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REVIEW

# Hyperlactataemia and lactic acidosis in HIV-infected patients receiving antiretroviral therapy

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**Summary** Nucleoside reverse-transcriptase inhibitors (NRTIs) have been associated with functional and structural mitochondrial abnormalities, leading to several adverse events, such as increased serum lactic acid levels and lactic acidosis. Mild-to-moderate, asymptomatic hyperlactataemia has been frequently reported in human immunodeficiency virus (HIV)-infected patients treated with NRTIs, with an estimated prevalence between 15% and 35%. On the contrary, symptomatic, severe hyperlactataemia and lactic acidosis are less common, with an incidence ranging from 1.7 to 25.2 cases per 1000 person-years of antiretroviral treatment, and are associated with a remarkable mortality rate, which varies from 30% to 60% in different studies. The clinical presentation of lactic acid syndrome is non-specific and includes asthenia, malaise, nausea, vomiting, abdominal pain, weight loss, tachypnoea, dyspnoea, liver steatosis and increased transaminase levels, and risk factors include previous or concurrent therapy with stavudine or didanosine. Management of symptomatic lactic acid alterations involves NRTI-therapy interruption and supportive care, while natural history of hyperlactataemia is still unknown, and it is uncertain whether asymptomatic patients with increased lactate concentrations are at increased risk of developing lactic acidosis.


**Contents**



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## Introduction

The recent availability of potent combination antiretroviral therapies has dramatically reduced the human immunodeficiency virus (HIV)-associated morbidity and mortality, and substantially improved the long-term prognosis of patients with HIV infection. However, the significant increase in life expectancy and the need for permanent antiretroviral treatment have led to the observation of new, frequent, and sometimes severe adverse effects associated with the antiretroviral agents.

Hyperlactataemia and lactic acidosis are two increasingly recognized adverse events of antiretroviral therapy for which only few data have been published to date. Particularly, increased serum lactate levels were described as frequent and potentially serious complications of treatment with nucleoside reverse-transcriptase inhibitors (NRTIs), which are usually included in the highly active antiretroviral therapy (HAART).[1–3]

In 1991, Lai et al.[4] observed a case of severe lactic acidosis and fatal fulminant hepatitis with diffuse microvesicular liver steatosis in a patient treated with didanosine. Lactic acidosis and hepatic steatosis were later described in association with use of most of the available nucleoside analogues. More recently, hyperlactataemia and hepatotoxicity have been associated with myopathy, cardiomyopathy, neuropathy, pancreatitis, lipoatrophy and pancytopaenia, and they were proposed as part of a common spectrum of disorders due to NRTI-related mitochondrial toxicity.[5–8]

In 2000, Carr et al.[9] described a syndrome of lipoatrophy, liver dysfunction and elevated serum lactic acid levels complicating nucleoside analogue therapy. In this study, total duration of NRTI treatment, stavudine use and higher age were significant predictors of peripheral fat loss, and this NRTI-related lipodystrophy syndrome differed from the protease inhibitor (PI)-associated lipodystrophy by the presence of hyperlactataemia, increased transaminase levels, recent gastrointestinal symptoms, and weight loss.

To date, at least 150 cases of severe hyperlactataemia and lactic acidosis associated with the administration of NRTIs have been described by the literature, but several epidemiological, pathological and clinical features of this adverse event are still today uncertain. In this review, prevalence, risk factors, clinical course, and medical management of hyperlactataemia following antiretroviral treatment are considered in the setting of the most recent and meaningful literature updates. These data were derived from a computer-assisted search of worldwide medical literature from 1990 through 2004 in the Medline database with use of the key words ''HIV'', ''antiretroviral therapy'', ''hyperlactataemia'', and ''lactic acidosis''.

## Classification, prevalence and risk factors

Hyperlactataemia is defined as a mild-to-moderate increase in serum lactate concentration (2–5 mmol/l), with normal pH value and bicarbonate level (pH $\geqslant$ 7.35 and bicarbonate concentration $\geqslant$ 20 mmol/l). This usually occurs in situations where tissues are well-perfused and buffering systems are able to prevent a fall in pH and metabolic acidosis.

On the other hand, lactic acidosis is defined as persistently and remarkably elevated serum lactate level (generally $>$ 5 mmol/l), associated with metabolic acidosis (pH $<$ 7.35 and bicarbonate concentration $<$ 20 mmol/l). In a widely accepted classification scheme, lactic acidosis may be divided into two types. Type A includes lactic acidosis occurring in association with clinical evidence of tissue hypoxia, while type B is represented by that one recognized without clinical signs and symptoms of tissue hypoxia. Therefore, metabolic complication observed in patients treated with NRTIs is considered a type B lactic acidosis.[10,11]

Although symptomatic hyperlactataemia and metabolic acidosis are thought to be rare adverse effects, recent studies have shown that asymptomatic increased lactate concentration is a frequent event in patients receiving NRTIs, with an estimated prevalence ranging from 15% to 35%.[12] On the contrary, the incidence of symptomatic hyperlactataemia and lactic acidosis varies from 1.2 to 25.2 cases per 1000 person-years of treatment with NRTIs, with a high variation in the calculated frequency due to the variety of case definitions employed.[1,12,13]

At the same time, the precise relationship between asymptomatic hyperlactataemia and lactic acidosis is still uncertain. To date, it is not clear