

Risk factors for lactic acidosis and severe hyperlactataemia in HIV-infected adults exposed to anti-retroviral therapy: An international case-control study

Alejandro Arenas-Pinto on behalf of the lactic acidosis international study group

Centre for Sexual Health & HIV Research, University College London, UK



Abstract

Background: Lactic acidosis (LA) and severe hyperlactataemia (HL) are rare but serious complications of antiretroviral therapy (ART). We conducted a case control study including 19 centres in 10 countries in Europe, the Americas and Australia to identify risk factors for HL/LA among HIV-infected adults exposed to ART.

Methods: LA cases were defined as arterial blood pH <7.35, bicarbonate <20 mmol/l and lactate above normal; HL was defined as two consecutive blood lactate >5 mmol/l, irrespective of acid-base status. Two controls per case were randomly selected from patients >16 years, on or previously exposed to ART, matched by centre and calendar year. Conditional logistic regression was used to identify risk factors.

Results: 110 cases (49 with LA) diagnosed between 1997 and 2004 and 220 controls were included. 36.4% of cases and 18.2% of controls were women (P<0.001). The median age was 42.4 years for cases (interquartile range [IQR] 36.0–52.5) and 40 for controls (IQR 35.0–47.1) (P 0.013). In the univariate analysis cases were more likely to be receiving d4T (odds ratio [OR] 3.63, 95% confidence interval [CI] 2.10–6.29) or ddI (OR 6.08, 95%CI 3.12–11.84) at the time of the event whereas controls were more likely to be exposed to AZT or 3TC. There was an even stronger association with exposure to a d4T/ddI-based combination (OR 25.31; 95%CI 7.43–86.23) compared with AZT/3TC-based combinations. Case status was associated with shorter duration of exposure to both dideoxynucleosides. In a multivariable model adjusting for age, gender and current CD4 count, HL/LA remained associated with shorter duration on ddI (adjusted (a)OR 9.26, 5.01 and 2.28 for patients exposed for <12, 12–24 and >24 months respectively). In addition, age above 40 years (aOR 2.6; 95%CI 1.08–6.29), female gender (aOR 5.97; 95%CI 1.92–18.5) and advanced HIV-induced immunosuppression were independently associated with HL/LA (aOR 3.89, 7.58 and 8.11 for patients with 200–349, 100–199 and <100 CD4 respectively).

Interpretation: LA/HL was strongly associated with exposure to dideoxynucleosides. The additional associations with female gender, advanced immunosuppression and possibly ethnicity have important consequences for choice of ART regimens in developing countries. The association with shorter duration of exposure argues against a mechanism depending on cumulative exposure and may support the hypothesis of a particular susceptibility in a small proportion of patients.

Background

- Almost all studies to date suggest that dideoxynucleosides, especially stavudine (d4T), are associated with the development of severe LA and this has been attributed to mitochondrial toxicity
- In the context of expanding access to anti-retroviral therapy (ART), it remains critically important to identify risk factors for NRTI-induced adverse events, quantify risk and produce evidence based guidelines for their use.

Patients and methods

- LA was defined as arterial blood pH < 7.35, blood bicarbonate < 20 mmol/l and blood lactate levels above the upper limit of the reference range in the relevant centre.
- HL was defined based on at least two consecutive readings of blood lactate higher than 5 mmol/l (45 mg/dl) regardless of their acid-base status (only a minority of controls had blood lactate results available at the time of their inclusion in the study).
- Two randomly selected controls were matched to their respective cases by centre and calendar year (controls were receiving outpatient care or admitted to hospital during the same calendar year as the event in their respective case).
- **Statistical analysis** was performed using STATA version 9.1 (Stata Corp LP, College Station, Texas USA). Conditional logistic regression was used to identify risk factors associated with the study outcome. Significance testing was based on the likelihood ratio test approach. A regression model was built using the stepwise forward approach, including in the process those factors found significant (p < 0.05) in the univariate analysis. Data on ART exposure were analysed based on single NRTI exposure irrespective of other ART each patient was taking simultaneously, as well as the NRTI combinations most frequently taken.
- Ethical approval was obtained from all relevant ethics committees where required.

Results (1)

- 110 cases (49 with LA) and 220 controls from 19 centres distributed in 10 countries were included.
- Cases were significantly older than controls: median (interquartile range [IQR] age for cases and controls was 42.4 (36.0 – 52.5) years vs. 40 (35.0 – 47.1) years respectively (P=0.011).

Results (2)

- The proportion of cases of non-white ethnicity (36/86, 41.8%) was significantly higher than among controls (49/157, 31.2 %) (P=0.032).
- The median blood lactate among cases was 6.8 (IQR 5.5 – 8.1) mmol/l compared with 1.4 (IQR 1.1–1.9) mmol/l among the 62/220 (28.2 %) controls with available data.
- The frequency of hepatitis B and hepatitis C infection was similar in cases and controls.
- HL/LA case status was associated with current exposure to d4T/ddI or the combination and the combination was associated with a higher risk than with either drug alone.
- The strength of the association between dideoxynucleosides and HL/LA was dependent on duration of current exposure. The OR for exposure to d4T and ddI between cases and controls was significantly higher when the current duration of treatment was under 12 months compared with longer than 24 months.
- After adjusting by other variables (age, gender and current CD4 level), the trend of reduction in odds ratios for HL/LA over time in those patients on ddI remained clear (OR= 9.26, 5.01 and 2.28 for patients exposed for less than 12, 12 to 24 and more than 24 months respectively) whereas the trend with d4T became less so.

Table 1 Description of the study population and univariate analysis

Variable	CASES		CONTROLS		OR	95 % CI	P
	Freq/Total (%)	Freq/Total (%)	N	%			
Demographics							
Age							
< 40	40/110 (36.4)	110/220 (50.0)	1				0.013
> 40	70/110 (63.6)	110/220 (50.0)	1.87	1.13 - 3.09			
Gender							
Male	70/110 (63.6)	180/220 (81.8)	1				< 0.001
Female	40/110 (36.4)	40/220 (18.2)	3.27	1.78 - 6.03			
HIV history							
Previous AIDS diagnosis	59/110 (53.6)	82/220 (37.3)	2.08	1.27 - 3.40	0.004		
Nadir CD4 (< 200)	69/91 (75.8)	101/188 (53.7)	4.38	2.08 - 9.22	< 0.001		
Previous MT ADR*	42/110 (38.2)	52/220 (23.6)	1.95	1.19 - 3.19	0.008		
Concurrent medical events							
Opportunistic infections	19/110 (17.3)	18/220 (5.2)	2.44	1.19 - 5.03	0.015		
Concurrent MT ADR*	43/110 (39.1)	20/220 (9.1)	5.87	3.14 - 10.98	< 0.001		
CD4 count							
> 350	28/100 (28.0)	128/212 (60.4)	1				< 0.001
200 - 349	27/100 (27.0)	39/212 (18.4)	5.66	2.48 - 12.90			
100 - 199	31/100 (31.0)	28/212 (13.2)	9.53	3.98 - 22.83			
< 100	14/100 (14.0)	17/212 (8.0)	7.36	2.64 - 20.49			
Current NRTI exposureⁿ							
Current ABC exp	13/105 (12.4)	38/199 (19.1)	0.60	0.30 - 1.20	0.152		
Current 3TC exp	40/105 (38.1)	144/199 (72.4)	0.13	0.06 - 0.26	< 0.001		
Current AZT exp	11/105 (10.5)	69/199 (34.7)	0.25	0.13 - 0.51	< 0.001		
Current ddI exp	64/105 (61.0)	55/199 (27.6)	6.08	3.12 - 11.84	< 0.001		
Current d4T exp	73/105 (69.5)	79/199 (39.7)	3.63	2.10 - 6.29	< 0.001		
Current exposure to NRTI combinations							
AZT / 3TC	7/105 (6.7)	50/199 (25.1)	1				< 0.001
d4T / ddI (+/- other ⁿ)	44/105 (41.9)	24/199 (12.1)	25.31	7.43 - 86.23			
d4T (+/- other ⁿ)	27/105 (25.7)	53/199 (26.6)	3.85	1.34 - 11.02			
ddl (+/- other ⁿ)	17/105 (16.2)	20/199 (10.1)	6.50	1.98 - 21.38			
AZT / 3TC / other ⁿ	3/105 (2.8)	13/199 (6.5)	1.80	0.38 - 8.60			
Other dual combinations*	2/105 (1.9)	20/199 (10.1)	0.78	0.14 - 4.37			
Single NRTI**	5/105 (4.8)	19/199 (9.5)	1.16	0.30 - 4.59			

*Mitochondrial-related ADR: peripheral neuropathy, pancreatitis, bone marrow suppression or myopathy
ⁿ Comparing patients on each NRTI drug against patients not receiving it
 *other: ABC, 3TC or TDF
ⁿ other: ABC, 3TC or TDF
ⁿ other: one or two of AZT, ABC, 3TC or TDF
ⁿ other: ABC or TDF
 *Other dual combinations: d4T/ABC, ddI/ABC, 3TC/ABC, 3TC/TDF, AZT/ABC, AZT/TDF
 ** Single NRTI exposure: ABC, AZT or 3TC in combination with NNRTIs and/or PIs

Table 2 Effect of current durationⁿ of NRTI

NRTI	Cases		Controls		Univariate		Multivariate**	
	N	%	N	%	OR	95% CI	OR	95% CI
d4T								
No	37	33.6	141	64.1	1			
< 12	37	33.6	26	11.8	5.71	2.93 - 11.12	3.67	1.94 - 11.29
12 to 24	17	15.5	20	9.1	3.80	1.66 - 8.69	6.23	1.59 - 24.38
> 24	19	17.3	33	15.0	2.17	1.08 - 4.35	5.28	1.39 - 20.05
ddl								
No	46	41.8	165	75.0	1			
< 12	33	30.0	21	9.5	8.54	3.80 - 19.20	9.26	2.47 - 34.67
12 to 24	16	14.6	14	6.4	6.87	2.55 - 18.51	5.01	1.02 - 24.56
> 24	15	13.6	20	9.1	2.99	1.31 - 6.84	2.28	0.57 - 9.10
3TC								
No	70	63.6	76	34.5	1			
< 12	19	17.3	50	22.7	0.39	0.20 - 0.76	0.78	0.26 - 2.38
12 to 24	7	6.4	25	11.4	0.31	0.12 - 0.81	2.05	0.43 - 9.72
> 24	14	12.7	69	31.4	0.17	0.08 - 0.37	0.34	0.09 - 1.32
AZT								
No	99	90.0	151	68.6	1			
< 12	7	6.4	24	10.9	0.43	0.17 - 1.07	3.53	0.70 - 17.73
12 to 24	1	0.9	14	6.4	0.14	0.02 - 1.03	0.16	0.01 - 2.41
> 24	3	2.7	31	14.1	0.15	0.05 - 0.53	0.97	0.19 - 5.04
d4T/3TC								
No	63	57.3	193	87.7	1			
< 12	27	24.5	14	6.4	9.50	3.86 - 23.34	6.38	2.01 - 20.28
12 to 24	10	9.1	7	3.2	8.77	2.58 - 29.84	4.77	1.04 - 21.87
> 24	10	9.1	6	2.7	7.08	2.10 - 23.81	9.55	1.39 - 65.56
AZT/3TC								
No	100	90.9	157	71.4	1			
< 12	7	6.4	25	11.4	0.42	0.17 - 1.03	0.86	0.24 - 3.15
12 to 24	1	0.9	13	5.8	0.13	0.02 - 1.01	0.18	0.02 - 1.88
> 24	2	1.8	25	11.4	0.13	0.03 - 0.55	0.97	0.19 - 5.04

ⁿ in months
 **Adjusted by age, gender, current CD4 count and other NRTI exposures

Table 3 Risk factors for HL/LA: multivariate model

NRTI Combination	Cases		Controls		Univariate		Multivariate	
	N	%	N	%	OR	95% CI	OR	95% CI
Age (> 40 years)	70	63.3	110	50	1.87	1.13 - 3.09	2.60	1.08 - 6.29
Gender (female)	40	36.4	40	18.2	3.27	1.78 - 6.03	5.97	1.92 - 18.50
Current CD4								
> 350	28	28.0	128	60.4	1		1	
200 - 349	27	27.0	39	18.4	5.66	2.48 - 12.90	3.89	1.20 - 12.55
100 - 199	31	31.0	28	13.2	9.53	3.98 - 22.83	7.58	2.40 - 23.89
< 100	14	14.0	17	8.0	7.36	2.64 - 20.49	8.11	1.88 - 34.99
Current NRTI Exposure								
AZT / 3TC	7	6.7	50	25.1	1		1	
d4T / ddI (+/- other ⁿ)	44	41.9	24	12.1	25.31	7.43 - 86.23	19.87	4.49 - 87.91
d4T (+/- other ⁿ)	27	25.7	53	26.6	3.85	1.34 - 11.02	4.14	1.03 - 16.68
ddl (+/- other ⁿ)	17	16.2	20	10.1	6.50	1.98 - 21.38	5.24	1.24 - 22.19
AZT / 3TC / other ⁿ	3	2.8	13	6.5	1.80	0.38 - 8.60	2.77	0.42 - 18.31
Other dual combinations*	2	1.9	20	10.1	0.78	0.14 - 4.37	0.53	0.07 - 4.22
Single NRTI**	5	4.8	18	9.1	1.16	0.30 - 4.59	1.38	0.26 - 7.24

*other: ABC, 3TC or TDF
ⁿ other: ABC, 3TC or TDF
ⁿ other: one or two of AZT, ABC, 3TC or TDF
ⁿ other: ABC or TDF
 *Other dual combinations: d4T/ABC, ddI/ABC, 3TC/ABC, 3TC/TDF, AZT/ABC, AZT/TDF
 ** Single NRTI exposure: ABC, AZT or 3TC in combination with NNRTIs and/or PIs

Interpretation

- Exposure to dideoxynucleosides is strongly associated with the likelihood of developing HL/LA.
- The combination of d4T / ddI was associated with a greater risk than either drug alone.
- The risk of developing HL/LA appears to be exposure time dependent. The association between HLLA and dideoxynucleosides became less strong with increasing duration of exposure to these drugs. The effect persists for ddl even when adjusted for other factors.
- Our data in part support the hypothesis that some individuals may be at much higher risk of developing serious NRTI-induced mitochondrial dysfunction. This may be particularly relevant in resource-limited settings where individuals at higher risk (women, those with advanced HIV disease and possibly those with an ethnicity associated predisposition) are overrepresented.
- Further work is needed to examine the risk for these severe complications in non-white populations and better understand susceptibility.