine Comparison (SENC) Trial: A Randomized, Open-Label Study in HIV-Infected Naïve Individuals. *HIV Clin Trials* 2002; **3:** 186–194
22. van Leth F, Phanuphak P, Stroes E, Gazzard B, Cahn P, Raffi F, *et al.* Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naïve patients infected with HIV-1. *PLoS Med* 2004; **1:** e73
23. Smith CJ, Levy I, Sabin CA, Kaya E, Johnson MA, Lipman MC. Cardiovascular disease risk factors and antiretroviral therapy in an HIV-positive UK population. *HIV Med* 2004; **5:** 88–92.
24. The WHO guidelines on "Antiretroviral Therapy for HIV Infection in Adults and Adolescents" (2006 revision) . http://www.who.int/hiv/pub/guidelines/ARVadultguidelines.pdf
25. Murata H, Hruz PW, Mueckler M. Indinavir inhibits the glucose transporter isoform Glut4 at physiologic concentrations. *AIDS* 2002; **16:** 859–863.