mutations remained raised as late as 6 years after treatment was stopped.

Should one be alarmed by the persistently high frequencies of *HPRT* mutations in this study? We do not think so. First, although often used as a marker for mutagenicity, the frequency of *HPRT* somatic mutations has not been linked directly to the risk of cancer. Second, use of mutations in *HPRT*—chosen because of its ability to cause a selectable phenotype (thiopurine resistance) ex vivo, in a group of patients exposed to chronic thiopurines in vivo—is vulnerable to the possible bias that *HPRT* (rather than other genes) could be particularly susceptible to mutagenesis, as acknowledged by Rice and colleagues.[3] Our previous analysis in children with acute lymphoblastic leukaemia showed no effect of chemotherapy on the frequency of *HPRT* deletions or on balanced translocations, with direct PCR assays that were not dependent on selection of thiopurine-resistance for mutation detection.[4] As also shown by Rice, the frequency was similar between patients who did or did not receive topoisomerase II inhibitors and alkylating agents.[4] Third, Rice and colleagues have raised the concern that children might be more susceptible to the genetic and cellular consequences of genotoxic agents. Actually, with the possible exception of neonates, young children have much greater clearance of cytotoxic agents than do older children or adults.[5] Moreover, clinical epidemiological data have, with few exceptions,[6] found no association between age and secondary cancer risk.[7] Some of the highest risks of secondary leukaemia have been reported in adults.[7] Based on past experience with similar treatment regimens, we would predict that few, if any, patients treated with the regimens described in Rice's article will develop secondary cancers.

The search for sensitive and specific predictors of the development of therapy-related cancers has been elusive. At one time or another, cumulative drug dose, treatment schedule, and co-administration of other antineoplastic agents, haemopoietic growth factors, or radiation have all been shown to increase the risk of therapy-related leukaemia.[7] More recently, advances in pharmacogenomics and molecular genetics have led to the identification of polymorphisms of genes encoding certain drug-metabolising enzymes, such as thiopurine methyltransferase, glutathione S-transferase, and cytochrome P450s, and defective DNA mismatch-repair as host risk-factors for the development of therapy-related leukaemia (figure).[8,9] Not surprisingly, none of these factors has shown absolute sensitivity or specificity as a predictor of genotoxicity, emphasising that multiple host-factors probably predispose to the development of this complication. A recent promising approach is the use of gene expression microarray analysis to do genome-wide searches for possible host genetic risk-factors. In an earlier study, we identified a gene expression profile that predicted the development of therapy-related acute myeloid leukaemia.[10] Our further analysis refined the search to a group of genes that included transcription factors, cyclins, and those involved in haemopoietic differentiation or leukaemogenesis. This finding provides a novel set of targets that could be used in assessing the germline predisposition to leukaemogenesis. But are we any closer to finding a combination of risk factors that will predict a future carcinogenic event with certainty? Only time will tell.

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The Global Fund's principal recipients . . . or neglected partners

The Global Fund to fight AIDS, Tuberculosis and Malaria recently released a progress report for its first 30 months.[1] The Fund has made pledges of US$5·4 million through 2008, and has committed $3·1 billion to almost 300 2-year programmes in nearly 130 countries, over four rounds of grants, and is on schedule to disburse nearly $1 billion to over 200 programmes by the end of 2004. However, the Fund must ensure the quick, efficient, and effective use of

these resources to stem the suffering caused by the three diseases.

The Fund's second significant achievement has been "the pioneering of a number of innovative structures to ensure country ownership, speedy and light-handed oversight, and performance-based funding . . . [of] Country Coordinating Mechanisms (CCMs), a variety of recipient structures, Local Fund Agents, and monitoring and evaluations systems." Unfortunately, the linchpin organisations in this management, the principal recipients, are being neglected and undervalued by the Fund secretariat, the CCMs, UN agencies, and donors. Principal recipients must be supported if the Fund is to be highly successful.

The Fund explains the role and responsibility of the principal recipients as: "The principal recipient is legally responsible for local implementation of the grant, including oversight of sub-recipients of grant funds and communications with the Country Coordinating Mechanism on grant progress."[2] The Fund has therefore clearly assigned the executive role to principal recipients and hence the legal responsibility for the funds and for achieving results. Principal recipients are in the unenviable position of being responsible for funds and results, yet have little or no control over the achievement of the expected results because most often activities are undertaken by subrecipients. If a country does not perform satisfactorily, it is the principal recipient that is informed by the Fund and that is responsible for the country's performance. Principal recipients have become the centre of international criticism for slow or non-performance, and have jeopardised their institutional future with little support from those who should be their allies, including the Fund secretariat. The reality is that once confirmed in its role, the principal recipient may be left to its own devices, without direct support from the secretariat or development partners. Despite their crucial role, principal recipients seem to be an afterthought for the Fund secretariat, overshadowed in attention and promotion by the CCMs and the technical review committee.

In the first rounds of funding the secretariat often chose the UN Development Programme as the principal recipient. Increasingly, and especially in Latin America, the Fund has sought national organisations to become principal recipients. The Fund promotes local organisations over international ones, with the laudable goals of developing local capacity and promoting local ownership.

Once named as principal recipient, national organisations may face several difficulties. National organisations are easy whipping posts for those looking to criticise the Fund's performance. Principal recipients are often portrayed as lumbering feet-dragging bureaucrats and middlemen who do nothing useful, but slow down the disbursement of funds and procurement of medications, and charge for the pleasure. The stress on national principal recipients can be

tremendous, creating an enormous emotional drain on small or young organisations. This pressure can become great enough to cause nominated national recipients to withdraw their candidacy, as was the case with the Corporación Kirimina in Ecuador (Quevedo M, Quito, Ecuador, personal communication). The Fund secretariat is in a difficult situation, trapped between a need to quickly disperse desperately needed funds and the goal of providing for country-led management and local capacity-building. But it can and should do more to actively strengthen and support local principal recipients.

When the Fund secretariat confirmed NicaSalud (a local federation of non-governmental organisations) as principal recipient for the three projects in Nicaragua, NicaSalud realised that it needed support for the international procurement of medicines. NicaSalud was without funds to hire the needed expert. It sent requests to 12 representatives of bilateral and multilateral donors and UN agencies in Nicaragua, requesting $21 000 to hire a consultant to prepare the institutional analysis, procurement plan, and training to handle the procurement contemplated under the Global Fund activities. Of the 12 requests, NicaSalud received one potentially positive telephone call, two negative telephoned replies, and five written negative responses. The reason most often given for the negative responses was that the activity was unplanned, and that although they did have

funds to support the Global Fund, that support was targeted at the CCMs and specific groups, not at the principal recipient. In the end, NicaSalud borrowed the funds from another project, hired the consultant, and submitted a procurement plan that was reviewed and approved by the local fund agent. 2 months later NicaSalud signed three agreements with the Fund.

The pressure can be intense. For example, the Agua Buena Human Rights Association criticised NicaSalud for its "bureaucracy" and questioned its effectiveness.[3] Another, more generalised comment comes from AIDSPAN: "a real and widespread problem, which is that once the Global Fund sends grant money to a Principal Recipient (PR), it sometimes takes months for the PR to move that money to the organisations that are actually doing the work."[4] At these moments of intense public pressure the principal recipients are usually alone, and defended by no one in the arena of public opinion.

The Fund is an ongoing experiment; the activities and results blossoming around the world. The Fund secretariat, donors and multilateral agencies, advocacy groups, and the CCMs need to make a fresh analysis of the role of principal recipients that should lead to valuing and supporting them as well as an appreciation of their difficult role.

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Until May 15, 2004, I was Executive Director of NicaSalud, a federation of 26 NGOs that is principal recipient for three Global Fund projects in Nicaragua. I was financed by the Global Fund to visit the principal recipient in Peru and attend the regional Global Fund meeting in Panama in November, 2003.
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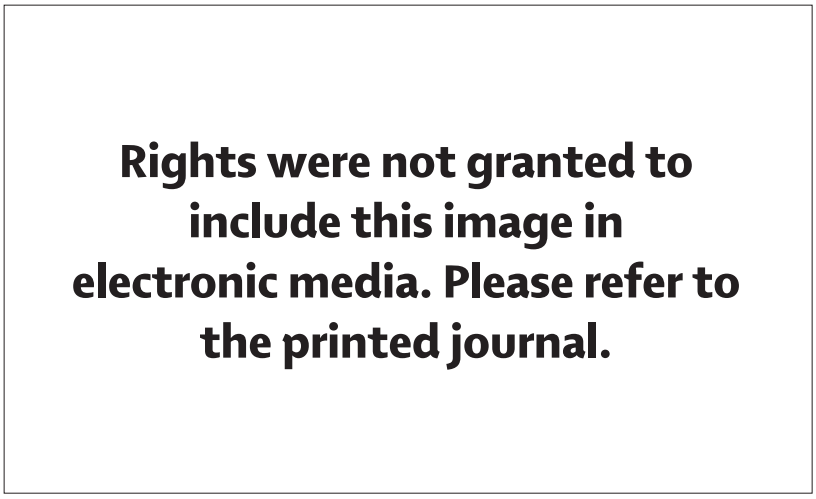
Standards of care in the antiretroviral rollout world

The Institute of Medicine recently emphasised the need to scale-up treatment for the global AIDS pandemic.[1] However, whereas national HIV antiretroviral rollout programmes offer a beacon of hope to millions of people, they are also beginning to pose ethical challenges to investigators involved in HIV research. On July 25, 2004, the South African AIDS advocacy group, the Treatment Action Campaign, highlighted discrepancies in the country's antiretroviral roll-out programme at district, provincial, and national levels.[2] This pattern will probably be mirrored in other countries when they implement national antiretroviral rollout programmes. However, differing standards of care within a country's public-health sector raise ethical dilemmas about what standard of care should apply to HIV studies in countries rolling-out antiretroviral drugs. Do standard-of-care provisions in international ethics guidelines for clinical trials apply to observational research? Does a standard of care become established as soon as an intervention is available, at any point, in the public-health sector? Is availability determined by theoretical access to the intervention or by how many people are actually accessing the intervention at a particular level in the rollout programme? UNAIDS,[3] WHO,[4] and the Institute of Medicine[1] offer no guidance on these issues.



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Guideline 29 of the Helsinki Declaration[5] and guideline 11 from the Council for International Organizations of Medical Sciences' (CIOMS) guidelines[6]—which offer ethical guidance on applicable standards of care in clinical trials that test the efficacy of a new method or intervention—do not explicitly govern observational research that does not involve a control group. Thus even if investigators involved in observational HIV research not including a control group do manage to secure antiretroviral funding for their research participants, there is currently no clarity or consensus on what standard of care should apply to their study in the context of a current or imminent governmental antiretroviral rollout programme. Non-governmental rollout initiatives should not be taken into account in determining standard of care because their outreach is often limited and their sustainability question-