

Correspondence

Adherence to HAART: Africans Take Medicines More Faithfully than North Americans

Amir Attaran

In 2001, the chief of the United States Agency for International Development (USAID), Andrew Natsios, gave this justification to the US Congress for why the agency opposed giving antiretroviral therapy (ART) to Africans with HIV:

“If we had [HIV medicines for Africa] today, we could not distribute them. We could not administer the program because we do not have the doctors, we do not have the roads, we do not have the cold chain...[Africans] do not know what watches and clocks are. They do not use western means for telling time. They use the sun. These drugs have to be administered during a certain sequence of time during the day and when you say take it at 10:00, people will say what do you mean by 10:00?” [1].

Natsios was not the only policy maker to justify withholding ART from Africans on the basis that weak infrastructure, or patients' inability to take tablets, would stymie adherence. Senior officials of the World Bank and Thai government said in *The Lancet*: “[ART] is not...a technology that most poor people could adhere to...[Further] The use of public funds to subsidise the treatment of patients in the poorest countries who are most able to comply...would be highly inequitable” [2].

Two new systematic reviews prove these speculations were mistaken [3,4]. Despite their continent's poverty, and schooled or not in time keeping, Africans overcome these barriers and are better than North Americans at taking ART. These studies correct the misconception of earlier, nonsystematic reviews that concluded that Africans' adherence to medicines is “often poor” [5].

The first review (which I coauthored) identified 31 studies from North America and 27 from sub-Saharan Africa examining adherence to ART [3]. The bottom line was simple: using the customary definition that “good adherence” means taking ART as prescribed 95% of the time or more, then 82% of Africans succeeded at that goal, compared with only 55% of North Americans (p is less than 0.001).

Some may see this result as surprising. To live in Nairobi means to face so many privations compared to New York that to overcome them and excel seems almost storybook untrue. But privation can cut both ways. People who have been denied the necessities of life, who then receive the gift of medicines and a chance to live, may be more likely to appreciate ART.

Although Africans take ART more faithfully than North Americans, there is room for improvement. Here is where the second review is instructive [4]. The authors identified 84 studies from rich and poor countries that qualitatively or quantitatively identified factors impeding or facilitating adherence to ART. The impeding factors in rich and poor countries were familiar ones: patients' aversion or forgetfulness about medicines; lack of trust in health workers; fears about AIDS or its treatment; and emotions of isolation.

The authors found only two qualitative studies of barriers and facilitators of adherence among patients in poor

countries [4]. There are accordingly few data on which to conclude that, for example, patients must give up alcohol, or must undergo directly observed therapy, to adhere to medicines, as some programs require [6,7]. Such measures may indeed be unnecessary.

In rich countries, the study failed to identify any obvious “big fix” that could turn non-adherent patients into adherent ones. On the other hand, for developing countries, “financial constraints” towered above the other reasons why poor patients may fail to adhere to ART. That is cruelly ironic, because the same international development policy makers who rejected the idea that poor people could adhere to ART also worked for financial donors such as USAID and the World Bank, and their passionate arguments against ART stalled the delivery of the one variable that helps adherence—money.

Where is the flaw that allowed speculation to get ahead of evidence in development policy making, and to reach the baseless conclusion that Africans could not adhere to ART, or needed to be commanded paternalistically (e.g., “you must abstain from alcohol”) to adhere to ART, when no such conclusion would be reached for rich people? More to the point, how can one recognize when a particular development policy is so baseless and speculative, the better to abandon it?

A serviceable answer, I believe, is that one should be highly suspicious whenever development policy makers sound dismissive of the people whom they are hired to help. The central aspiration of development work is helping the poor and sick become richer and healthier. Such an aspiration is incompatible with speculating that certain foreigners are incapable of enjoying the fruits of development. I believe that the views of Natsios and the World Bank and Thai officials, speculating that Africans could not adhere to ART, were dismissive in just this way.

Dismissing patients in this way leads to a lower standard of medical care. The medical establishment is more sensitive to the standard of care than is the development establishment, and so the medical establishment must be vigilant—and vocal—against bad development policy. Development policymakers have also freely opined that Africans could not manage to take artemisinin-based combination therapies for malaria, or second-line treatments for tuberculosis. We now know that Africans are capable of all these things—but overcoming the dismissals and excuses took years, during which millions died. ■

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Competing Interests: In 2003, the World Bank commissioned AA to write about AIDS drug procurement and resistance. In 2001, he coauthored an editorial for the *Washington Post* calling for Andrew Natsios' resignation. AA was the Academic Editor on the study in *PLoS Medicine* commented on in this letter [4], and collaborated with several of the study authors on a second systematic review of adherence to HIV medicines [3].

“The Right Stuff”: The Global Burden of Disease

Bolajoko O. Olusanya

PLoS Medicine is one of the few journals with a dedicated forum for neglected diseases, and the suggestion by its editors that journals should give preference to diseases based on their relative contributions to the global burden of disease is noteworthy as a positive step towards optimising the global research agenda [1]. Undoubtedly, the recent report by Mathers and Loncar, like earlier versions of the Global Burden of Disease (GBD) study, represents the best effort yet at providing a level playing field for diverse diseases and health conditions globally [2]. A key feature of this project is the evaluation of health outcomes in terms of mortality and burden of disease indexed by disability-adjusted life years (DALYs). However, a few concerns still linger on the application and current scope of the study which have significant implications for health-care policy, particularly in the developing world.

The concept of the “burden of disease” was introduced to redress the inequality and inequity occasioned by the exclusive use of mortality as the summary measure of population health [3,4]. The DALY was thus intended to provide information on non-fatal health outcomes of diseases that have been largely neglected in health planning because of the “conceptual and definitional complexity of measuring morbidity and disability in populations” [5]. However, it is uncertain how far the well-intentioned paradigm shift in disease evaluation has been achieved, as global health initiatives are still rarely concerned with reduction in “burden of disease” besides mortality. This is also applicable to health planning at country or community level. In fact, the significance of noncommunicable/chronic health conditions such as cardiovascular diseases, cancer, diabetes, and mental illness is still being predominantly promoted on the basis of case fatality rather than disease burden. Conceptually, DALY and its variants like quality-adjusted life years (QALYs) represent equitable measures of population health that

should be more actively promoted, but more work is required to address some of the methodological and equity concerns that have been raised since their introduction to global health [6,7].

The continued ranking of childhood diseases alongside adult diseases in the GBD report often portrays children as “young adults”. This practice distracts from diseases and conditions that have significant impacts on optimal early childhood development. Moreover, the risk of death for children younger than five years is projected to fall by more than 40% between 2005 and 2030, while life expectancy globally is expected to improve significantly by 2030, with the largest increases occurring in Africa and South Asia [1]. This trend is likely to bring to the fore the neglected discourse on the quality of life for the many survivors of acute childhood illnesses, particularly as the years lived with disability for chronic diseases of childhood onset far exceed those of adult onset. For instance, it is difficult to justify the continued failure to address a highly preventable perinatal condition such as neonatal jaundice, which may not be a leading cause of mortality but currently causes substantial burden in low-income countries [8].

Similarly, hearing loss of adult onset remains one of the ten leading causes of DALYs globally, particularly in high-income and middle-income countries, but is not expected to be a leading health problem in low-income countries by 2030 [1]. While this is gratifying to note, the current trend in the prevalence of disabling hearing loss (which more than doubled from 120 million in 1995 to about 278 million persons in 2005, two-thirds of whom reside in developing countries) may have much greater impact than projected, considering the envisaged improvement in life expectancy [9]. But more importantly, the exclusion of hearing loss of childhood onset or the failure to adequately account for permanent childhood hearing loss in these projections underrepresents the true burden of hearing loss. It disfranchises about 718,000 babies born annually in the developing world with neonatal hearing loss from available time-bound early detection and intervention services now a standard of neonatal care in developed countries [10].

The call by Mathers and Loncar for more robust studies across the regions of the world must not be overlooked or considered lightly. As new evidence emerges from such studies, the projected trend and ranking in many countries may ultimately differ from the overall global and regional picture in the current GBD report. Meanwhile, systematic steps to address these and other concerns should be considered urgently to effectively promote the concept of the burden of disease. Invariably, we all need to be guided by a variety of sources and perspectives in determining “the right stuff” for the heterogeneous populations of the world. ■

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Gut Mucosa in HIV Infection: "Immune Milk" Solution

Shawn J. Green

In recent weeks, three noteworthy papers, published in *PLoS Medicine*, *The Journal of Virology*, and *Nature Medicine*, direct our attention to the gut as a critical target in HIV-1 infection and portal for therapeutic intervention.

In *PLoS Medicine*, Mehandru and colleagues report that over half of the CD4⁺ T cells in the gut mucosa are lost within the first few weeks after HIV-1 infection and remain consistently low, compared to peripheral blood sources, despite long term antiretroviral therapy; furthermore, of the few CD4⁺ T cells that persist in the gut, a significant increase in immune activation is observed [1]. Consistent with earlier observation in SIV models, Veazey reminds us that the battle against HIV-1 should focus on the intestinal mucosa with therapeutic strategies to reduce gut immune activation [2].

The longitudinal study in *The Journal of Virology* by Guadalupe and colleagues showed a similar discordance in CD4⁺ T cells between restoration in peripheral blood and significant delay in the gut mucosa of chronic infected individuals during antiretroviral therapy. Here, the depletion in CD4⁺ T cells was associated with an increase in gut immune activation, CD8⁺ T cells, and associated inflammation with a corresponding decrease in epithelial growth and repair-associated genes in gut mucosal tissue [3]. Brenchley and colleagues suggest in *Nature Medicine* that HIV infection causes this breakdown in the gut mucosa resulting in a "leaky gut," thus allowing translocation of gut-derived endotoxin and the subsequent triggering of immune activation [4].

Collectively, these observations suggest that an orally active therapeutic, used in conjunction with antiretroviral therapy, be designed to both block gut-derived microbial translocation and stimulate restitution of the gut epithelium. The hope would be to restore immunological integrity of the intestinal mucosal barrier, thereby controlling immune activation, both locally, in the gut mucosa, and systemically by suppressing

cellular targets distal to the gut that may directly contribute to the progression of AIDS [5–8].

The design for such an orally active therapeutic may be found in the complex formula of bovine colostrum and "immune milk," which has long been recognized to offer passive protection from a broad number of enteric bacterial and viral pathogens, primarily via the transfer of immunoglobulins and suppression of gut-associated inflammation with promotion of mucosal repair and regeneration.

The gut in chronic HIV-1-infected individuals appears to be reminiscent of newborn calves. Calves are born with a highly immature mucosal immune system and "leaky gut" which, if not immediately corrected, results in death due to infection and associated systemic immune activation. However, the cow's first milk rescues her calves from harmful gut microbes with a uniquely complex cocktail enriched with neutralizing polyclonal antibodies, cytokine tissue repair factors, and immune enhancing probiotics, such as *Lactobacillus* species.

Regular consumption of biologically active bovine colostrum has been known for years to promote the development of infantile gut-associated lymphoid tissue and enhance CD4⁺ levels, while suppressing CD8⁺ and inflammatory bowel disease (IBD), including ulcerative colitis and Crohn disease [5]. The severity of IBD is often correlated with gut microbial-endotoxin translocation, which now appears in chronic HIV-1-infected individuals [4]. Similar to bovine colostrum, "immune milk" from properly vaccinated cows affords passive immunity against bacterial, viral, and fungal infections in the human gastrointestinal tract, as well as taming gut inflammation [8].

Hence, there may be lessons learned from Bessie's "immune milk." If viewed as a unique formula that has evolved to complement gut immunity, "immune milk" may also provide relief in chronic HIV-infected individuals. Initial studies have already shown that ingestion of colostrum alleviates refractory diarrhea in HIV patients with a corresponding increase in both body weight and peripheral blood CD4⁺ T cells [9,10]. As we learn more about the gut microenvironment in HIV-infected individuals, Bessie may prove to be a worthwhile platform for the consideration of "immune milk" exhibiting both microbial endotoxin and HIV-neutralizing activity along with its innate anti-inflammatory and tissue repair and regenerative properties. ■

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Educating Health Professionals about Drug and Device Promotion: A Nepalese Perspective

P. Ravi Shankar

I read with interest the article by Mansfield et al. regarding educating health professionals about drug and device promotion [1]. Teaching about drug promotion is becoming increasingly important here in Nepal. During their pharmacology training at the Manipal College of Medical Sciences, Pokhara, medical students are taught to critically analyze drug advertisements and other promotional material against the World Health Organization’s ethical criteria for medicinal drug promotion [2]. Their abilities in the critical analysis of drug promotional materials are evaluated during the pharmacology practical examination. The students are also taught to critically evaluate drug promotion by medical representatives (MRs) using the medium of role-play [3].

The four recommendations made by the authors are important, but developing countries may face problems in their implementation. We recommend that all health professionals be educated about decision making and evaluation of evidence and promotion. Our department runs a drug information center in the teaching hospital and we are trying to use this center to promote evidence-based medicine. However, there are no formal courses on evaluating the evidence. Doctors do not have an adequate knowledge of statistics to arrive at evidence-based decisions.

The authors’ second and third recommendations pose further problems. Conferences in Nepal continue to be heavily sponsored by the pharmaceutical industry. MRs have unrestricted access to doctors in our hospital and in most other hospitals in Nepal. One-to-one visits, personal gifts, and other methods of sponsorship are the norm. Academic detailing is absent. I am personally ambivalent about banning one-to-one detailing. Many health professionals in South Asia are in private practice or work in small hospitals. It is an unfortunate fact, but MRs may be their only source of

information about medicines. Banning MRs may deprive them of this source, however biased it may be. Exposing students to misleading presentation, fostering false beliefs, debunking these beliefs, and explaining the misleading techniques is an effective approach, used in our department during teaching critical evaluation of medicinal drug promotion.

We have had mixed success regarding educating health professionals to avoid promotion or look at it critically. We have been able to influence students during the first two years of their training. The influence of our training is considerably eroded once students are in their clinical phase. Enlisting the support of clinicians, making them aware of irrational promotion, and using their services to teach doctors in training is vital if we are to make progress. Education regarding the most reliable sources of information is lacking in South Asia. Health organizations, professional associations, and other bodies should develop information sources which are readily accessible to prescribers. Western information sources may have many limitations in developing countries.

So far, no medical student organizations in Nepal have taken up the issue of pharmaceutical promotion. The curriculum of Kathmandu University recommends teaching students to assess promotional materials. However, many medical schools do not address this vital issue. Meanwhile, the Nepalese pharmaceutical industry is coming of age. The pharmaceutical giants based in our Southern neighbor, India, are also active in Nepal. It is time for medical professionals to get their act together to ensure a proper relationship with the industry. ■

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Educating Health Professionals about Drug and Device Promotion: Authors’ Reply

We thank Prof. Ravi Shankar for his thoughtful reflections [1] on our recommendations for education about drug and device promotion [2]. Prof. Shankar is one of the few who have published an evaluation of education about drug promotion [3], so we are pleased that he concurs with most of our recommendations. We agree with him that implementation of our recommendations will be difficult. The main barrier to implementation is the widespread denial by health professionals that we are often adversely influenced by promotion. This denial arises partly from ignorance of the

evidence about promotion and partly from a refusal to accept that evidence, because it is viewed as insulting our self-esteem [4]. We believe health professionals need to move from overconfident illusions of invulnerability to accept that we are human, so it is normal for us to be misled by persuasive promotional techniques [5].

Prof. Shankar seems to believe that doctors can be taught to “critically evaluate drug promotion” [1] so as to “optimise time spent with medical representatives” [3], although he acknowledges only “mixed success” with his medical students [1]. By contrast, we are pessimistic that doctors will ever be able to gain more good than harm from visits by sales representatives in any country. All the relevant evidence of which we are aware suggests that exposure to promotion correlates with less appropriate prescribing [6]. Furthermore, the skills required to avoid being misled may take many years to learn, and many hours to apply after each visit. There is no proven method for overcoming normal human vulnerabilities such as the tendency to believe attractive, socially skilled people, especially if they have built up trust over many visits. Consequently, we believe the onus is on anyone who claims that it is possible for health professionals to learn how to gain net benefit from sales representatives’ visits to produce evidence to support that claim.

Prof. Shankar is ambivalent about our recommendation that health professionals avoid promotion because in his country, Nepal, sales representatives “may be their only source of information about medicines.” We share Shankar’s concern about lack of relevant independent information for doctors in many countries. In all countries, whoever pays for health care will get better results at lower cost by funding independent information, rather than paying direct and indirect costs from inappropriate drug and device use caused by misleading promotion. Payers for health care are more likely to fund such initiatives if they understand how harmful drug promotion is. Even if no such initiatives are forthcoming, we reject the idea that any information—even if it is misleading—is better than no information at all. The majority of new drugs are more expensive than their older analogues, but no better (and sometimes worse). Patients would be better off if doctors were ignorant non-prescribers of such drugs rather than misinformed frequent prescribers.

Current patterns of health professionals’ interactions with the drug and device industry are causing much harm [6]. Our three main tasks are to develop optimal recommendations for improvement, identify barriers to implementation, and develop methods for overcoming those barriers. We appreciate any input, including Prof. Shankar’s reflections, that will help us improve our performance on those tasks. ■

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Structural Violence and Clinical Medicine: Free Infant Formula for HIV-Exposed Infants

Ted Greiner, Christophe Grundmann, Katherine Krasovec, Christian Pitter, Catherine Wilfert

We wholeheartedly agree with Paul Farmer and colleagues [1] that it is vitally important to examine social, as well as molecular, causes of disease. Unless we carefully consider the full range of factors that underlie a given problem, we may produce “solutions” with unintended and deleterious consequences. In this light we express our concern about the infant feeding approach advocated in their article to reduce mother-to-child transmission of HIV in Rwanda.

While exclusive replacement feeding reduces the risk of transmission between HIV-positive mothers and their infants, it does not adequately address the specters of infection and undernutrition that accompany avoidance of breast-feeding. We are convinced—by data from regions that are similar to Rwanda and even from African countries with higher standards of living—that replacement feeding from birth is a dangerous and inappropriate approach for HIV-affected families in countries like Rwanda.

In addition, avoiding breast-feeding from birth can be exceedingly risky, particularly in the same regions where the risk of mother-to-child transmission of HIV is highest. While Partners in Health (PIH) offers high-quality health-care support and financial assistance to reduce the risks associated with breast-feeding avoidance in two districts in Rwanda, it is impossible to eliminate those risks. Researchers have found that children in Ghana, Peru, and India who are not breast-fed between the ages of six weeks and six months have a ten-fold higher risk of death [2]. A multi-country analysis by the World Health Organization (WHO) showed that infants who were born to mothers with little education and were not breast-fed had a five-fold increased risk of death from six to 11 months of age. Since about 5% of breast-fed Rwandan babies already die in the first six months of life

and another 3.5% from six to 12 months [3], it is essential that PIH substantiate the mortality, nutrition, and morbidity outcomes resulting from their approach before promoting it more widely.

Given that breast-feeding avoidance increases the risk of death from other causes, even as it decreases the risk of HIV transmission, is there a net gain? The concept of “HIV-free survival” combines the likelihood of surviving with the likelihood of not becoming HIV infected, allowing a more comprehensive assessment of the risks and benefits of infant feeding. In Botswana [4] and the Ivory Coast [5], rates of HIV-free survival were no better among formula-fed infants than among infants breast-fed for three to six months. At this year’s WHO Consultation on HIV and Infant Feeding in Geneva, reports showed high death rates in ongoing trials in Kenya, Uganda, and Malawi associated with breast-feeding cessation at three to six months. These results were despite earlier assumptions that breast-feeding cessation at this age might be safe, while avoiding most of the HIV transmission associated with prolonged breast-feeding [6]. Since these carefully controlled studies represent best-case scenarios for replacement feeding, most actual program settings will favor breast-feeding (actually, disfavor replacement feeding).

The risk of mother-to-child HIV transmission in the first six months in a country like Rwanda, where 81% of women are still exclusively breast-feeding at four to six months [3], is relatively low—probably approximately 0.3% per month [7]. It may be even lower in districts like those in which PIH works, where eligible HIV-positive mothers begin receiving highly active antiretroviral therapy during pregnancy, because the majority of postnatal HIV transmission is from mothers with low CD4+ cell counts [8].

Scientific evidence amply demonstrates the significant risks that accompany replacement feeding and the safety and effectiveness of exclusive breast-feeding for the first six months, and continued breast-feeding thereafter as appropriate and safe. Around the world, researchers, programmers, and policy makers are becoming increasingly convinced that the infant feeding counseling component of prevention of mother-to-child transmission of HIV programs must focus on optimizing HIV-free survival rates, not simply on HIV transmission. Accomplishing this means taking full account of all factors, both social and molecular, that are at work in a particular context, and tailoring responses to meet them. ■

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Blindness Survey Methods: Response from Sudan Study Authors

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We thank the authors [1,2] for the two perspectives on our articles [3,4]. Our study estimated the prevalence of blindness in Mankien at 4%, which Kuper and Gilbert describe as being “beyond the range” of the studies reviewed by Pascolini et al. [5]. The review did not include any studies from the ten states that compose southern Sudan. The nearest surveys reported were conducted in 1998 in Al-Ginena province of Southern Darfur—which is within the 16 northern states of Sudan governed from Khartoum, and was not directly affected by the war in the south. The Al-Ginena studies show a blindness prevalence of 3.2% in all ages [6,7]. Yet despite the geographical proximity, two decades of civil war in the south were accompanied by the absence of a health infrastructure, and no preventive health services to speak of, which makes southern Sudan unique. Comparisons with other parts of Sudan or with other countries are probably not justified or meaningful.

Our survey was conducted in Mankien, which was anecdotally known to be endemic for severe blinding trachoma, and this was subsequently confirmed by our trachoma survey, which showed an overall prevalence of trichiasis and bilateral corneal opacity of 9.6% and 3.1%, respectively [3]. The prevalence of blinding cataract in Mankien was consistent with expectation, and would presumably have been higher had there been a systematic over-sampling of the blind. It is the prevalence of blinding trachoma that sets the population apart from all others reported and reviewed by Pascolini et al. These survey data from Mankien are extremely valuable in that they demonstrate the way uncontrolled trachoma can ravage

inaccessible and underserved communities who have, quite literally, been off the map until recently. The war affected the whole of southern Sudan, and extremely high levels of active trachoma and trichiasis have been observed in all the areas that we have managed to survey in recent years [8]. Although not generalizable to the ten southern states, these data from Mankien are probably indicative of the overall situation in southern Sudan.

We acknowledge the survey limitations highlighted by Kuper and Gilbert, and have addressed them in the discussion. Our sampling methodology has been used in similar surveys in Kenya [9], Bangladesh [10], Tehran [11], Cameroon [12], and Pakistan [13]. Use of basic eye examination technique by auxiliary health-care workers in blindness surveys has been suggested for settings without ophthalmologists [14], which is entirely consistent with what the integrated eye care workers are trained to do. Kuper and Gilbert's difficulty appears to stem from the findings, rather than the methodology. They offer two interpretations to explain the data, whilst not acknowledging the most parsimonious explanation, and that is that these data are an accurate reflection of the situation on the ground; we cannot risk not accepting this. The international community must rise to the challenge of planning and offering service for blindness prevention interventions in these desperately needy communities. We should not let an academic argument as to whether the prevalence of blindness is really 4% or whether it is, perhaps, a little lower be the basis for continued neglect.

We fully agree with both Kuper and Gilbert, and Buchan that there is need for a concerted effort to survey the entire region, provide resources, and deliver services to the marginalized and poverty stricken communities in southern Sudan. ■

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