

## Correspondence

## Reassurance: Medically Unexplained Physical Symptoms

**Bill Anderson**

Escobar et al.'s discussion of medically unexplained physical symptoms is useful, and could trigger a renewal of how the medical profession works [1]. We are in transition at the present, and what we have been trained for is less and less relevant. This disjunction between our training and practise has given rise to a generation of unhappy doctors.

The traditional "doctor" dealt with symptoms and illnesses for which there was no useful explanation and became expert in managing these. We have completed a century or more of science and pathology and have trained doctors to derive their interventions from an (often cursory) consideration of the patient's illness and the application of reason within this scientific framework, in the unshakable belief that this strategy gave the best and at times the only possibility of assisting the patient in a meaningful way. The practical effects of such practices were rarely if ever examined. This approach had many successes but lots of failures, and we have moved on. We now have built upon the science a growing evidence base which to date principally addresses disease states (pathological processes) rather than illnesses (patients' experiences).

There is however no reason why evidence-based approaches cannot be applied to the management of symptoms and illness as well as disease states. As we develop that evidence base, the nature of clinicians can change. We will not require all "doctors," for want of a better word, to be comprehensively trained in bioscience. There will be more need for them to deploy skills in implementing well-developed, evidence-based interventions and fitting them to the illness the patient is experiencing. Such "doctors" will deliver most care and pay better attention to the patient's symptoms and illness than we do today. We will of course require another different sort of "doctor" who will do the research and the sifting to develop the evidence base upon which therapies will become universally dependent. ■

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## Multidrug-Resistant TB in the Philippines: Totem and Taboo

**Jose Luis Portero, Maria Rubio**

Tupasi et al. [1] show the feasibility and cost-effectiveness of treating multidrug-resistant tuberculosis (MDR-TB) in a resource-limited setting. These conclusions could lead to error since the tertiary hospital where the pilot project was carried out is not representative of the average health-care setting available for the Filipino tuberculosis patient.

Resch et al. [2] highlight that this analysis is not an independent evaluation and that the intervention was set in ideal conditions. In the field, this pilot project will find serious difficulties in implementation within the government-run Filipino National Tuberculosis Program (NTP), where the majority of tuberculosis patients are diagnosed and treated. Moreover, in recent years Filipino tuberculosis health policy has not supported the development of capacities for mycobacteria culture and susceptibility tests in the public regional laboratories, missing the opportunity to strengthen competence on tuberculosis resistance management in the whole country. Taking into account the geography (an archipelago) and the structure of the NTP, a community-based pilot project carried out by the governmental health centers closer to the patients would have been more appropriate to study the feasibility and the real cost-effectiveness in a resource-limited setting.

The selection of 118 patients out of 171 eligible may bias the final results increasing the cure rate, since the most difficult patients to treat, by any circumstance, are also more problematic to enroll. A long-term follow-up of the patients may modify the final cure rate. It would have been important to analyze if any failure patient developed further resistances during the treatment, and the related public health implications, as well as a more in-depth discussion of the resistance patterns and its relationship with the tailored treatment and the final outcome. Identification of independent variables linked with favorable outcome are needed to design future strategies. On the other hand, the absence of data about the HIV status of the patients is remarkable, considering the ideal conditions of the study and the increasing number of cases in the Philippines.

Cost-effectiveness analysis may be holistic and may contemplate the MDR-TB control program with the rest of the activities of the NTP in order to evaluate the convenience and priority of each intervention. Unfortunately, the study does not support comprehensible strategies to control MDR-TB in the community. Patients, families, social activists, and health personnel related to tuberculosis control can offer important points of view. A larger consensus may avoid the switch of MDR-TB control from taboo to totem. ■

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2. Resch SC, Salomon JA, Murray M, Weinstein MC (2006) Cost-effectiveness of treating multidrug-resistant tuberculosis. *PLoS Med* 3: e241. doi:10.1371/journal.pmed.0030241

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## Multidrug-Resistant TB in the Philippines: Authors' Reply

The comments of Garner et al. [1] and Portero and Rubio [2] on our article, "Feasibility and Cost-Effectiveness of Treating Multidrug-Resistant Tuberculosis: A Cohort Study in the Philippines" [3] warrant a response. This reply is written on behalf of all authors of the original article.

Garner et al. focus on four issues: 1) lack of independence because of author affiliations and financial support from the Global Fund to fight AIDS, TB and Malaria (GFATM); 2) whether results can be replicated beyond the pilot project that was studied; 3) the need to pay attention to health system capacity; and 4) financial sustainability. Portero and Rubio state that Makati Medical Center (MMC) is a tertiary institution operating under "ideal" conditions not typical of other health facilities, and that lack of attention to building laboratory capacity may hinder service expansion. They also argue that a community-based care approach should have been studied at the pilot stage.

The standard methods used for statistical analysis and economic evaluation in our study [4–6], a rigorous peer-review process, and the application of previously established methods for the evaluation of multidrug-resistant tuberculosis (MDR-TB) treatment [7] provide for objectivity in the results that are reported. We strongly disagree with the insinuation that the participation of the World Health Organization or funding from the GFATM biased either the analysis or the way in which results were reported.

Pilot projects are often an important first step in implementing and evaluating new interventions. At the same time, it is well recognized that results can be different when services are scaled up. We agree that care is required when interpreting results from pilot projects, and that evaluation of MDR-TB treatment when implemented at a larger scale is necessary. Our article identifies the factors that we believe need to be replicated if results are to be reproduced elsewhere. In the meantime, it is important to highlight that while housed in a tertiary facility, the project was based in an outpatient clinic; that the cost-effectiveness results are consistent with those for a national programme in Peru [7]; and that community-based care is now available. Since 2004, patients have been treated at their local public health centre, which has helped to increase cure rates and reduce default rates compared to those observed during the study period [8].

We agree that health system capacity should be considered when new interventions are implemented. In the Philippines, expansion of MDR-TB treatment has been planned such that treatment sites will typically manage one to three patients at any given time. Decentralization of services to a larger

number of treatment sites is helping to integrate MDR-TB treatment into existing TB treatment services provided at primary health-care level, while increasing accessibility for patients. Treatment sites will be overseen by larger treatment centres, selected according to various criteria including their capacity and willingness to take on additional responsibilities. Laboratory and human resource capacity are being enhanced at treatment centres and treatment sites, just as capacity was enhanced at MMC during the pilot phase. Such costs (including infrastructure and training) were included in our cost-effectiveness analysis, and Garner et al. are incorrect when they state that they were not. All resources used in the start-up and implementation phases of the project were costed, in line with standard guidelines [4].

It is true that most of the current funding for MDR-TB treatment is from the GFATM. However, the government has provided additional funds for TB control, including MDR-TB treatment, since 2005. Funding for the treatment of new drug-susceptible cases has not been reduced. This demonstrates that MDR-TB treatment can be provided without compromising basic tuberculosis control. Indeed, some of the investments needed for expansion of MDR-TB treatment, such as building laboratory capacity, may strengthen the health system as a whole.

Regarding more specific criticisms [2], the lack of HIV testing and long-term follow-up are acknowledged in our article (though HIV prevalence remains low, at less than 0.1%) [9]. We specifically compared patients who were enrolled with patients who were eligible but not enrolled. The two groups were similar, except that enrolled cases had more, rather than less, severe patterns of drug resistance. Results are referred to in our article and reported in supplementary material. As reported in our article, we analyzed the relationship between several variables and treatment outcomes; the only statistically significant result was that women appeared more likely to be cured than men. Also, contrary to the claim made by Portero and Rubio, Resch et al. made no suggestion that our study lacked independence [10].

In conclusion, the overall goal of our study was to contribute to the evidence base on the management of MDR-TB in low- and middle-income countries. We support the development and implementation of evidence-based management strategies for all TB patients. ■

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## HIV-1 Viral Load Assays for Resource-Limited Settings: Clades Matter

Wolfgang Preiser, Jan Felix Drexler, Christian Drosten

The paper by Fiscus et al. [1] gives an excellent overview of current technologies to measure HIV-1 viral load (VL), and highlights the problems with finding assays that, whilst affordable and practicable, provide reliable and high-quality results to guide patient management in resource-constrained settings.

One concern, which in our mind does not receive enough attention in the paper, is HIV variability. The assays' ability to reliably quantitate non-B HIV-1 subtypes and strains is of paramount importance, given the predominance of non-B HIV infections in developing countries [2]. Unfortunately, genotype bias has not been assessed systematically for most of the assays described in the paper.

In our recent paper, "Ultrasensitive Monitoring of HIV-1 Viral Load by a Low-Cost Real-Time Reverse Transcription-PCR Assay with Internal Control for the 5' Long Terminal Repeat Domain" [3] (which is found by Fiscus et al.'s PubMed search strategy for "HIV-1 viral load AND resource-limited settings" but presumably just missed the deadline for [1]), we describe an inexpensive assay targeting the conserved long terminal repeat (LTR) domain of HIV-1.

In addition to comparing the assay with three commercial tests using patient samples from Brazil, South Africa, India, and Germany, we also extensively determined its ability to accurately quantitate different HIV-1 subtypes. For this we used two HIV-1 subtype reference panels (National Institute for Biological Standards and Control: HIV-1 M subtypes A, B, C, D, circulating recombinant form [CRF] AE, F, G, H, and HIV-1 N and O; German National Reference Centre for Retroviruses: HIV-1 M subtypes A, B, C, D [2 samples], CRF AE, F, G, and HIV-1 O [2 samples]), as well as 12 plasma samples from patients infected with non-B subtypes, including genotypes not present in the reference panels, e.g., CRFs AE and AG and subtype J, as determined by sequence analysis.

We demonstrated that LTR is highly suitable for the quantification of "exotic" HIV-1 genotypes: For all genotypes,

except for groups N and O, the overall results of virus quantification using different assays were highly concordant. For HIV-1 M clades and CRFs, the differences between our assay and the Roche Monitor assay were below 0.5 log; this excellent comparability between the assays is clinically acceptable. The reduced risk of genotype bias makes monitoring of HIV-1 VL feasible, to improve individual patient management as well as hopefully delay the emergence and spread of antiretroviral drug resistance.

Our test is at least as good as commercial tests with regard to performance and technical features: The internal control allows recognition of inhibition and thus falsely low or negative results; its accuracy at least equals that of commercial assays; its analytical sensitivity (down to 32 copies/ml according to industry-agreed evaluation procedures including probit analysis) and broad quantification range are sufficient for both treated and untreated patients; and it is much cheaper than comparable commercial assays—less than US\$10 for reagents per sample and below US\$20, including the service licence payable to Roche. Its only disadvantage is that it still requires relatively expensive equipment, a certain infrastructure, and skilled personnel. Large-scale feasibility studies have commenced in Brazil, and Stellenbosch University in South Africa is going to set up the assay for viral load testing.

Given the large and sadly still rapidly increasing populations of HIV-1-infected individuals in many resource-constrained countries, together with the drive to provide universal access to antiretroviral treatment and the looming danger of antiretroviral drug resistance as a significant public health problem jeopardising the success of antiretroviral treatment programmes [4,5], the potential benefit of affordable HIV-1 VL assays is enormous. The challenge lies in ensuring that these assays are adequate for the respective situation, particularly with regard to HIV-1 strain diversity. ■

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## HIV-1 Viral Load Assays for Resource-Limited Settings: Authors' Reply

We thank Drs. Preiser, Drexler, and Drosten for their letter [1] and share their concerns regarding HIV-1 viral load assays in resource-limited settings. The real-time RT-PCR (reverse-transcriptase polymerase chain reaction) assay they have developed had not yet been published when our review was submitted or revised. As noted in Table 1 of our review, many of the current viral load assays require additional evaluation with different subtypes and others may underestimate non-B subtypes. In addition, under the heading "What is needed for implementation of simplified viral load testing?" we state "First, each country must determine if the assay will quantify subtypes common in the region and is appropriate for the technical staff and laboratory equipment available."

In-house assays require production, optimization, validation, and quality assurance of all reagents, which is challenging in any circumstances, and would be extremely difficult in laboratories in most resource-limited settings. Real-time PCR instruments are expensive and maintenance in many places would be a problem. What is really needed is a technologically much simpler, much less expensive, perhaps semi-quantitative assay for measuring viral load. ■

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## Enrolling Adolescents in Research on HIV: Young Women Must Be Included

Alana de Kock, Stephanie Skoler, Khatija Ahmed, Sumen Govender

As researchers managing an HIV prevention microbicide trial, which takes place across three provinces, we would like to commend Singh et al. for their informative article on the need to include adolescent women in HIV prevention trials [1]. This commendation is based on our clinical trial experience where we have enrolled 16- and 17-year-old women and are actively continuing with their follow-up.

In our study, we include these young women, who are often those at highest risk for HIV infection, for several reasons. Most notable among these are:

(1) All participants in HIV prevention trials (regardless of the arm to which they are randomised) have a reduced risk of HIV infection, due to the intervention of preventive counselling and education that is ethically required for participants in such trials. In addition, access to sexually transmitted infection (STI) diagnosis and treatment and referrals for partner treatment while in the clinical trial further serves to reduce risk factors for HIV infection and STI re-infection.

(2) These young women are sexually active and at risk, and form part of the end-user constituency for a proven microbicide. This sexual activity is evidenced by statistics from the Human Sciences Research Council for 2005 for South Africa, which show that the prevalence of HIV in the 15- to 34-year-old group is 20%. Furthermore, the Children's Bill passed in June 2005 [2] says that young women can have access to contraception from the age of 12 years without parental consent. It is thus ethically imperative that young women should be included in the testing of such products.

(3) Including those currently at greatest risk for infection ensures that the study will be able to detect the efficacy of the intervention.

It is clear that both the participants and the research question benefit from the inclusion of younger women in communities where HIV risk is high and education, counselling, and new prevention technologies are needed.

Younger women are most at risk when it comes to sexual transmission of HIV [3]. Clinical HIV prevention trials provide an environment where confidentiality can be maintained and where young women can be educated on methods to protect themselves in a confidential and consistent manner through trial participation. Thus, the inclusion of young women in such trials is an opportunity to empower the younger generation of young women across communities. To deny that these young women are sexually active would be to turn a blind eye to an important epicentre of the epidemic, and counterproductive to the HIV prevention research agenda.

The age of consent for adolescent participation in clinical trials without obtaining legal guardian/parental support is a major factor that complicates their involvement in HIV prevention trials and other health-care research. The requirement for parental consent that often accompanies the ethical approval process of most studies is at times an insurmountable barrier and distances the young women that require this type of intervention from securing access to these potential prevention options. As Singh et al. point out, there are many salient reasons why adolescents can and should be considered capable of giving informed consent without parental assent or approval.

Researchers must continue to work in collaboration with local and scientific communities, ethics committees, and policy makers to ensure that the need for the participation of young women in HIV prevention trials is understood. It would seem then that both researchers and ethicists should work with actual examples of ethical research activities that include adolescents without parental involvement, in order to develop guidelines for adolescent research in the field of HIV that are both protective and practical. ■

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## HIV-1 Subtype and Reverse Transcriptase Genotype: Role for Geographical Location and Founder Effects

Akinyemi I. Ojesina, Phyllis J. Kanki

In a previous issue of *PLoS Medicine*, Kantor et al. [1] published very impressive results from an international multicenter collaboration in which they reported significant overlap between subtype B drug resistance mutations and mutations associated with at least one non-B isolate in HIV-1 reverse transcriptase (RT) and protease. This information is very useful for planning large-scale global surveys for antiretroviral drug resistance.

The authors described subtype-specific polymorphisms as mutations that were significantly more prevalent in each non-B subtype than in subtype B viruses from untreated persons. Amongst these was an A98S mutation in HIV-1 reverse transcriptase, which was described as a subtype G-specific polymorphism.

In Nigeria, the predominant variants of HIV-1 are the circulating recombinant form CRF02\_AG and subtype G. The 98S polymorphism was not found in 35 of 35 sequences obtained from a group of HIV-1-infected drug-naïve Nigerians, and the consensus at this position was A98 [2].

Kantor et al. [1; Table 1 and Figure 4] describe how 207 out of 294 (70%) of the subtype G samples were obtained from Portugal and Spain, while approximately half of the subtype G samples had polymorphisms (with respect to subtype B consensus) at RT position 98. We hypothesized that a significant correlation exists between the samples from Portugal and Spain and the presence of the A98S polymorphism in HIV-1 reverse transcriptase reported by the authors. It is however possible that this polymorphism is similarly prevalent in subtype G sequences from other countries.

We therefore interrogated the Stanford HIV Drug Resistance Database [3], where the updated results from this international collaboration maintain detailed RT mutation data for subtype G isolates. The output has detailed information on GenBank accession numbers and publication data, from which we deduced the country of sampling. In all, amino acid residue information for RT position 98 was available for 500 subtype G isolates from both drug-naïve and treated persons: 351 isolates (70%) with the A98S polymorphism, 143 isolates (29%) with the wild type A98A residue, and six isolates (1%) with the A98G mutation.

In order to determine if A98S is a subtype G-specific polymorphism, only the 165 isolates obtained from drug-naïve persons with either A98S or A98A were used in this analysis. 57 (34.5%) of these selected isolates were from Portugal and Spain. 51 (89.5%) of the isolates from Portugal and Spain had the A98S polymorphism, compared with only 10 (9.3%) of the 108 isolates from other countries combined. Therefore, a very strong association exists between the presence of the A98S polymorphism and sampling from Portugal and Spain ( $p$  is less than 0.0001). This suggests that the A98S polymorphism in HIV-1 subtype G is not subtype-specific, but may be the consensus amino acid residue for samples from Portugal and Spain. Indeed, this polymorphism has been previously reported as being unique to samples from these countries [4].

Considering that various HIV-1 variants have geographical bias [5], it is possible that patterns of subtype-specific polymorphisms may be differentially predominant in certain geographical locations with respect to others. The presence of specific mutations in drug-naïve individuals may influence decisions on the choice of therapeutic regimens [6]. Therefore, the description of subtype-specific polymorphisms without stratifying by geographical location, or controlling for the role of closely related founder viruses, may result in misleading generalizations. Examination of the role of the source of samples in multicenter studies may be pertinent in assigning the tag of subtype-specific polymorphisms, especially for HIV-1 variants with significant transcontinental distribution, for example, HIV-1 subtypes C and G. ■

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## Cost-Effective Control of Drug-Resistant TB: Listening to Other Voices

Jose Luis Portero, Maria Rubio

Drug-resistant tuberculosis is mainly a phenomenon caused by physicians, patients, and health-care systems through incorrect treatments, noncompliance, and poor delivery of tuberculosis services, respectively. These man-made facts could be avoided with appropriate actions. However, the weakness of health systems in the tuberculosis high-burden countries hampers successful control.

Public health priorities in resource-poor settings have marginalized tuberculosis cases resistant to first-line treatment. Nevertheless, patients have been claiming their rights to be treated despite their drug resistance pattern. Nowadays, tuberculosis programs try to address drug resistance issues. However, pilot experiences in low-resource settings do not fully answer to the real challenges in the field to scale up second-line drug treatments [1].

Governments from high-burden countries must enhance their commitments with their respective communities to provide better health and to alleviate poverty. Regarding drug-resistant tuberculosis control, these actions would improve organization and effectiveness in all levels of the tuberculosis programs to avoid misuse of resources. In addition, it is a must to address ignorance about tuberculosis transmission and treatment, social stigma, and discrimination. However, the current program design to control drug-resistant tuberculosis underestimates the environment of poverty suffered by the patients. In this sense, it is paradigmatic that one of the obstacles to following the treatment in the last pilot project published was that the patients were unable to buy symptomatic drugs to relieve the second-line drug side effects [2]. Governments, the World Health Organization, physicians, and technocrats must open their eyes to the reality in the field [3].

Unfortunately, we are far worldwide from a reliable system to fight drug-resistant tuberculosis. The complexity and requirements of treating resistant cases generally exceed the average available health care. In the other hand, the current cost of second-line anti-tuberculosis drugs is unbearable for the developing world and is a great obstacle to the scaling-up of the treatment. The cost of the drugs and the laboratory supplies is not appropriate for developing countries. No significant steps have been taken to put in practice a coordinated system to manage drug resistance in the community. Cost-effectiveness studies do not usually reflect the hidden costs for the patients and the real cost of the interventions in the present conditions. Feasibility measures do not take into account most of the socioeconomic barriers in the field.

There is a lack of independent opinions regarding drug-resistant tuberculosis, so the article by Resch et al. is very valuable [4]. Tuberculosis experts are in danger of listening only to their own words enclosed in a technocrat circle. It would be desirable to open tuberculosis control to civil society and to listen to other voices. ■

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