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Rational Choices for Allocating Antiretrovirals in Africa: Treatment Equity, Epidemiological Efficiency, and Feasibility

David P. Wilson, Sally M. Blower

We agree with the thesis of Rosen et al. [1] that, despite initiatives such as the World Health Organization's "3 by 5" program, rationing of HIV/AIDS antiretroviral therapy (ART) will be necessary in the majority of African countries. Difficult choices will need to be made, and choices will be constrained due to the limited health infrastructure and lack of qualified health personnel in many African countries. Rosen et al. outlined a number of useful rationing systems and selection criteria [1].

However, some of the strategies they suggest are unfortunately not feasible in practice. For example, targeting behavioral core groups (high-risk groups, e.g., female sex workers) may well be impossible as it is not always possible to identify behavioral core groups. Furthermore, once the prevalence of HIV becomes extremely high in the general population (as it already is in many African countries), the concept of a behavioral core group will be relatively meaningless.

Previously, it has been shown, by using mathematical modeling, that targeting a virologic core group for treatment could be a very effective public health strategy for controlling herpes epidemics [2]. Only relatively few of the individuals infected with herpes simplex virus type 2 (HSV-2) are high viral shedders, and these individuals constitute the virologic core group. These individuals disproportionately contribute to the HSV-2 incidence rate. Thus, treating only the relatively few individuals who constitute the virologic core group has been shown to have a substantial effect on reducing the incidence of herpes [2]. Such a public health strategy for controlling herpes epidemics would be feasible, as it would be possible to identify the high viral shedders (i.e., the virologic core group) [2]. Such a strategy would also ensure that relatively few drugs would be needed to achieve epidemic control.

We suggest that when considering how to ration antiretrovirals among individuals with HIV in Africa, instead of targeting behavioral core groups, HIV virologic core groups should be targeted. Individuals with HIV who constitute the HIV virologic core group would be easy to identify simply by measuring viral load. The virologic core group will be composed of individuals with a high viral load. These individuals would not only be people in the late stage of disease, but would also include recently infected individuals, who have a high viral set point. Targeting the HIV virological core group would have several advantages: it would increase treatment equity (as these individuals have the greatest need for treatment), it would be epidemiologically efficient, and it would also be feasible. Whereas targeting the HIV behavioral core group would decrease treatment equity, it may or may not be epidemiologically efficient and would not be feasible.

Treatment equity and epidemiological efficiency are likely to have very different weights in each African society. Previously, we have shown, by using operational research methodology, that it is possible to use mathematics to decide how to achieve treatment equity [3]. Thus, it is possible to devise a mathematically ethical solution to decide how to allocate a scarce supply of antiretrovirals if the objective is to achieve treatment equity [3]. We have shown that treatment equity is only possible in some areas of South Africa if each of the available health-care facilities treat individuals with HIV in a large catchment area (radius of approximately 40–60 km^2) [3]. Hence, in some African countries, it may be impossible to achieve treatment equity even if it is possible to achieve a rationing strategy that would ensure the maximum reduction of the epidemic. Therefore, government officials and health policy experts in each African country will have to decide the relative weight that they wish to place on treatment equity versus epidemiological efficiency when they decide how to ration their scarce supply of antiretrovirals. We also stress that when using mathematical models to evaluate any rationing strategy, single scenarios should not be used to make complex decisions. There is a large degree of variability in the parameters that define each strategy and a great deal of heterogeneity in how a given strategy will be implemented. Accordingly, we recommend that time-dependent uncertainty boundaries should always be presented in any analysis when modeling is being used for health policy decision making [4]. In addition, detailed time-sensitivity analyses should also be presented so that it is possible to evaluate the robustness of the results [4].

Finally, we would like to stress the tremendous value in preferentially making ART available to mothers with HIV (especially women who are pregnant or breast-feeding), both to prevent vertical transmission and to act as a therapeutic intervention for the mother. Not only would this rationing strategy reduce the burden of orphan support, but the treatment regimen is relatively cheap and is extremely effective in reducing transmission to infants and increasing the life expectancy of the mother. Therefore, we strongly recommend that no pregnant woman with HIV be overlooked in the rationing of ART. ■

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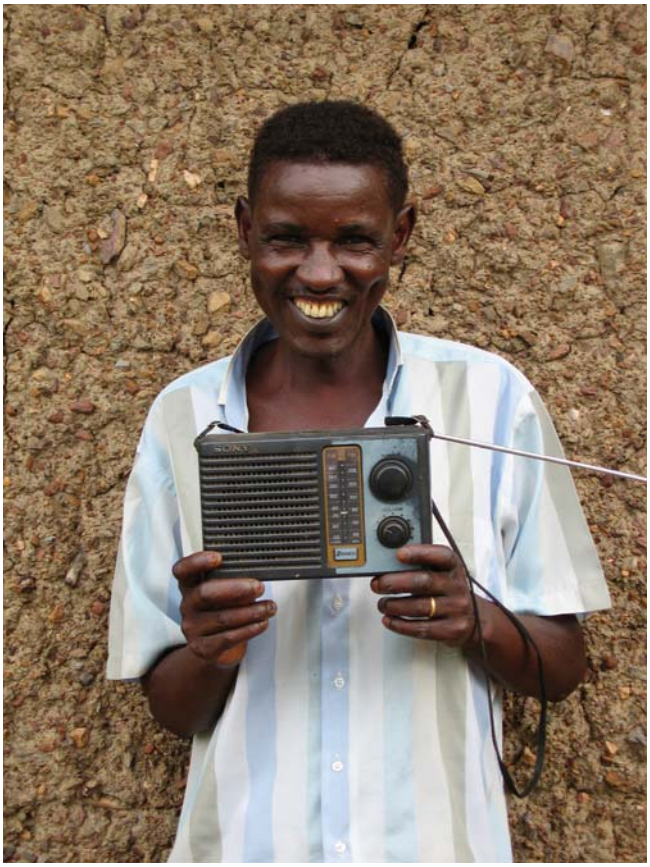
How to Take HIV Antiretroviral Medications on Time without a Watch in Rural Uganda

Marissa Maier, Mwebesa Bwana, Nneka Emenyonu, Larry Pepper, David R. Bangsberg

Castro has advocated that adherence to HIV antiretroviral therapy should be understood within a patient's clinical and social context [1]. Over 90% of worldwide HIV infection occurs in resource-limited settings [2]. Some have suggested that individuals living in extreme poverty may have difficulties with adherence to medication [3], including Andrew Natisios, who said Africans "don't know what Western time is" [4]. While recent reports suggest that adherence to HIV antiretroviral therapy in resource-limited settings may be as good as or better than resource-rich settings [5–7], the question remains: how do people take medications on time without a watch?

In rural western Uganda, there is, for example, a 40-year-old man who is HIV-positive, has no education, and works as a farmer. He lives with his brother, sister-in-law, and three nieces in a three-room, mud-walled house without electricity.



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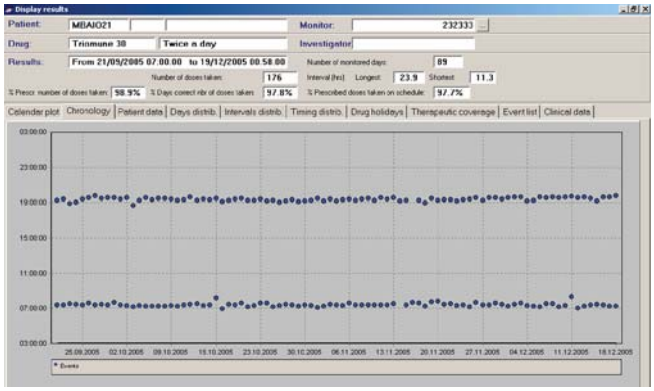
Patient with his radio



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Electronic medication monitor adherence record of time of bottle openings for morning and evening doses

He owns a lantern, a bed, a sofa, a bike, and a radio, but does not own a watch. He was diagnosed with HIV in April 2005 and started generic D4T/3TC/NVP (Triomune) four months after developing disseminated herpes zoster and Kaposi sarcoma with a CD4 count of 151. His adherence was measured with an electronic medication monitor that records a date-time stamp in flash memory each time the pill container is opened. Over the 89 days of monitored treatment, he had 98.9% adherence by electronic monitor and took 90% of prescribed doses within ten minutes of 7:20 a.m. and within 17 minutes of 7:20 p.m. When asked how he knew when to take his dose, he said that he knows it is time to take his medications by "listening to Radio West's 'News and Announcements' every morning and evening."

While population levels of adherence will likely drop as treatment access expands and people begin to experience toxicities of long-term therapy, he is an example of how patients can have precise, if not perfect, adherence with creative solutions in a resource-limited setting. ■

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Clinical Trials Registration

Frank W. Rockhold, Ronald L. Krall

We read with great interest the recent Policy Forum by Karmela Krleža-Jerić in *PLoS Medicine* on clinical trial registration [1]. GlaxoSmithKline (GSK) is committed to enhancing the transparency of clinical trial information through protocol registration and through registration of the results of clinical trials.

We are, therefore, disappointed that the article suggests the pharmaceutical industry is reluctant to embrace greater transparency and disclosure. In September 2004, GSK became the first company, and we believe the first trial sponsor, to establish a publicly available, Internet-based clinical trial register to provide results from all GSK-sponsored clinical trials of marketed medicines. The register currently has over 2,000 records, and there are now similar registers and databases across industry. Indeed, as Krleža-Jerić notes, in January 2005, industry made a commitment to disclose clinical trial information (summary protocol and results) on clinical trial registers and databases, which has been followed by a further position paper in September 2005. This latter position paper confirms industry's support for the agreement reached at the World Health Organization (WHO) Technical Consultation Meeting on Clinical Trials Registration Standards held on 25–27 April 2005. Moreover, industry has launched a clinical trial portal to enable and to facilitate access to clinical trial information.

The article focuses on the registration of clinical trial protocol information, and we agree that it is important to alert physicians and patients of the opportunity to participate in and to serve as a public record to ensure results are publicly disclosed. However, we are surprised that Krleža-Jerić makes little mention of results registration. It is registration of results (not summary protocol information) that helps to ensure that researchers, physicians, and others are aware of all the relevant information from clinical trials of medical interventions and can review the literature appropriately—it is this which can affect patient care.

With regard to registration of summary protocol information, we can appreciate that the discussion and debate around the WHO minimal dataset and the five data elements may have given the impression that industry is not embracing the concept of transparency and disclosure. However, industry has made the point about competitively sensitive information for a very good reason—that disclosure of one or more of these five data elements early in the process of drug development may undermine medicine development. The discovery and development of medicines is fundamental in the social contract that the pharmaceutical industry has with society, and undermining this contract is not in the interests of patients and society in general. Nonetheless, it is important to recognise that delay of one or more data elements will be by exception only. Industry will, whenever possible, disclose all 20 data elements in the WHO minimal dataset. GSK, for example, will only delay registration of one data element for some early phase (exploratory) trials, and that has to be approved by our Chief Medical Officer, Ronald Krall. All GSK-sponsored trials that, to use the International Committee of Medical Journal Editors (ICMJE) terminology, are "clinically directive" will be registered with all 20 data elements. The GSK approach is fully aligned with the ICMJE policy. Therefore, we do not believe that an escrow mechanism or another elaborate mechanism is required or justified for such a small number of data elements in such a small number of trials. We would, however, be concerned if in practice the frequency of delays was high. Therefore, a pragmatic way forward would be to review practice after 12–18 months to assess the extent of the issue (if any).

We hope these comments are helpful and constructive. We would be happy to discuss our views with the author in greater detail at any time if that would be helpful. ■

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Author's Reply

It is a great pleasure to read that GlaxoSmithKline (GSK) is committed to registering its trial protocols and results [1]. I am also happy to hear that GSK intends to disclose at least the 20 items of the World Health Organization (WHO) minimal dataset, and does not believe there is a need for escrow. What a great example!

However, GSK's own registry is not what I would describe as an unbiased registry. It is a good and convenient tool to have—for GSK—but trials should be registered in a neutral, unbiased registry such as ClinicalsTrials.gov, the International Standard Randomized Controlled Trial Number (ISRCTN) Registry, or the Australian Clinical Trials Registry (ACTR).

Such registration will be a great step forward, as previously GSK and many other companies have often provided

incomplete information to trial registries, when registering their trials. Following personal communication from D. Zarin at the time of the publication of my paper in *PLoS Medicine* [2], the National Institutes of Health (NIH) performed further analysis, and a paper was published in the *New England Journal of Medicine* [3]. This paper illustrates that even now—and despite medical journal editors' statements, WHO Guidelines, as well as other pressures such as the Ottawa Statement—industry inputs into ClinicalTrials.gov, which is the most often used trial registry, although improved, still leave much to be desired.

I disagree with Rockhold–Krall's statement regarding results versus protocol. Both are needed to ensure awareness of the relevant information for informed clinical decision making. I limited myself to protocol registration, because this is the first step that we need to take, and it has been much discussed lately. Without properly registered protocol information, we do not know the extent to which all the planned outcomes are reported or the nature and quality of the trial.

In other words, if we focus on results registration without knowing what was really studied, and thus not knowing which results were not reported, we are in an environment of outcome reporting or even of publication bias.

In the preregistration era, results were published, but as there was no up-front (prospective) trial registration, there was no way of knowing the real quality of such publications. Such up-front (prospective) protocol registration will enable the validation of the completeness of results reporting, which in turn will save a lot of sponsors' resources, particularly those of the pharmaceutical industry, and many lives. I would hesitate to participate, either as a trialist or as a study participant, in a trial that had not publicly disclosed at least 20 items. I would hesitate even more to prescribe or to use a drug developed through such a nontransparent process. However, I would be willing to consider prescribing and using a drug if I had a chance to analyse its potential risks and benefits. That would not have been possible without trial registration as we would continue to rely on the evidence based upon published results only, without knowing the scope of their accuracy

As of February 2006, we can say that we have defined, at a global level, a minimum-required protocol dataset via WHO's trial registration project (http://www.who.int/ictrp). We shall now move on to registration and public disclosure of results. Of course, at the same time, we shall continue registering trials in member registries that provide at least 20 items. This must be done globally.

The lessons learned in building the culture of registration will be used to improve the quality of results reporting. Had we moved on to results too soon, it would have distracted us from pinning down the essential protocol information, which would have opened the window for continuing manipulation of results presentations.

Furthermore, from a public health perspective, it is my hope that we shall revisit and further develop the minimal protocol dataset once we have been through the exercise of defining the registration of the results. This is why the Ottawa Group is continuing a dialogue beyond the minimal dataset.

I have no illusions that all data for all trials will be registered, right now, but we have made a good start in requesting a minimal 20-item dataset. I agree with Rockhold and Krall that we shall have to see how many of these 20 will be kept secret.

Discovery and development in medicine is, indeed, a very important activity for society, and the pharmaceutical industry plays an important role. With regard to the social contract between industry and society, let me point out that social contracts are based upon mutual respect and confidence, and they are open to revisions. Trial registration—as a tool of transparency, knowledge sharing, and accountability—will help restore the confidence of society in the pharmaceutical industry, which is currently very fragile, and thus enable the (re-)establishment of a (new) social contract between these two parties.

I have looked again at the continually growing list of endorsements of the Ottawa Statement (OS) Part 1 [4] (available at http://ottawagroup/ohri/ca), and there is still no industry endorsement. Neither Rockhold nor Krall has signed the OS1, not even after their letter. Since they have declared they are "all for registering", I am inviting them both again to sign the OS1, and to comment and consider endorsing the OS2 on principles of implementation [4]. ■

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Mitochondria: More than Mitochondrial DNA in Cancer

Bora Baysal

In their *PLoS Medicine* article, entitled "A critical reassessment of the role of mitochondria in tumorigenesis," Salas et al. [1] reviewed reports describing identification of mitochondrial DNA (mtDNA) mutations in several tumors. They identified many instances where the purported mutations in tumors corresponded to certain populational haplotypes, suggesting that contamination or sample mix-up could be a better explanation for these mtDNA variations found in tumors. This manuscript has important implications for this research field by questioning the validity of conclusions drawn in several high-profile publications that laid foundations for the role of mtDNA in cancer. While it is essential to investigate the origin of mtDNA variations found in certain tumors, the conclusion in the abstract that "the role of mitochondria in tumorigenesis remains unclarified" is simply incorrect.

The causal link between mitochondrial abnormalities and tumorigenesis was provided by the positional cloning of the hereditary paraganglioma gene at chromosome band 11q23 as the *SDHD* subunit gene of mitochondrial complex II (succinate dehydrogenase) in the year 2000 [2]. Since then, the role of mitochondria in cancer is further highlighted through identification of over 100 mutations in the *SDHB*, *SDHC*, and *SDHD* subunit genes in hundreds of index cases and families with hereditary and sporadic paragangliomas and pheochromocytomas [3]. Furthermore, fumarase gene mutations in a distinct hereditary tumor syndrome characterized by multiple skin and uterine leiomyomatosis and renal cell cancer—hereditary leiomyomatosis renal cancer (HLRCC)—further strengthened the role of mitochondria in cancer [4].

Although it is clear that Salas et al. question specifically the mutations in mtDNA of tumors, they did not acknowledge the causal link between mitochondria and cancer provided by the discovery of nuclear-encoded mitochondrial gene mutations. This is especially important because, in their unfortunate title and in their conclusion, the authors seem to make a sweeping statement against the role of mitochondria in cancer. It is essential to emphasize to readers that it is the mtDNA, but not mitochondria, which has a questionable role in tumorigenesis. ■

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Authors' Reply

We gratefully acknowledge the letter by Bora Baysal [1], which emphasizes that there is some interesting evidence for the role of mitochondria in tumorigenesis mediated by nuclear DNA factors—an issue that was outside the scope of our article [2]. We, however, do not entirely agree with him that the title of our contribution [2] is "simply incorrect"; it could probably be described as somewhat imprecise or ambiguous. In fact, the originally submitted, more precise, title of our contribution was "A pitcher of cold water on mutational hotspots in mitochondrial DNA and the hot debate about the role of mitochondria in tumorigenesis." In any case, the *Oxford English Dictionary*, for example, states that "reassess" is "to assess again, especially differently (derivatives: reassessment [noun])"; synonyms of assess would be "evaluate or estimate." Certainly, the role of the mitochondria has to be reassessed since the role of their most essential element, the mitochondrial genome, remains obscure in view of dozens of studies on the potential association of tumorigenesis with mitochondrial DNA (mtDNA) that are based on obviously flawed data. Since those inadvertent circumstances (contamination and sample mix-up) are not mitochondria-specific but lab-specific, there would also be good reason to reassess other spectacular DNA findings in regard to potential laboratory errors.

We would like to stress that mtDNA somatic mutations are by no means uncommon either in normal tissues or in tumors, but the natural pattern of these somatic mutations (most commonly involving the polycytosine stretches and other well-known hotspot mutations) is quite different from those that were published in the papers criticized in our article [2]. Consistent with the title of our article [2] would be the possibility that the nuclear-mediated effect on the mitochondrial function could perhaps be mtDNA haplogroup–specific—but certainly not in the form of the artefactual instabilities, as claimed in those dubious publications (which, however, in one case, have now been explicitly defended [3], but unfortunately, without carrying out the necessary "forensic-type" analysis looking into potential sample mixture of the previously analyzed samples [4] and without determining whether the patient received blood transfusion before the onset of the disease [5]). Rather, some complex susceptibility background for tumorigenesis might be anticipated—in analogy to some mtDNA diseases such as Leber's hereditary optic neuropathy (LHON) [6]. ■

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Prioritizing Investment in Medical Education

Fawad Aslam

The dire need to reform medical education in South Asia has been well emphasized in the *PLoS Medicine* Editorial [1]. It is encouraging to note that efforts are under way to devise strategies to bring about this reformation. However, for such reforms to be effective, it is crucial that the opinions of medical students and young doctors are also taken into account. Students' roles should be enhanced from those of mere consumers of medical education to those of contributors [2]. They are important stakeholders, and their active participation in policymaking will facilitate the creation of more robust solutions.

The need for drastic improvement in health research in South Asia is well established. The need for research in medical education is perhaps even greater. Unfortunately, indigenous data pertaining to medical education in this region are limited. Only a small number of studies have attempted to explore the concerns of students and doctors in matters pertaining to, for example, medical decision making and health research [3,4]. The establishment of a research culture is fraught with difficulties but is not impossible [5]. It is my opinion that, to bring about reform, both a "bottom-up" and a "top-down" approach are needed. The former needs ample student exposure to research during medical school. The latter is essentially linked to the availability of funds. No amount of community-oriented training, for example, will compensate for the deficiency of properly qualified health professionals in rural areas. It is only when there is sufficient financial and professional security that the greater purpose of educational reform will stand fulfilled. It is hard to envisage how this can be achieved when the bulk of budgetary spending pertains to debt-servicing and defense expenditure.

Alongside medical education, parallel investment should be sought in health education, not only because our physicians are not cognizant of current treatment practices [6], but also because our patients have a poor knowledge of common diseases that afflict them [7]. The interaction of better-informed patients and properly qualified doctors may significantly improve community health. For impoverished nations, the importance of preventive medicine is manifold as it offers the most economical way of combating disease. There is some evidence to suggest that our medical students are not "prevention" oriented, and, thus, more emphasis must be placed on preventive medicine [8].

It is also hoped that such investment will lead to nationally oriented research activities and not to a mere replication of Western studies. The study evaluating the significant protective effects of hand washing in children from common childhood diseases is one such example [9]. Another example is a study evaluating the effects of garlic on dyslipidemia [10]. Further studies of this kind may prove helpful in combating the cardiovascular disease epidemic in Pakistan. Garlic is potentially a much cheaper alternative to statins, the latter being unaffordable for most segments of Pakistani society. Similarly, medical education institutions such as Aga Khan University in Pakistan, which is a private-sector entity, have started problem-based, community-oriented teaching in medical schools. The outcome of these curricular changes remains to be seen. Indeed, there is hope for South Asia, but for such hope to materialize, we need selfless individuals, strong institutions, and perhaps above all a more just and realistic distribution of the national financial resources. ■

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