Correspondence

Symptomatic Hyperlactatemia: Lessons Learned Using a Point-of-Care Device in a Health Care Center– and Nurse-Based Antiretroviral Program in Rwanda

To the Editor—We read with interest the article by Songa et al. [1], because we are similarly confronted with the frequent occurrence of symptomatic hyperlactatemia/lactic acidosis (SH/LA) in our program in Rwanda. With current efforts to decentralize antiretroviral treatment, most patients will soon receive treatment through health care centers that are staffed mainly by nurses and that have fewer diagnostic tools available. Songa and colleagues encourage field-testing of point-of-care devices (POCDs) in Africa. We report our experience with access to a POCD at a health care center– and nurse-based antiretroviral treatment program.

Médecins Sans Frontières started offering antiretroviral treatment on a decentralized level in Rwanda in 2003, supporting 2 urban government clinics in Kigali [2]. The program relies extensively on nurses for provision of care and has seen a fast scaling-up (i.e., >3000 patients have started receiving treatment).

In 2005, a standardized clinical protocol was developed to screen for mitochondrial toxicities. With training and after use of the protocol, nurses developed good clinical skills, initiating treatment changes under medical supervision. A high rate of lipoatrophy was observed [2].

In 2006, a POCD for determination of the lactate level (Accutrend Lactate; Roche) [3] was introduced for patients with clinically suspected SH/LA. We used this tool to document 20 cases of SH/LA.

Table 1. Lessons learned in a health care center– and nurse-based antiretroviral treatment program.

<table>
<thead>
<tr>
<th>Experience with a clinical approach</th>
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<tr>
<td>Given practical training, protocols, and supervision, nurses are able to recognize SH/LA readily and to initiate clinical management</td>
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<td>Ready access to care, located in health care centers, encourages early diagnosis</td>
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Potential advantages of a POCD for determination of the lactate level

- High predictive value of normal or high lactate level (>5 mmol/L)
- Potential for less switching of treatment regimens (SH/LA can be ruled out)
- Potential for more-accurate and earlier diagnosis, with
  - Less morbidity or mortality and/or shorter therapy interruption
  - More-controlled treatment interruptions (“tail-protection”)
  - Higher chance of successful rechallenge (particularly zidovudine)
- Easy application in health care centers and is user-friendly* |

Facilitation of training and enhances confidence of medical staff in the diagnosis and management of SH/LA

Potentially cost-effective, by reducing morbidity/mortality and fewer switches to more-expensive drugs

Potential problems with a POCD for lactate testing

- Few data on incidence and clinical significance of subclinical hyperlactatemia in Africa
- Requirements for sample collection not assessed in antiretroviral treatment programs in Africa include risk of transient or artificial increases in the lactate level caused by, for example, exercise, dehydration, feeding, or infection (e.g., malaria)
- Potential for overswitching of treatment (associated with false-positive results) if there is poor clinical judgment or training
- Laboratory errors or artificial increases
- Poor correlation of symptoms with lactate levels
- Frequent occurrence of mimicking conditions

Different case definitions of SH have been used in Africa [1, 5, 6], and the optimal threshold of lactate level for treatment interruption is not known

Although lactate levels correlate with disease severity, substantial variability exists at the individual level [6, 7]

Potential delays in restarting antiretroviral treatment after clinical recovery without clinical benefit

Currently expensive (MSF price, excluding taxes, $226 per machine and $2.3 per test strip)

Requires steady supply of test strips and control solution

**NOTE.** MSF, Médecins Sans Frontières; POCD, point-of-care device; SH/LA, symptomatic hyperlactatemia/lactic acidosis.

* Defined as a device that is hand-held or portable, that requires minimal training, that provides results in <60 s, that can be used with whole blood (finger-prick), that is battery driven (1.5 V), that does not require refrigeration, and for which control solutions for performance checks are available [3].
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tended, the optimal time to reinstitution has not been es-
tablished [9]. We have observed clinical
recovery before biochemical recovery and have rarely seen cases of recurrence using
our clinical approach. Given the risk of severe infection (particularly tuberculosis) during treatment interruption, returning to antiretroviral treatment as soon as pos-
sible is important. Correlation of POCD results and clinical status will be an im-
portant operational research question.

The potential for artificial elevations in the lactate level is high [8–10], particularly in a resource-limited setting, where pa-
tients often walk for hours in hot weather to visit the clinic and face long waiting periods. Despite recommendations regard-
ing adequate preparation for testing [11], it is challenging to ensure that the patient is well hydrated, has been fasting, and has avoided exercise. Given the unique circumstances in Africa, additional studies are needed to balance the POCD’s validity against its feasibility and accept-
ability [9]. Even then, the true incidence of subclinical hyperlactatemia has to be defined, because this will clearly affect the predictive value of a particular lactate level [12]. Given their nonspecific nature, symptoms suggestive of SH/LA have been shown to correlate poorly with lactate lev-
els and have not consistently improved with switches or interruptions in treat-
ment, making the diagnosis of mild or moderate symptomatic hyperlactatemia challenging and requiring substantial clinical judgement [13–15]. With the signifi-
cant number of diseases in Africa that can mimic SH/LA on the basis of transient hyperlactatemia, we have to guard against
overdiagnosis. On the other hand, with infectious diseases considered to be po-
tential triggers for SH/LA [8, 12], the as-
sumption that subclinical hyperlactatemia rarely progresses to severe disease [9] has to be reassessed in Africa.

Another issue is whether the POCD can assist in the timing of reinstitution of ther-
apy. Although normalization of the lactate level is generally recommended, the optimal time to reinstitution has not been es-
tablished [9]. We have observed clinical
recovery before biochemical recovery and have rarely seen cases of recurrence using
our clinical approach. Given the risk of severe infection (particularly tuberculosis) during treatment interruption, returning to antiretroviral treatment as soon as possible is important. Correlation of POCD results and clinical status will be an im-
portant operational research question.

The optimal use of a POCD remains to be determined, but if used with a stan-
ardized approach and investment in clin-
ical training for nurses, the POCD can be a useful device in resource-poor settings.

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Reply to van Griensven et al.

To the Editor—We thank van Griensven et al. [1] for sharing their experience with the lactate point-of-care device. We are also glad that symptomatic hyperlactatemia and lactic acidosis (SH/LA) are becoming a topic of debate and interest in resource-limited settings where stavudine-containing regimens are prescribed for the majority of the patients.

We agree that clinical judgment is crucial in the diagnosis and management of this syndrome; training of health care workers should not only promote the early recognition of symptoms of SH/LA, but should also promote the exclusion of other causes of elevated lactate levels. Although there could be a possibility of over-diagnosis, our case series [2] revealed that 83% of patients had other symptoms of mitochondrial toxicity, suggesting that switching to other drugs would be beneficial for these patients.

After the publication of our case series, the Infectious Diseases Institute received a donation of a point-of-care device (Accutrend Lactate; Roche) [4] with 2000 test strips. At present, we are performing a validation analysis to compare the point-of-care device measurements with measurements from the Makerere University–Johns Hopkins University Core Laboratory, which follows Good Laboratory Practice guidelines and which is certified by the College of American Pathologists.

In addition, we submitted 2 proposals and plan to start the 2 following studies in October 2007.

1. A cross-sectional study involving measurements of serum lactate levels in a cohort of patients receiving antiretroviral treatment (any regimen), to determine the true prevalence of hyperlactatemia. A limitation of the study that we published [2] was that the information was obtained by review of the charts. Enrolling patients in this cross-sectional study will allow us to design a structured interview to exclude other causes of hyperlactatemia, such as opportunistic infections and transient elevations of lactate levels resulting from exercise or dehydration.

2. A prospective study. Patients with asymptomatic hyperlactatemia will be followed up, and lactate measurements and a structured interview will be performed every 3 months. This will allow us to verify whether subclinical hyperlactatemia rarely progresses to severe disease, as suggested from experience in western countries [3], and that, therefore, regimen changes are not recommended for this category of patients.

We hope that these studies can answer some of the issues raised by van Griensven et al. [1]. Regarding the cost issue, we believe that, in programs in which thousands of patients are receiving stavudine-containing regimens, with consideration of the high mortality rate for SH/LA, measurements of the lactate level should be made. Three years after starting the roll-out of free antiretrovirals in sub-Saharan Africa, antiretroviral treatment programs have had to take into account toxicity issues and to provide tools to manage drug-related complications.

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References


HIV-1 Subtype C Seronegative AIDS

To the Editor—We thank Novitsky and colleagues [1] for their interesting report about a seronegative patient infected with HIV-1 subtype C. We too have recently given a seronegative AIDS diagnosis to a patient, the second adult case we have seen at our institution with presumed HIV-1 subtype C infection. This patient received a diagnosis of disseminated tuberculosis and had a CD4+ T cell count of 20 cells/μL. Results of HIV antibody tests—including rapid (Determine HIV-1/2, Abbott and Capillus; Trinity Biotech) and third-generation ELISA (Dade Behring)—were negative. However, a fourth-generation HIV antibody–p24 antigen combination ELISA (Axysym; Abbott) was weakly reactive, and an HIV p24 antigen–only ELISA (Elecys; Roche) was also weakly reactive. Viral RNA was detected in the plasma at 2,500,000 IU/mL (Nuclisens EasyQ; bioMérieux), and results of an HIV DNA PCR (Amplicor HIV-1; Roche) were positive.

We presume that the HIV antibody–p24 antigen combination ELISA was weakly reactive because of the presence of the p24 antigen in the patient’s sample and not because of HIV antibody. This patient had a total serum IgG level of 31.25 g/L, which excludes a primary immune deficiency as a reason for the absence of HIV-specific