## Authors' Reply: Teaching Health Workers Malaria Diagnosis

With reference to the letter commenting on our paper [1] from Drakeley and colleagues [2], they have some justification in stating that one size does not fit all. However our Web site, which is the basis for their comment, was originally designed on a wholly voluntary basis for Australia. We have been overwhelmed by the interest and acceptance of this site worldwide. Not only have we had more than 750,000 visitors to the site but have issued free CD-ROMs to institutions in 149 countries.

The fact that it was warmly embraced by so many others from around the world bears testimony to its usefulness as, indeed, do the tens of thousands of letters and E-mails thanking us for our efforts. We have made some modifications on our annual update in response to suggestions and changes in approach. The main section of interest has been the section on diagnosis, testing, and teaching, and perhaps the reason for this is the high quality of the illustrations. One only has to look at the site to recognize that we have not given equal weight to all sections, as Drakeley and colleagues point out. The emphasis is on diagnosis, testing, and teaching. Many large organizations have requested a substantial number of copies of the CD-ROM, and in Germany one organization has been printing its own (with permission). We are aware of some superb CD-ROMs on malaria put out from other sources, but they are expensive for organizations with a very small budget.

We accept that diagnosis by thick film is the norm in Africa and a number of other countries and, in fact, have spent many years ourselves diagnosing malaria from thick films in India and Southeast Asia. We have described how to make thick films and have provided a picture. We have mentioned the staining of films, but we have not described how to prepare the stains because we considered that outside our brief. It is important with Web sites to be concise, otherwise they won't be read. The actual diagnosis of malaria is the same for Africa, India, South America, and Southeast Asia, and it is the proper diagnosis that we believe is paramount. We know that language can be a serious problem. We have provided a version in French and Spanish. The French version we are told is useful for certain parts of Africa. When other languages have been requested, we have suggested that a small booklet should be written in the local language by those with local knowledge.

In regards to the comments on treatment, this section was written by T. M. E. Davis, who holds the Chair of Medicine at the University of Western Australia and is a consultant on malaria to Thailand and Cambodia. If we sought an expert on treatment for every endemic region, we would never get the material into print. One is not always able to use the drugs of choice in Southeast Asia because up to 50% of antimalarials sold in some areas are fake. It has been stated that children should not be given tetracyclines, but that has already been made very clear on the site.

We are aware that the site needs to take into account various interests and situations, which is why we have included our E-mail addresses on the site. We presume that as experts in the field Drakeley and colleagues would have been aware of the site either in Tanzania or the London School of Tropical Medicine, where a number of CD-ROMs have been requested and sent. We hope and expect that eventually a group with the enthusiasm of these correspondents will accept the challenge and produce a site that will overcome the problems that are the cause of their concern. We fully understand the difficulty of doing this on a voluntary basis. In the meantime, we will continue to service the site and hope that the very large number of users will continue to find it helpful. Finally, we state once again that if concise suggestions for improvements are sent to us by E-mail we will give them serious consideration. Our E-mail contact is now sandy.treadgold@health.wa.gov.au. ■

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# Allocating Antiretrovirals in South Africa: Using Modeling to Determine Treatment Equity

**David P. Wilson, Sally M. Blower**

Recently *PLoS Medicine* published our paper entitled "Designing Equitable Antiretroviral Allocation Strategies in Resource-Constrained Countries" [1]. We were disappointed to find that the editorial perspective written by the World Health Organization (WHO) ethicists regarding our paper [2] was based upon a substantial misunderstanding of our novel quantitative analyses and our important results. Hence, they misunderstood the significance of the health-policy implications of our results. Thus, we wish to correct the record.

Firstly, Capron and Reis [2] misunderstood our quantitative analyses. They stated that "Wilson and Blower developed a mathematical model that could inform policy-makers' decisions regarding the optimal distribution of treatment sites to ensure equal access by all individuals infected with HIV." However, our model does not determine the optimal distribution of treatment sites. As we clearly state in our paper [1] (and is also stated in the synopsis [3]), we developed a model that policy makers can use to make decisions regarding how to achieve the optimal allocation of scarce antiretrovirals among the available health-care facilities (HCFs) if the objective is to ensure treatment equity. We also calculated how the optimal allocation of antiretrovirals would vary if the number of HCFs utilized increased and/or the size

of the catchment area that each HCF services increased [1]. Thus, we took the treatment sites (i.e., HCFs) as given, and we used their specific spatial location in South Africa as inputs to our model in order to determine optimal antiretroviral allocation strategies under a variety of conditions.

Secondly, Capron and Reis [2] misunderstood our important results. They stated that "applying this tool to the South-African province of KwaZulu–Natal, Wilson and Blower were able to confirm mathematically the intuitive assumption that using a maximum number of centers, at the least possible distance from most affected populations, would lead to the greatest fairness in the geographical distribution of ART [antiretroviral therapy]." We agree that if these had been our results, they would have been trivial and obvious. However, Capron and Reis [2] did not discuss our actual results: we determined how to decide how many drugs to allocate to each of the available HCFs in order to achieve an optimal allocation if the objective is to ensure treatment equity. This is a very complex problem and the antiretroviral allocation strategies that we calculated (by using our model) to be optimal are very complex (see Figure 3 in our paper, which graphically shows the proportion of drugs that should be allocated to each of the available HCFs). Furthermore, we also determined what catchment area each HCF should service; specifically, we calculated that each HCF should serve (if the objective is to achieve treatment equity) a catchment area of 40–60 km. Thus, our results demonstrate (to our knowledge for the first time) that patients infected with HIV will have to travel extremely large distances (i.e., 40–60 km) in order to receive antiretrovirals, if the objective is to achieve treatment equity in South Africa. We stress that currently it is unknown what the actual size of the catchment area is around HCFs in South Africa. Catchment areas may in fact be very small. Thus, we suggested [1] that a primary goal should be to obtain empirical data of the distances that patients in South Africa are willing (or able) to travel in order to receive antiretrovirals. We have been the first to provide a quantitative assessment of the necessary size of the catchment area, and our results have identified that there is an urgent need to collect these critical data for quantifying the size of the catchment areas around HCFs. We have determined that the size of the catchment area will be a critical component in the ability to achieve treatment equity in South Africa. We also compared the optimal antiretroviral allocation strategies that we calculated with the current plan of the South African government for allocating antiretrovirals [4], and we determined that the current antiretroviral allocation strategies in South Africa will not achieve treatment equity. Taken together, our quantitative results are novel and controversial, providing important quantitative insights into a complex public-health problem.

We applaud the ambitious "3 by 5" WHO target for the antiretroviral rollout. However, the WHO has not yet devised a quantitative policy for determining how to allocate antiretrovirals in situations where the demand for drugs greatly exceeds the supply [5]. Health-policy officials in each country will have to make these important and difficult decisions, and they will all make different decisions based upon what objectives they wish to optimize and prioritize. There are a multitude of factors to consider (these factors are well described in the recent *Institute of Medicine* report [6]). We stress that the alternative to a quantitative rational approach for allocating scarce resources is an ad hoc approach, which is how the scarce supply of antiretrovirals is currently being distributed in many resource-constrained countries. Our operations research modeling approach is based upon spatial heterogeneity in the distribution of HCFs in South Africa and the spatial heterogeneity of the HIV-infected population. The most important "real world" result is that we show that what the South African government is currently doing is inequitable. We show them how to achieve equity, if they wish to do so. We hope that our novel approach for deciding how to allocate antiretrovirals will be of use to the WHO and also to the relevant authorities in the many resource-constrained countries who will soon have to make very difficult decisions as to who lives and who dies. Our analysis is to our knowledge the first analysis to show how a rational and scientific solution can be reached for deciding how to allocate a limited amount of antiretrovirals, if the goal is to achieve treatment equity. Clearly, other goals must be taken into consideration (and our model can be modified to include these other goals); however, we hope that treatment equity will be a very high priority during the antiretroviral rollout that is just beginning. ■

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## Authors' Reply

In response to our commentary [1] on their paper, "Designing Equitable Antiretroviral Allocation Strategies in Resource-Constrained Countries" [2], Wilson and Blower assert that we misunderstood both their analysis and the importance of their results [3]. Rather than "setting the record straight," what may be needed is more effort to bridge the differences in disciplinary approach that create a greater appearance of disagreement than is actually the case.

On a factual level, we believe Wilson and Blower's results were appropriately described for the purposes of our commentary. As their letter points out, they applied the operations research methods to model the allocation of antiretrovirals (ARVs) among 17 health-care centers in KwaZulu–Natal, based on a hypothetical distribution of HIV/AIDS among the communities in that province. Their article characterizes this as "an elegant and simple theoretical framework," but they object to our concluding that it could "inform policy-makers' decisions regarding the location of HIV services," since they took the treatment sites as given. Yet their article compared the alternatives of using all 54 centers in the province, at one extreme, and of using only a single treatment site (in Durban), at the other extreme; in each case, the possibility of allocating to a larger number of centers is equivalent to the creation of additional centers closer to remote groups of patients.

Wilson and Blower write that geographic accessibility is improved if the number of health-care facilities is increased, and they calculated that it would be optimal if all 54 facilities in the province of KwaZulu–Natal distributed the medicines, instead of just 17. We took this result to confirm the need to reach out and build capacity. We are sorry if we were mistaken in assuming that Wilson and Blower would want to see their stated objective of ensuring fair distribution applied in the real-world context of many poor countries with a high HIV burden and where fairness in ARV care cannot be achieved solely by allocating resources among the existing sites.

A wider gap in perception can be seen in Wilson and Blower's repeated conflation of "optimal," "equal," and "equitable," combined with their suggestion that decision makers who fail to apply their model must be following an "ad hoc approach." The central point of our commentary was that various ethical theories reach very different conclusions about what result would be optimal, and that even among those aiming to achieve the greatest equity (rather than some other optimum), many would not take equality as the measure of equity. Wilson and Blower themselves recognize that apparent equality of access (in terms of distance to treatment) needs further study to determine whether patients can in fact access treatment. We need to know whether some distances are simply too far for patients to travel for chronic care, and when distances of equal length affect access very differently because of the characteristics of particular patient populations, transportation systems, and so forth.

Wilson and Blower seem unwilling to accept the notion that, in the furtherance of a rational strategy to achieve equity, some health authorities might decide, for example, to allocate a disproportionate share of ARVs to traditionally disadvantaged populations. Wilson and Blower's model could still be useful in allocating resources among the centers chosen (or established) to reach the target population, but the calculation would have to take account of more information about the centers and the population, lest assumptions about catchment areas produce a formal equality that does not translate into actual equality in access, much less into equitable access in light of all relevant factors.

Plainly, we share Wilson and Blower's aim of optimizing countries' responses to the tragedy of treatable, but untreated, HIV/AIDS. Any tools that are useful to that end are welcome. But besides using models to distribute ARVs in a way that optimizes spatial equality, governments that want to achieve equity will need also to overcome nongeographic barriers to accessing treatment. These include ignorance, stigma, discrimination, and outright criminalization of vulnerable groups, as well as fees at point of service that are prohibitive for the poor. All of these are given attention within the context of the "3 by 5" program of the World Health Organization and the United Nations Joint Programme on HIV/AIDS, including in the guidance document on equitable access to ARV treatment cited in our commentary [4]. ■

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## The Debate over Placebo-Controlled Trials

**Frankllin Miller**

Turner and Tramèr provide a cogent argument in favor of the ethical use of placebo controls despite "proven effective treatment" [1]. However, they are wide of the mark citing the APPROVe trial in support of their position. Because there is no established treatment to prevent adenomatous polyps, few commentators would have any objections to the use of placebo controls in this study. Nevertheless, they are right to suggest that it would have been desirable to have included a placebo control in the VIGOR study to provide a more rigorous assessment of safety. Whether, all things considered, a placebo control would have been ethical in this study of treatment for rheumatoid arthritis is debatable.

Another issue not discussed in this *PLoS Medicine* Debate is the value of placebo controls in early "proof of concept" efficacy trials, despite the existence of established treatment. The efficiency of seeking a rigorous efficacy signal before moving on to larger-scale trials (and exposing as few subjects as possible to drugs that might not work or turn out to be toxic) is a valid ethical reason for using placebo controls, provided subjects are not exposed to undue risks of harm from withholding established treatment [2]. ■