First-line NRTIs and Risk of New Onset Diabetes in HIV-infected Adults in Thailand

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INTRODUCTION

- HIV and diabetes are two chronic diseases with severe public health burdens in Thailand. In 2013:
    - –prevalence of HIV in adults (aged 15-49 years) was 1.1%
    - –prevalence of diabetes in adults was 6.4%
- Long-term exposure to some antiretrovirals (ARVs), in particular thymidine analogue nucleosides, is known to be associated with a higher risk of diabetes. However, this risk may vary according to ARVs.

Objective

To estimate the risk of new onset diabetes and its association with four different nucleos(t)ide reverse transcriptase inhibitor (NRTI)-containing first-line regimens in HIV-infected adults in Thailand.

MATERIALS AND METHODS

Study Design and Study Population

- Study design: multicenter, prospective PHPT cohort (NCT00433030)
- Study population: HIV-1 infected adults of the PHPT cohort who:
    - initiated antiretroviral therapy (ART) between January 2000 and December 2011,
    - had no diabetes before ART initiation,
    - had at least two plasma glucose measurements,
    - received exclusively and for at least 2 years tenofovir disoproxil fumarate (TDF), zidovudine (ZDV), stavudine (d4T) or didanosine + stavudine (ddI+d4T) as part of their first-line regimen.

> **Definition of Diabetes**
> Confirmed fasting plasma glucose ≥126 mg/dL or random glucose ≥200 mg/dL (American Diabetes Association)

Statistical Analysis

- Incidence rate: number of new cases of diabetes divided by total number of person-years of follow-up (PYFU).
- Fisher's exact test to compare characteristics at ART initiation between the four groups.
- Cox proportional hazards model to assess the association between the four NRTI-containing regimens and the risk of new onset diabetes, adjusting for all variables significantly different across the four groups.
- p-values <0.05 considered statistically significant (two-sided).
- All analyses were performed using Stata software version 10.1

RESULTS

Flowchart of the Study Population

> 2,092 HIV-infected adults enrolled in the PHPT cohort between January 1, 2000 and December 31, 2011

> 1,572 adults excluded:
> - 203 received ART before enrollment
> - 295 had no or only one glucose measurement
> - 1,074 did not receive, exclusively and for at least two years, TDF, ZDV, d4T or ddI+d4T as part of their first-line regimen

> 520 HIV-infected adults included in the analysis

Characteristics of the Study Population

- Of the 520 HIV-infected adults:
    - –329 (63%) female
    - –Median age: 34.1 years (Interquartile range: 29.5-40.1)
    - –Median BMI: 20.7 kg/m^2 (18.9-22.9)

Figure 1. Distribution of the NRTIs contained in the first-line regimen of the study population

ddI+d4T 10 (2%)
d4T 35 (7%)
ZDV 146 (28%)
TDF 329 (63%)

- TDF, ZDV and d4T are usually in addition to lamivudine or emtricitabine

Incidence Rate of Diabetes

- 13 cases identified (3,318 PYFU)
- Incidence rate: **3.9 per 1,000 PYFU** (95% CI: 2.3-6.7)

Table 1. Characteristics of the study population at ART initiation.

Characteristics	Exposure to first line regimen containing				
	TDF n = 329 n (%)	ZDV n = 146 n (%)	d4T[a] n = 35 n (%)	ddI+d4T n = 10 n (%)	p-value[b]
Female gender	190 (58)	100 (68)	29 (83)	10 (100)	**< 0.001**
Age ≥30 years	274 (83)	80 (55)	17 (49)	4 (40)	**< 0.001**
Body mass index ≥25 kg/m^2	45 (14)	25 (18)	1 (3)	0 (0)	0.09
Positive hepatitis B surface antigen *(8 missing)*	2 (1)	5 (4)	2 (6)	0 (0)	**0.02**
Positive hepatitis C antibody *(11 missing)*	0 (0)	11 (8)	3 (11)	1 (10)	**< 0.001**
Triglycerides ≥140 mg/dL *(87 missing)*	143 (44)	48 (46)	0 (0)	0 (0)	0.29
Total cholesterol ≥160 mg/dL *(89 missing)*	164 (51)	52 (49)	0 (0)	0 (0)	0.63
HIV RNA load ≥5 log$_{10}$ copies/mL *(12 missing)*	120 (36)	58 (41)	11 (33)	1 (25)	0.68
CD4 count <200 cells/mm^3 *(6 missing)*	235 (72)	106 (74)	25 (74)	7 (70)	0.91
CDC stage B or C	136 (41)	62 (42)	13 (37)	5 (50)	0.88

[a] Excluding patients on ddI+d4T
[b] Fisher's exact tests

- Variables for gender, age, hepatitis B surface antigen and hepatitis C antibody were significantly different across the four groups.

Table 2. Association between NRTI-containing first line regimens and the occurrence of diabetes during follow-up.

First line regimen containing	Diabetes n = 13	Total n = 520	Unadjusted Analysis		Adjusted Analysis[a]	
			Hazard Ratio (95% CI)	p-value[b]	adjusted Hazard Ratio (95% CI)	p-value[b]
TDF	3	329	1		1	
ZDV	6	146	4.9 (1.2 - 19.7)	**0.03**	6.6 (1.6 - 27.5)	**0.01**
d4T[c]	1	35	6.0 (0.6 - 58.3)	0.12	9.4 (0.9 - 95.1)	0.06
ddI+d4T	3	10	22.4 (4.0 - 126.6)	**< 0.001**	73.2 (11.5 - 465.2)	**< 0.001**

[a] Adjusted for gender, age, hepatitis B surface antigen and hepatitis C antibody
[b] Wald test
[c] Excluding patients on ddI+d4T

- Patients exposed to a first-line regimen containing ZDV or ddI+d4T were at a significantly higher risk of diabetes than a TDF-containing regimen (adjusted analysis).

CONCLUSIONS

- Low incidence rate of diabetes in this lean and predominantly young, female population as compared to rates found in other cohorts and in the general adult population in Thailand.
- Patients exposed to a first-line regimen containing ZDV or ddI+d4T were at a significantly higher risk of diabetes than those exposed to a first-line regimen containing TDF.
- Our results provide further support for the current WHO guidelines recommending phasing out d4T and ddI, starting TDF-containing first-line regimens and preserving ZDV for the second line.

LIMITATIONS

- Our study population is predominantly composed of relatively young women and thus may not be representative of the adult population living with HIV in Thailand and Southeast Asia.
- Some data at ART initiation were not measured and were imputed for the Cox proportional hazards analyses.

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SUPPORT