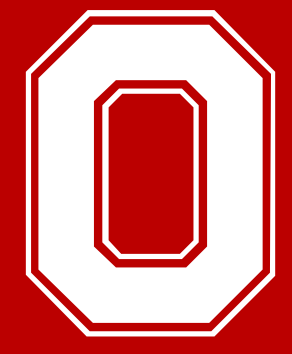




Hyperlactatemia and Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI): Still present even with modern antiretroviral therapy (ART)



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BACKGROUND

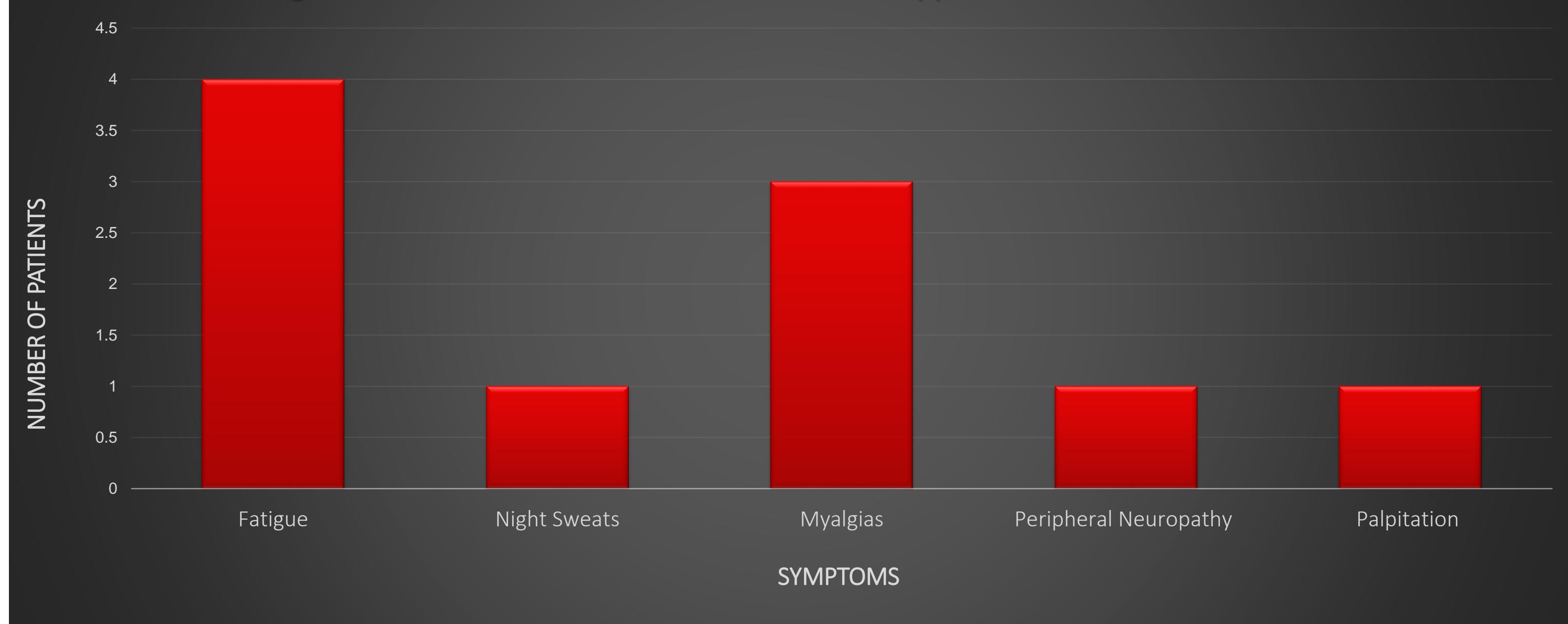
- Hyperlactatemia and lactic acidosis represent a rare but dangerous adverse effect of NRTIs.
- Various symptoms such as abdominal pain, nausea, emesis, fatigue, dyspnea, weight loss, neuropathy, palpitations, and night sweats have been associated with hyperlactatemia.
- These symptoms are thought to be related to mitochondrial dysfunction and toxicity associated with use of older NRTIs such as zidovudine, didanosine, and stavudine.
- The incidence and prevalence of symptomatic hyperlactatemia on zidovudine, didanosine, and stavudine have been previously reported as 10.8-59.4 cases/1000 person-years^{8, 20, 21, 22, 24}.
- These estimates of incidence and prevalence may vary depending on the number and specific NRTI agent present in an antiretroviral regimen.
- We present a case series of 4 patients with NRTI-associated hyperlactatemia while on modern ART.

METHODS

- This is a retrospective review of patients evaluated by a one provider at the Infectious Diseases Clinic at The Ohio State University Wexner Medical Center between September 2019 to December 2022.
- All patients received a standardized assessment of symptoms associated with hyperlactatemia or lactic acidosis including fatigue, night sweats, palpitations, abdominal pain, nausea, emesis, diffuse myalgias, and shortness of breath.
- Hyperlactatemia was defined as a serum lactate of 1.6-4 mmol/L and lactic acidosis was defined as a serum lactate of >4mmol/L.

RESULTS

Figure 1: Clinical Manifestations of Hyperlactatemia/ Lactic Acidosis



RESULTS

Table 1: Summary of Clinical Characteristics of patients with NRTI-associated hyperlactatemia/ lactic acidosis

	Case 1	Case 2	Case 3	Case 4
Age (years)	60	34	57	80
Sex	Female	Male	Male	Male
Years since diagnosis of HIV	18	2	3	22
CD4 lymphocyte count at the time of HIV diagnosis (cells/mm ³)	49	6	145	419
Body Mass Index (kg/m ²)	29.4	19.5	32.9	32.1
Antiretroviral therapy received (duration, month)	DTG/ABC/3TC (36)	BIC/TAF/FTC (24)	DTG + TAF/FTC (36)	RAL + ABC/3TC (168)
Clinical manifestations	Diffuse myalgias, fatigue	Fatigue, palpitations, night sweats	Diffuse myalgias, fatigue	Diffuse myalgias, fatigue, peripheral neuropathy
Duration of Symptoms (months)	36	8	6	60
Concurrent medications	None	Sertraline	Atorvastatin	Isosorbide Mononitrate, Lisinopril, Omeprazole, Potassium Gluconate, Warfarin Sodium, Aspirin, Lovastatin, Levetiracetam

Table 2: Lab Values at the time of diagnosis of NRTI-associated hyperlactatemia/ lactic acidosis

CD4 lymphocyte count (cells/mm ³)	487	189	553	781
HIV-1 RNA load (copies/mL)	<40	<40	<40	<40
Serum lactate while on ART (mmol/L)	1.9	2.3	2.6	3.9
Serum lactate after holding ART (mmol/L)	0.4	0.4	0.6	1.1
AST (U/L)	18	18	40	22
ALT (U/L)	18	16	56	20
Creatine kinase (U/L)	40	16	56	207
Antiretroviral therapy received after recovery	DTG/RPV	DTG/RPV	DTG/RPV	DTG + DOR
Outcome	Symptom resolution	Symptom resolution	Symptom Resolution	Symptom Resolution

Table 3: Summary of Clinical Characteristics

Age, years (mean)	57.8
Race	Caucasian: 75% Black or African American: 25%
Mean Duration of Symptoms before reporting (months)	27.5
Serum Lactate at the time of diagnosis of symptomatic hyperlactatemia (mean, mmol/L)	2.7
Serum Lactate after stopping ART for 2 weeks (mean, mmol/L)	0.6

CONCLUSION & FUTURE SCOPE

- Despite improved tolerability of modern ART, clinicians should be aware of and monitor for symptoms of this potentially life-threatening side effect.
- Management strategies are not well defined for hyperlactatemia; however, early diagnosis may allow for safe outpatient management. NRTI-sparing regimens may facilitate resolution of symptoms related to lab abnormalities without compromising viral suppression.
- This case series highlights the insidious nature of symptoms related to NRTI-associated hyperlactatemia thought to be related to mitochondrial dysfunction.
- Additional studies are needed to clarify the frequency and risk factors of hyperlactatemia on newer ART.
- Understanding the clinical significance of symptomatic and asymptomatic hyperlactatemia over time and its relationship to mitochondrial dysfunction may provide additional guidance regarding management and long-term implications in an aging population.

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