Authors' reply

We thank Duncan Smith-Rohrberg and colleagues and Stephen Lawn and co-workers for their comments concerning our algorithm[1] and their pledge for the availability of more viral load testing in resource-limited settings. For the moment, however, we have to confront the reality faced by most countries struggling with antiretroviral treatment scale-up: viral load testing remains expensive, requires a well-equipped laboratory, well-trained personnel, and is not available in most resource-limited settings.

For these reasons, WHO is still not recommending viral load tests for regular monitoring of antiretroviral treatment in resource-limited settings.[2] Two randomised trials in Africa—the Centers for Disease Control and Prevention (CDC) study in Tororo, Uganda[3] and the Development of Antiretroviral Therapy in Africa (DART) study[4] in Uganda and Zimbabwe—were initiated in 2004, comparing clinical monitoring only with clinical and routine laboratory monitoring. Both studies are still ongoing, meaning the data safety monitoring boards have not stopped them because patients in the laboratory arm were doing better than patients in the clinical monitoring only arm. However, it is unlikely that these studies will provide a definite answer concerning the value of viral load testing to monitor antiretroviral therapy in resource-limited settings. Indeed, viral load testing is only done in one of the three study arms in the CDC Tororo study. Moreover, the primary outcomes of both studies are the development of an AIDS-defining illness or death and not drug resistance, a marker that may teach us more about the long-term outcome of the antiretroviral therapy.

Smith-Rohrberg and colleagues' suggestion that our algorithm primarily uses signs of clinical and immunological failure is not true. A very important element of our algorithm is the assessment of adherence. Adherence monitoring is potentially even better then viral load monitoring, because when a viral load is detectable, often it is already too late: resistance mutations may already be present.[5] In the developed world, despite guidelines that recommend routine virological monitoring every 3–4 months[6] and the very large budgets spent on this, we have not been too successful in avoiding resistance.

Viral load testing, as proposed by Lawn and colleagues, could be used as a way to improve adherence, but for the moment is very costly. Other adherence promoting strategies—eg, strengthening treatment counselling, using treatment supporters, using pharmacy refill data to establish a system to correct non-adherence and to trace treatment defaulters, providing pill boxes, etc—are probably more cost-effective.

Our algorithm is a way to increase access to viral load testing in resource-limited settings by targeting it to those patients where the viral load result potentially influences therapeutic decision making and thus reduces the overall cost. In cross-sectional studies done in resource-limited settings, the number of patients that have an undetectable viral load after 1 year of first-line therapy is relatively high.[7,8] We believe that using the proposed algorithm, viral load testing may only be needed for a subset of patients. This is confirmed by the first evaluation of our algorithm in South Africa by Lawn and colleagues, who showed that our algorithm is a substantial improvement over existing WHO recommendations. In their study the development of prurigo was also a sign of treatment failure. The sensitivity of our algorithm, however, remains low. The problem is that in modifying the algorithm to increase its sensitivity, the specificity may decrease and, as a consequence, patients will be switched unnecessarily to more complicated and more expensive second-line regimens.

One viral load test without the possibility of resistance testing or the possibility to repeat the viral load test after an attempt to improve adherence may have limited value because of the difficulty of distinguishing between an adherence problem only and a resistance problem. Moreover the interpretation of a viral load result in resource-limited settings may be difficult. Low levels of viraemia may be caused by episodes of malaria and other coinfections.[9] In the absence of alternatives to a failing regimen, the resources for viral load measuring will not benefit the patient. Finally, the question of when to switch treatment and at what level of viral load remains unclear in resource-limited settings; early switching may not necessarily benefit the patient.

We agree, however, that without any access to viral load testing the diagnosis of virological failure will be delayed. Therefore, we also decry complacency about the development and "roll out" of cheaper technologies to measure viral load.

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1 Colebunders R, Moses KR, Laurence J, et al. A new model to monitor the virological efficacy of antiretroviral treatment in resource-poor countries. *Lancet Infect Dis* 2006; **6:** 53–59.
2 WHO. What's new in the revised ART guidelines for adults and adolescents? http://www.who.int/hiv/mediacentre/fs_2006guidelines_art/en/ (accessed May 22, 2006).
3 Bunnell R, Ekwaru JP, Solberg P, et al. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. *AIDS* 2006; **20:** 85–92.
4 Kalebu P, DART Trial Team. 48 week virological response to a triple nucleoside/nucleotide analogue regimen in adults with HIV infection in Africa within the DART trial. 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment; Rio de Janeiro, Brazil; July 24–27, 2005.
5 Kantor R. Evolution of resistance to drugs in HIV-1-infected patients failing antiretroviral therapy. *AIDS* 2004; **18:** 1503–11.
6 Department of Health Services, USA. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Department of Health and Human Services, 2005.
7 Colebunders R, Moses K, Laurence J, et al. First line antiretroviral therapy in Africa: how evidenced based are our recommendations? *AIDS Rev* 2005; **7:** 148–54.
8 Ivers LC, Kendrick D, Doucette K. Efficacy of antiretroviral therapy programs in resource-poor settings: a meta-analysis of the published literature. *Clin Infect Dis* 2005; **41:** 217–24.
9 Whitworth JA, Hewitt KA. Effect of malaria on HIV-1 progression and transmission. *Lancet* 2005; **365:** 196–97.

Meticillin-resistant *Staphylococcus aureus* in rural Asia

Emma Nickerson and colleagues' recommendations[1] to identify workable surveillance and control strategies against meticillin-resistant *Staphylococcus aureus* (MRSA) infection in rural Asia are correct. Prospective activities must address the role of the private sector in health care in otherwise poor populations. Non-governmental organisations involved in health and private care providers are a large and increasing entity. Private health workers would be available in places where there is no public sector support.[2] The recent dissatisfaction with public providers in China is driving poor patients to private providers.[3] Traditional microbiology or molecular biology laboratories are not usually available in private health-care centres in Asia. Thus, funds must be spared at a global level to develop standardised, simpler laboratory tests for MRSA detection. An exemplary protocol is the use of a disk diffusion method using cefoxitin disks. This method gives results that are comparable to PCR for the *mecA* gene.[4]

MRSA screening with the cefoxitin disk diffusion protocol[4] has been operational at a private sector tertiary care hospital in Delhi, India, since Sept 2004. The 140 bed multispecialty hospital caters to a population in the metropolis and adjoining townships. There were seven MRSA patients during Sept–Oct 2004. During May 2005, three cases were identified in the intensive care unit of the hospital. Dialogue between clinical microbiologists and clinicians ensured a switch from betalactam to non-betalactam antimicrobials. The first patient was a 70-year-old man hospitalised with cerebral infarction, benign prostate hyperplasia, and urinary tract infection. He developed MRSA pneumonia. A switch from an aminoglycoside and cephalopsporin combination to the quinolone ofloxacin led to an effective response and significant clinical improvement. The second patient was a 50-year-old man admitted with haemorrhage in the left basal ganglion. During his stay he underwent craniotomy with haematoma evacuation, and developed MRSA septicaemia. The patient was switched from treatment with an aminoglycoside/cephalosporin combination to treatment with the glycopeptide vancomycin, resulting in recovery. The third patient was a 77-year-old man admitted with a fracture of the neck of femur, diabetes mellitus, chronic renal failure, and acute coronary insufficiency. He developed MRSA pneumonia and modification of his treatment from cephalosporins to vancomycin was associated with recovery. All three patients recovered from their MRSA infection before discharge from the hospital.

Irrespective of the genetic characters of MRSA in rural Asia,[1] simplified assay procedures like the cefoxitin disk would be of benefit. Workable MRSA control strategies in Asian countries[1] would have to be coupled with clinicians. Coordinated discussion with clinicians with regard to rational chemotherapy should aid in better outcomes in MRSA cases, even from private health providers.

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1 Nickerson EK, Wuthiekanum V, Day NP, Chaowagul W, Peacock SJ. Meticillin-resistant *Staphylococcus aureus* in rural Asia. *Lancet Infect Dis* 2006; **6:** 70–71.