METABOLIC AND ANTHROPOMETRIC CHANGES ONE YEAR AFTER SWITCHING FROM DIDANOSINE/STAVUDINE TO TENOFOVIR IN HIV-INFECTED PATIENTS

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Abstract

Background: Nucleoside analogues such as Didanosine and Stavudine are known to cause metabolic and body habitus changes during antiretroviral therapy. The most frequently observed are lactic acidosis, hypercholesterinaemia, hypertriglyceridaemia and lipodystrophy.

Methods: Over one year we monitored a cohort of 43 patients who switched from either Stavudine, Didanosine or the combination of both to Tenofovir. A group of 11 patients was kept on their original regimen and acted as control group. Blood samples were taken every 3 months from baseline, anthropometric measurements were performed at baseline, after 6 and 12 months.

Results: During observation the levels of lactic acid and cholesterol decreased significantly in the switch group while virologic and immunologic efficacy remained stable. Serum creatinine levels rose significantly in patients switched to Tenofovir, but remained within physiological limits. The mean skin fold thickness increased significantly by 1.8 mm in the switch group after 6 months (p ≤ 0.001 - p = 0.032).

Conclusion: These results implicate an improvement of lipid profiles, serum lactate and lipodystrophy in HIV-positive patients after switch to Tenofovir. As a moderate increase in serum creatinine levels was observed, the renal function of patients on a Tenofovir-based regimen should be monitored closely.

Key words: Tenofovir, Stavudine, Didanosine, switch, lipodystrophy, cholesterol, triglycerides, lactate, hba1c, uric acid, nucleoside analogues, renal function

INTRODUCTION

Since the introduction of highly active antiretroviral therapy (HAART) in the treatment of HIV-infection in the late 1990s the toxicity of drugs has become an increasingly important issue in HIV-therapy. Due to decreased morbidity and mortality [12, 28] patients experience long term adverse effects of antiretroviral therapy now that were unknown or negligible before.

Amongst these adverse effects, hypercholesterinaemia and hypertriglyceridaemia have to be highlighted due to their frequency as well as lactic acidosis for its potentially life threatening consequences. While acute severe lactic acidosis (>10mmol/l) is associated with a mortality of approximately 80% [5, 6, 13], hypercholesterinaemia and hypertriglyceridaemia may increase the long term risk for myocardial infarction and vasculopathy in this population [9, 14, 25-27]. Another relevant side effect of antiretroviral drugs is represented by the lipodystrophy syndrome, which is aesthetically disturbing and may affect patient's adherence.

Nucleosidic Reverse Transcriptase Inhibitors (NRTI) as well as Protease Inhibitors (PI) were observed to cause metabolic and anthropometric alterations [15, 22]. The NRTIs didanosine and stavudine are known to cause the most significant changes in lactic acid levels and lipid profiles [3, 16, 31]. Recent studies suggest that the nucleotidic reverse transcriptase inhibitor tenofovir seems to cause less metabolic changes/lipodystrophy or could even ameliorate these effects [15, 21].

METHODS

PATIENTS

In our open label, not randomised, prospective study we monitored the metabolic and anthropometric changes of 43 patients after substituting only tenofovir DF for either stavudine (n = 16), didanosine (n = 9), or stavudine in the combination of both (n = 18) without any other drug substitution during the entire follow-up. A control group of 11 patients remained on their previous regimen containing stavudine (n = 7) or stavudine and didanosine (n = 4). Data for this study was collected from February 2003 to August 2004 in the Department of Infectious Diseases, University of Munich, Germany. Eligible patients were HIV-infected, immunologically stable adults receiving triple antiretroviral therapy including stavudine and/or didanosine, who had a stable viral load < 2000 copies/ml at baseline, and suffered a NRTI toxicity that caused the replacement from stavudine and/or didanosine to tenofovir in routine clinical practice. All patients gave written informed consent. The study was approved by institutional ethic committees. Exclusion criteria were a documented resistance or incompatibility to tenofovir DF, liver cirrhosis, acute viral hepatitis, chronic renal impairment or serum-creatinine over 1.4 mg/dl.

Blood samples were taken at baseline, after 1, 3, 6, 9 and 12 months. Samples were analysed for CD4 cell count, HIV-1 viral load, cholesterol, LDL, HDL,

triglycerides, HbA1c, uric acid, lactic acid, serum creatinine and phosphate. Skin fold thickness (maxillary, upper arm, forearm, pectoral, abdominal, thigh and lower leg) as well as circumference of limbs and hips were measured at baseline, after 6 and 12 months as previously described in literature [31].

The estimated glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation incorporating age, race, sex and serum creatinine levels [20].

LABORATORY MEASUREMENTS

Serum levels of total cholesterol, HDL-C, LDL-C and triglycerides were measured after a fasting period of 10-12 hours with routine essays (GPO/PAP-method (triglycerides), CHOD/PAP-method (cholesterol), homogeneous enzymatic precipitation (HDL/LDL)). In values of TG < 300 mg/dl LDL-C was calculated using the Friedewald equation. In every control complete standard haematology and biochemistry analysis were also performed, as well as CD4 lymphocyte count and plasma HIV viral load.

STATISTICS

Data was collected using a Microsoft Excel database and transferred to SPSS for further statistical analysis. The results of continuous variables are presented as the median absolute value with 95% confidence intervals (CI). Mann-Whitney U Test was used as appropriate for comparisons of quantitative variables, with significance levels placed at $p < 0.05$.

RESULTS

Baseline characteristics of the 54 patients are shown in Table 1. Reasons for switching therapy from didanosine/stavudine to tenofovir (>1 reason may apply per patient) included hypercholesterinaemia (27 patients), hypertriglyceridaemia (32 patients) and lipodystrophy (19 patients). One patient received concomitant lipid-lowering therapy before entering the study, in two patients it was added after 6 months. Nevertheless, computation taking this into account as a possible confounding factor showed that the results were not influenced in.

IMMUNOLOGICAL AND VIROLOGICAL OUTCOME

At the time of the switch, the mean CD4+ T cell count was 454 cells/mL (range, 107–993 cells/mL), and CD4+ T cell counts remained stable throughout the 12 months following the switch to tenofovir without significant change in and between both groups. However a tendency to higher CD4 cell counts was noticed in the switch group. The median plasma viral load was <50 copies/mL at the time of switch, with 46 patients (85.2%) having a load of <50 copies/mL. The proportion of patients with a plasma viral load of <50 copies/mL increased to 88,4 % 12 months after switching to tenofovir.

METABOLIC CHANGES

The serum cholesterol level in the switch group decreased significantly over the time monitored ($p = 0.035$ at month 12). Regarding the sub groups, patients switching from stavudine to tenofovir benefit the most from the new regimen. For patients substituting didanosine no significant change in cholesterol could be observed. Changes in the control group were not significant ($p = 0.912$ at month 12).

Levels of lactic acid decreased significantly in the switch group in month 6 and 9 ($p = 0.029$, $p = 0.028$) whereas no changes in lactic acid levels could be found in the control group ($p = 0.168$).

A significant decrease of uric acid was noticed in the switch group from month 3 on ($p \leq 0.001 - p = 0.012$), whereas the control group showed no change.

We found an increase of HbA1c levels in the switch group. From month 6 on it was significant ($p \leq 0.001 - p = 0.016$). This is noticeable because a change of neither glucose nor insulin levels was observed in this group.

No significant changes could be observed for LDL cholesterol levels and triglyceride levels (though there was a tendency to lower triglyceride levels in the switch group). HDL cholesterol levels decreased significantly after first 6 months in patients switched from stavudine to tenofovir ($p = 0.003$), but returned

Table 1. Baseline characteristics of the 54 patients.

Median age [years (range)]	46 (25-71)
Male sex [n (%)]	38 (70)
Median CD4 cell count [/μl]	454
Patients with HIV-RNA <50 copies/ml [n (%)]	46 (85,2)
Patients with HIV-RNA <400 copies/ml [n (%)]	50 (93)
Mean Stavudine and/or Didanosine exposure length [years]	3,3 (1-6)
Patients with cholesterol >220 mg/dl [n (%)]	27 (50)
Patients with triglycerides >200 mg/dl [n (%)]	23 (43)
Patients with triglycerides >500 mg/dl [n (%)]	9 (17)
Patients receiving lipid lowering therapy [n (%)]	3 (6)
Patients with lipodystrophy [n (%)]	19 (35)

Table 2. Metabolic changes over one year.

| Group Outcome	Switch Baseline	Control	Switch 6 months	Control	Switch 12 months	Control	Switch P month 6 /	Control P month 12
Mean total cholesterol mg/dl	228.56	224.27	205.73	232.00	203.69	227.44	0.036 / 0.035	0.871 / 0.912
Mean HDL cholesterol mg/dl	45.18	45.91	39.36	50.00	43.43	46.63	0.003 / 0.766	0.605 / 0.331
Mean LDL cholesterol mg/dl	129.25	130.11	123.83	136.88	116.45	131.17	0.114 / 0.165	0.546 / 0.315
Mean triglycerides mg/dl	342.64	244.00	234.65	230.22	223.51	184.00	0.339 / 0.268	0.951 / 0.240
Mean HbA1c %	5.131	5.430	5.463	5.438	5.514	5.383	<0.001 / 0.016	0.204 / 0.426
Mean uric acid mg/dl	5.74	5.47	5.041	6.220	4.903	5.480	<0.001 / 0.001	0.875 / 0.252
Mean lactic acid mmol/l	1.839	1.664	1.463	1.600	1.472	1.513	0.029 / 0.055	0.678 / 0.603
Mean serum creatinine mg/dl	0.818	0.845	0.833	0.844	0.9	0.889	0.736 / <0.001	0.282 / 0.347
Mean serum phosphate mg/dl	2.70	2.76	2.735	2.843	2.776	2.760	0.463 / 0.755	0.580 / 0.716
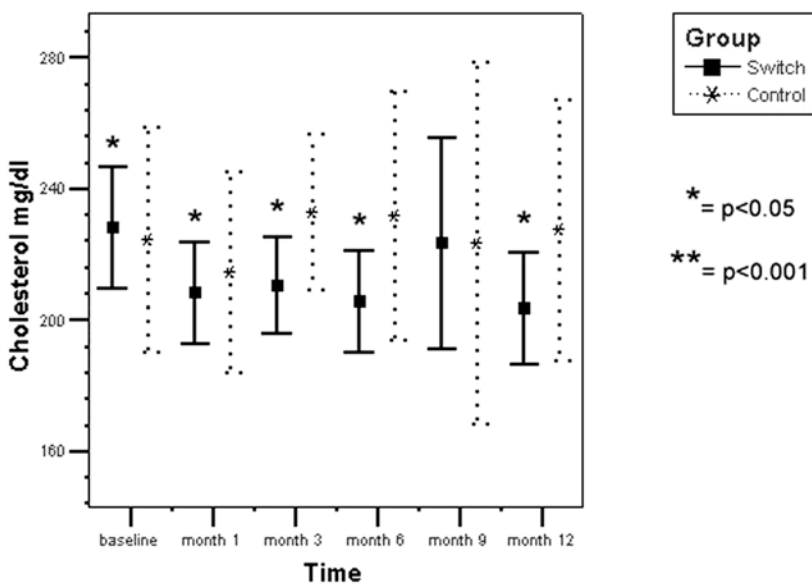
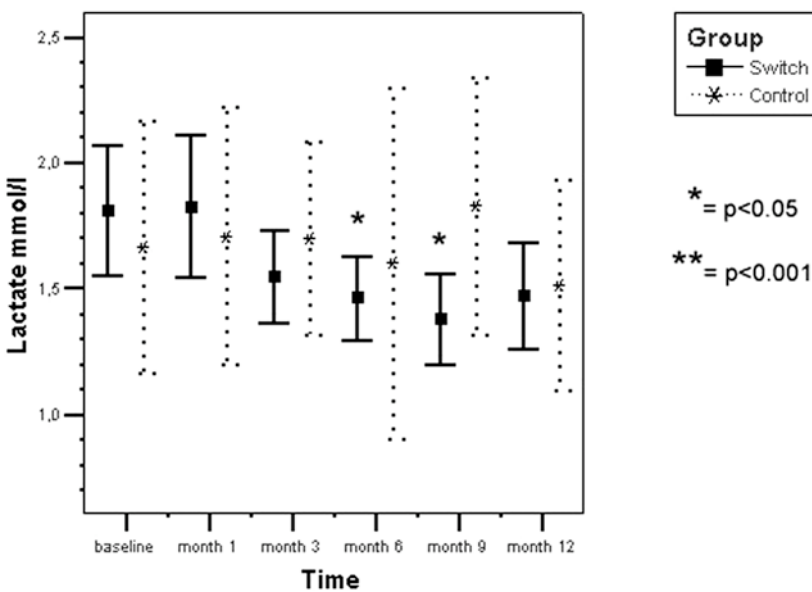*Fig. 1.* 95% Cl for cholesterol mg/dl.

Fig. 2. 95% Cl or lactic acid mmol/l.

to baseline values after 12 months. Analysis of antiretroviral combiantion compounds did not show specific patterns explaining according to concomitant antiretrovirals (data not shown).

Serum creatinine levels increased significantly after 1, 3, 9 and 12 months in the switch group (p ≤0.001 -
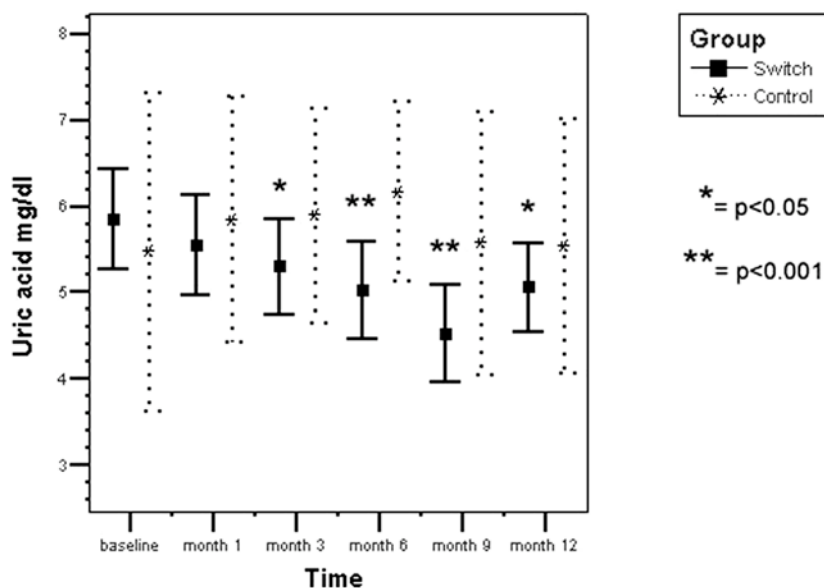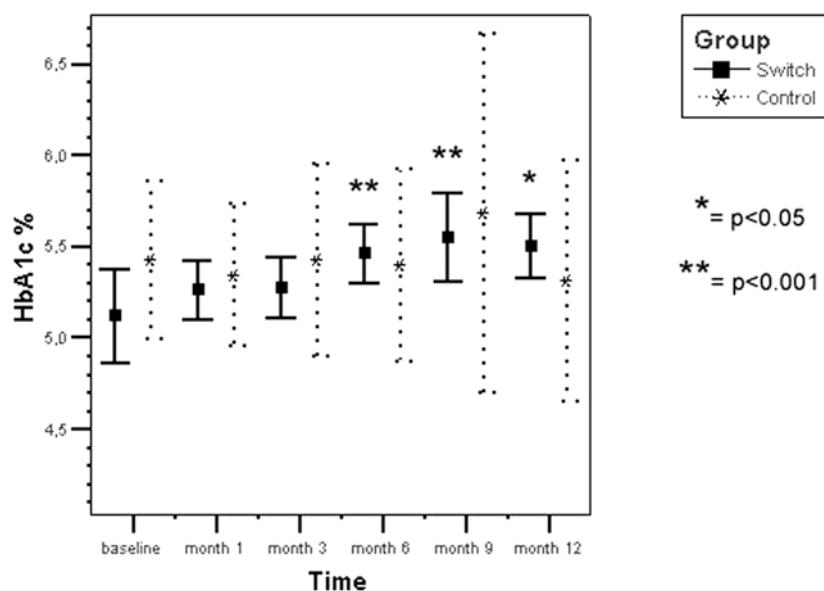
Fig. 3. 95% Cl for uric acid mg/dl.

Fig. 4. 95% Cl for HbA1c %.

p = 0.031). However the mean raise of creatinine levels was maximal 0.07 mg/dl and mostly remained within the physiological range. The estimated glomerular filtration rate showed a significant decrease (97.2 to 88.4 ml/min/1.73m²; p<0.01) for patients switched from stavudine to tenofovir as well as for patients switched from stavudine/didanosine to tenofovir (103.7 to 94.1 ml/min/1.73m²; p<0.05). Body weight did not change significantly in either group and did not influence the calculation of GFR. As an early indicator of renal tubular toxicity serum phosphate did not show any significant change during 12 months (p = 0.076).

ANTHROPOMETRIC OUTCOMES

The measurements of body circumferences could not show any significant changes neither in the switch nor in the control group. In contrast, the measuring of skin fold thickness provided significant increases in the switch group after 6 months (p = <0.001 - p = 0.032 at month 6). In particular maxillar skin folds and those on the limbs showed significant increases (maxillar: p ≤0.001, limbs: p = <0.001 - p = 0.032), whereas abdominal and pectoral skin fold thickness increased insignificantly (p = 0.274 - p = 0.302).

DISCUSSION

In this study patients were not switched to a new regimen because of virologic or immunologic failure but due to expected or already occurred adverse effects of therapy. Therefore as expected, efficacy of viral suppression and immunologic competence remained stable after therapy change. The results, which do not show any significant difference in CD4 cell count or viral load from the switch to the control group, align with other studies that approve a similar immunologic and virologic efficacy for tenofovir as for established antiretroviral drugs [15]. In terms of efficacy a switch

from didanosine or stavudine to TDF seems to be safe.

Dyslipidaemia as an aspect of lipodystrophy syndrome is very common in patients receiving HAART including NRTIs or PIs. It mainly appears as a rise of triglycerides and/or total cholesterol. In a study with more than 1600 patients a significantly augmented and earlier incidence of hypercholesterinaemia was observed in patients using stavudine [17]. In comparison with this, regimens including tenofovir did not show episodes of elevated cholesterol levels. In view of the elevated cardiovascular risk of patients with drug induced dyslipidaemia [9, 14] a therapy switch seems to be a possible solution for lowering patients serum lipids. Thus in a cohort of heavily pretreated patients with hypercholesterinaemia and hypertriglyceridaemia a switch from stavudine to tenofovir caused a significant decrease of dyslipidaemia already after 12 weeks [10]. Also in our trial we observed a significant decrease of total cholesterol in the group with switch from stavudine and/or didanosine to tenofovir ($p = 0.036$ after 6 months, $p = 0.035$ after 12 months). The significance for the entire switch group is based partially on highly significant decreases in the sub group with switch from stavudine to tenofovir ($p = 0.003$ - $p = 0.007$). The decrease of serum cholesterol in the other switch sub groups was not statistically significant though there was a trend to lower cholesterol levels. We achieved similar result for LDL-cholesterol. Decreases were only significant in the switch sub group with switch from stavudine to tenofovir. HDL-cholesterol levels decreased significantly over 6 months after the switch ($p = 0.003$ - $p = 0.031$) and returned to baseline values after 9 and 12 months. The metabolism of this remains to be investigated. Unlike other studies we did not find a reduction of triglyceride levels in the switch group ($p = 0.217$ - $p = 0.612$). Triglycerides in the control remained stable.

As tenofovir has a lower affinity to mitochondrial γ-polymerase, we expected reduced mitochondrial toxicity after the switch resulting in lower lactic acid levels. In vitro-tests with human liver cells showed a significantly lower production of lactic acid in cells treated with tenofovir (+20%) than for cells treated with e.g. Zidovudine (+200%) [2]. In our patients a decrease of lactic acid serum levels was observed, that was significant after 6 and 9 months ($p = 0.029$, $p = 0.028$, mean decrease 0.31 - 0.35 mmol/l). Levels of lactic acid did not change in the control group.

The values of uric acid decreased significantly in the switch group from month 3 on. The most likely explanation for this effect is that Diadnosine has a well known side-effect of uric acid elevation. Mean uric acid levels were elevated before the switch so a slight decrease can also be taken as a benefit.

We could observe a significant increase of HbA1c values in the switch group from month 6 on ($p \leq 0.001$ - $p = 0.016$) without a coexistent change in serum glucose or insulin levels. An isolated increase of HbA1c values without an increase in serum glucose or change of other diabetes markers can not be explained with glucose intolerance or prediabetes under HAART. Inaccuracy of HbA1c measurement in HIV-infected patients is described in the literature as result of haemolytic side effect of other drugs. But in these cases lower HbA1c levels were measured because of a reduced lifespan of erythrocytes and associated lower exposure of haemoglobin to high serum glucose concentrations [29]. In other trials an isolated increase of HbA1c values was found that was negatively correlated with CD4 cell count and positively correlated with serum-ferritin values [19, 30]. As these studies were conducted before the HAART era another mechanism than drug toxicity seems supposable. It was discussed if HIV-positive patients, whose immune system is confronted with a multitude of infectious agents, have an elevated serum iron emergence as consequence of the degradation of these agents. Other studies showed, that raised glycosilation of haemoglobin follows this constellation. In our patients no correlation between HbA1c levels and CD4 cell counts could be found, serum-ferritine was not determined. So a coherent conclusion about elevated HbA1c levels after switch to tenofovir can not be given at this point.

First studies concerning efficacy and adverse effects of Tenofovir did not show any severe renal toxicity of this agent [1, 15, 32]. Several papers describe renal impairment and tubular dysfunction in patients receiving Tenofovir [4, 7, 8, 11]. To date, it is not yet clear from the literature or our results whether the observed initial decline in GFR during the first 12 months of therapy will continue or whether it will reach a plateau [33]. In our patients we could find a significant increase of serum creatinine levels with a mean increase of 0.026 to 0.071 mg/dl ($p \leq 0.001$ - $p = 0.031$). The estimated GFR decreased significantly in the stavudine switch group. These observation are in accordance with others, that found a decreased GFR after switch to Tenofovir [18] which also remained in physiological limits.

Lipoatrophy as an aspect of lipodystrophy syndrome is very common in patients treated with stavudine over a longer period. Former Studies proved that a switch from stavudine to other NRTIs could lead to a clinical improvement of lipoatrophic changes [23, 24]. In our patients there was a statistically significant increase of skin fold thickness of average 1.8 mm in the switch group after 6 months. Unfortunately these measurements were only conducted with 8 patients at month 12. So no more significant results could be found at this point. Moreover the method used is susceptible to errors. Various examiners have different ways of measuring with the calipermeter and results are often more an estimation of skin fold thickness. In our study an inter-investigator difference can be excluded due to the fact that all measurements were taken by the same person.

In conclusion a substitution of stavudine/didanosine to tenofovir may reverse dyslipidaemia in HIV-treated patients while immunologic and virologic efficacy remains stable. This is the first study to show also significant changes of serum-lactate, uric acid and HbA1c. On the other hand keeping track of the renal function of patient is obligatory. A positive effect of a therapy switch on lipodystrophic changes seems possible but must be observed more closely.

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REFERENCES

1. Badiou S, Merle De BC, Terrier N, Baillat V, Cristol JP, Reynes J. Is tenofovir involved in hypophosphatemia and decrease of tubular phosphate reabsorption in HIV-positive adults? J Infect 2005.

2. Birkus G, Hitchcock MJ, Cihlar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors. Antimicrob Agents Chemother 46: 716-23, 2002.

3. Blanco F, Garcia-Benayas T, Jose de la CJ, Gonzalez-Lahoz J, Soriano V. First-line therapy and mitochondrial damage: different nucleosides, different findings. HIV Clin Trials 4: 11-9, 2003.

4. Callens S, De RA, Colebunders R. Fanconi-like syndrome and rhabdomyolysis in a person with HIV infection on highly active antiretroviral treatment including tenofovir. J Infect 47: 262-3, 2003.

5. Carr A. Lactic acidemia in infection with human immunodeficiency virus. Clin Infect Dis 36: S96-S100, 2003.

6. Carr A, Morey A, Mallon P, Williams D, Thorburn DR. Fatal portal hypertension, liver failure, and mitochondrial dysfunction after HIV-1 nucleoside analogue-induced hepatitis and lactic acidaemia. Lancet 357: 1412-4, 2001.

7. Coca S, Perazella MA. Rapid communication: acute renal failure associated with tenofovir: evidence of drug-induced nephrotoxicity. Am J Med Sci 324: 342-4, 2002.

8. Creput C, Gonzalez-Canali G, Hill G, Piketty C, Kazatchkine M, Nochy D. Renal lesions in HIV-1-positive patient treated with tenofovir. AIDS 17: 935-7, 2003.

9. d'Arminio A, Sabin CA, Phillips AN, Reiss P, Weber R, Kirk O, El-Sadr W, De WS, Mateu S, Petoumenos K, Dabis F, Pradier C, Morfeldt L, Lundgren JD, Friis-Moller N. Cardio- and cerebrovascular events in HIV-infected persons. AIDS 18: 1811-7, 2004.

10. Domingo P, Labarga P, Palacios R, Guerro MF, Terron JA, Elias MJ, Santos J, Ruiz MI, Llibre JM. Improvement of dyslipidemia in patients switching from stavudine to tenofovir: preliminary results. AIDS 18: 1475-8, 2004.

11. Earle KE, Seneviratne T, Shaker J, Shoback D. Fanconi's syndrome in HIV+ adults: report of three cases and literature review. J Bone Miner Res 19: 714-21, 2004.

12. Escolano Hortelano CM, Ramos Rincon JM, Gutierrez RF, Masia CM, Hernandez A, I, Benito SC, Padilla US, Martin-Hidalgo A. [Changes in the spectrum of morbidity and mortality in hospital admissions of HIV infected patients during the HAART era]. Med Clin (Barc) 122: 1-5, 2004.

13. Falco V, Rodriguez D, Ribera E, Martinez E, Miro JM, Domingo P, Diazaraque R, Arribas JR, Gonzalez-Garcia JJ, Montero F, Sanchez L, Pahissa A. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. Clin Infect Dis 34: 838-46, 2002.

14. Friis-Moller N, Sabin CA, Weber R, d'Arminio MA, El-Sadr WM, Reiss P, Thiebaut R, Morfeldt L, De WS, Pradier C, Calvo G, Law MG, Kirk O, Phillips AN, Lundgren JD. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med 349: 1993-2003, 2003.

15. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, Coakley DF, Lu B, Toole JJ, Cheng AK. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA 292: 191-201, 2004.

16. Galli M, Ridolfo AL, Adorni F, Gervasoni C, Ravasio L, Corsico L, Gianelli E, Piazza M, Vaccarezza M, d'Arminio MA, Moroni M. Body habitus changes and metabolic alterations in protease inhibitor-naive HIV-1-infected patients treated with two nucleoside reverse transcriptase inhibitors. J Acquir Immune Defic Syndr 29: 21-31, 2002.

17. Jones R, Sawleshwarkar S, Michailidis C, Jackson A, Mandalia S, Stebbing J, Bower M, Nelson M, Gazzard BG, Moyle GJ. Impact of antiretroviral choice on hypercholesterolaemia events: the role of the nucleoside reverse transcriptase inhibitor backbone. HIV Med 6: 396-402, 2005.

18. Julg BD, Bogner JR, Crispin A, Goebel FD. Progression of renal impairment under therapy with tenofovir. AIDS 19: 1332-3, 2005.

19. Kabadi UM, Gopal V, Hood L, Kabadi MU, Platt K. Elevated glycosylated hemoglobin concentrations in AIDS. AIDS 6: 236-8, 1992.

20. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130: 461-70, 1999.

21. Llibre JM, Domingo P, Palacios R, Santos J, Perez-Elias MJ, Sanchez-de la RR, Miralles C, Antela A, Moreno S. Sustained improvement of dyslipidaemia in HAART-treated patients replacing stavudine with tenofovir. AIDS 20: 1407-14, 2006.

22. 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 14: 1309-16, 2000.

23. Martin A, Smith DE, Carr A, Ringland C, Amin J, Emery S, Hoy J, Workman C, Doong N, Freund J, Cooper DA. Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. AIDS 18: 1029-36, 2004.

24. McComsey GA, Ward DJ, Hessenthaler SM, Sension MG, Shalit P, Lonergan JT, Fisher RL, Williams VC, Hernandez JE. Improvement in lipoatrophy associated with highly active antiretroviral therapy in human immunodeficiency virus-infected patients switched from stavudine to abacavir or zidovudine: the results of the TARHEEL study. Clin Infect Dis 38: 263-70, 2004.

25. Neumann T, Woiwod T, Neumann A, Miller M, Von BC, Volbracht L, Esser S, Brockmeyer N, Gerken G, Erbel R. Cardiovascular risk factors and probability for cardiovascular events in HIV-infected patients - part III: age differences. Eur J Med Res 9: 267-72, 2004.

26. Neumann T, Woiwod T, Neumann A, Ross B, Von BC, Volbracht L, Brockmeyer NH, Gerken G, Erbel R. Cardiovascular risk factors and probability for cardiovascular events in HIV-infected patients. Part II: gender differences. Eur J Med Res 9: 55-60, 2004.

27. Neumann T, Woiwoid T, Neumann A, Miller M, Ross B, Volbracht L, Brockmeyer N, Gerken G, Erbel R. Cardiovascular risk factors and probability for cardiovascular events in HIV-infected patients: part I. Differences due to the acquisition of HIV-infection. Eur J Med Res 8: 229-35, 2003.

28. Palella FJ, Jr., Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 338: 853-60, 1998.

29. Polgreen PM, Putz D, Stapleton JT. Inaccurate glycosylated hemoglobin A1C measurements in human immunodeficiency virus-positive patients with diabetes mellitus. Clin Infect Dis 37: e53-e56, 2003.

30. Ricart W, Fernandez-Real JM, del PM, Mascaro J, Garcia-

Bragado F. The cause of elevated glycosylated haemoglobin concentrations in AIDS. AIDS 7: 1274-5, 1993.

31. Saint-Marc T, Partisani M, Poizot-Martin I, Bruno F, Rouviere O, Lang JM, Gastaut JA, Touraine JL. A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. AIDS 13: 1659-67, 1999.

32. Schooley RT, Ruane P, Myers RA, Beall G, Lampiris H, Berger D, Chen SS, Miller MD, Isaacson E, Cheng AK. Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. AIDS 16: 1257-63, 2002.

33. Gallant JE, Parish M, Keruly J, Moore R. Changes in renal function in patients treated with Tenofovir DF (TDF) compared to nucleoside reverse transcriptase inhibitors (NRTIs). 3rd IAS Conference 2005, Rio de Janeiro 24-27 July 2005, Abstract TuPe2.3C18.

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