Predicting the Impact of Antiretrovirals in Resource-Poor Settings: Preventing HIV Infections whilst Controlling Drug Resistance

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Abstract: There is currently an opportunity to carefully plan the implementation of antiretroviral (ARV) therapy in the developing world. Here, we use mathematical models to predict the potential impact that low to moderate usage rates of ARVs might have in developing countries. We use our models to predict the relationship between the specific usage rate of ARVs (in terms of the percentage of those infected with HIV who receive such treatment) and: (i) the prevalence of drug-resistant HIV that will arise, (ii) the future transmission rate of drug-resistant strains of HIV, and (iii) the cumulative number of HIV infections that will be prevented through widespread use of ARVs. We also review the current state of HIV/AIDS treatment programs in resource-poor settings and identify the essential elements of a successful treatment project, noting that one key element is integration with a strong prevention program. We apply both program experience from Haiti and Brazil and the insights gleaned from our modeling to address the emerging debate regarding the increased availability of ARVs in developing countries. Finally, we show how mathematical models can be used as tools for designing robust health policies for implementing ARVs in developing countries. Our results demonstrate that designing optimal ARV-based strategies to control HIV epidemics is extremely complex, as increasing ARV usage has both beneficial and detrimental epidemic-level effects. Control strategies should be based upon the overall impact on the epidemic and not simply upon the impact ARVs will have on the transmission and/or prevalence of ARV-resistant strains.

Key Words: AIDS, tuberculosis, mathematical modeling, developing countries, prevention, treatment, public policy.

INTRODUCTION

By 1995, it was clear that combination antiretroviral (ARV) therapy would lead to clinical improvement and alter dramatically both the quality of life and life expectancy for people living with advanced HIV disease [1]. Although supply has rarely kept pace with demand, even in developed countries, ARVs are now available to the fortunate few across the globe. However, debates regarding the use of these agents in the resource-poor settings in which HIV takes its greatest toll have slowed effective and coordinated responses in the most heavily burdened countries in Africa, Asia, and the Americas. Like tuberculosis, AIDS has become primarily a disease of the poor [2]. Clinicians, epidemiologists, and health policy experts have not kept pace with the pandemic itself, since both the virus and treatment for it have preceded experts to poor and heavily burdened parts of the world: studies conducted by the World Health Organization have demonstrated the ready availability of ARVs in cities across Africa, Asia, and Latin America to any who can afford to pay. It is thus incorrect to ask, though many policymakers continue to do so, if it is wise to introduce ARVs to Africa or to other poor and heavily burdened regions. Wherever HIV/AIDS is a leading killer of young adults, ARV demand already exists and is felt by manufacturers and distributors, to say nothing of the sick and those who care for them. Subjecting this process to market forces alone will lead to what tuberculosis experts term “therapeutic anarchy” [3]. Drug supply and demand is currently left to a mysterious force termed “the market,” which means that those who can pay for care have access to it, while those who cannot afford the entire regimen will often purchase only partial regimens; the poorest often lack treatment altogether.

There is both an opportunity, and a pressing need, to plan carefully the proper use of ARVs in the developing world. Previously we have used mathematical models to understand the epidemiological impact of ARVs and to predict the public health impact that they might have on HIV epidemics in developed countries [4-10]. Here, we use mathematical models to predict the potential impact that low to moderate usage rates of ARVs might have in developing countries. We use our models to determine the relationship between the specific usage rate of ARVs (in terms of the percentage of those with HIV infection who receive treatment) and: (i) the prevalence of drug-resistant HIV that will arise, (ii) the future transmission rate of drug-resistant strains of HIV, and (iii) the cumulative number of HIV infections that will be prevented. We then briefly review the current state of AIDS treatment programs in resource-poor settings and identify the essential elements of a successful treatment project, noting
Mathematical models can be used as health policy tools [4,6-9], and (when coupled with uncertainty analyses) can be used to predict the future [4-12]. This approach has been used both to understand the impact (on certain HIV epidemics) that ARVs have already had, and to predict the future epidemiological consequences of ARVs in developing countries, where therapy has been widely available since 1996 [4-10]. In particular, the HIV epidemic in the gay community in San Francisco has been extensively modeled. In this community, it is estimated that 50-90% of HIV-infected gay men have been treated with ARVs [4]. In most developing countries, in contrast, usage rates of ARVs are very low; even rapid uptake, such as that advocated during the 2001 United Nations Special Session on AIDS, will not lead to comparable rates of usage within the coming decade. Therefore, here we predict the potential impact of ARVs in developing countries under the assumption that treatment rates will be low to moderate. Specifically, we assume that anywhere from 10% to 50% of HIV-infected individuals will receive ARVs. We predict the effect of these usage rates of ARVs (using a previously published mathematical model [4]) on: (i) transmitted resistance, (ii) the prevalence of ARV-resistance, and (iii) the cumulative percentage of infections prevented due to ARVs. We use uncertainty analyses (based upon a Monte Carlo sampling scheme) to make predictions [13]. For the uncertainty analysis we generated 1,000 different computer simulations, each of which was run for 10 years. We then used multivariate sensitivity analyses to determine the key factors that would substantially increase or decrease the magnitude of the three epidemiological variables. We have previously described the methodological details of uncertainty analysis and multivariate sensitivity analyses [13].

The mathematical model that we used includes the potential effects of ARVs on the transmission dynamics of both drug-susceptible and ARV-resistant strains of HIV. The model is specified by five ordinary differential equations; these equations have been described in detail elsewhere [4]. The model allows for both acquired and transmitted resistance to occur. Acquired resistance develops because of a variety of factors that include patient adherence, the mutation rate of HIV, and the clinical efficacy of the drug regimen; we modeled the aggregate effect of these host, viral, and drug factors by a single parameter, r, defined as the annual percentage of treated drug-susceptible cases that acquire ARV-resistance. The model generates cases of acquired ARV-resistance at a certain rate that is a time-dependent function of: (i) the number of infected drug-susceptible cases present at that time, (ii) the percentage of HIV-infected individuals receiving ARVs at that time, and (iii) the rate at which treated drug-susceptible cases are transformed into ARV-resistant cases (as specified by the single aggregate parameter r). The potential treatment effects of ARVs are modeled by assuming that ARVs increase average survival time and reduce infectivity in treated individuals by reducing viral load. In this model, treatment with ARVs has three possible outcomes: (i) a patient can respond to ARVs and remain as a non-progressor for a specified amount of time, (ii) the patient can experience clinical failure and death without developing drug resistance, or (iii) the patient can fail therapy virologically (that is, serum viral load is no longer suppressed by ARVs) and acquire drug resistance. The model also allows individuals to cycle on and off ARVs over time, and for ARV-resistant strains to be sexually transmitted.

To predict the potential impact of ARVs we conducted an uncertainty analysis by assigning each parameter in the model a probability density function (pdf). The pdf reflected either the uncertainty in the value of the parameter (which was specified by setting a bounded range of possible values) or the degree to which the parameter could vary if it was being used as an experimental variable. We used both the usage rate of ARVs and the rate at which ARV-resistant strains emerge during treatment (r) as “experimental variables,” because the precise value that either of these variables will have when ARVs are widely used in developing countries is currently unknown; indeed, this value is disputed even in developed countries in which such agents are widely used. We varied the usage rates of ARVs from a minimum of 10% to a maximum of 50%, as usage rates are likely to be low to moderate in developing countries. We varied the rate of emergence of ARV-resistance (i.e., the value of r) over a wide range, from a minimum of 20% to a maximum of 70%. The pdf for each of the other model parameters reflected the uncertainty in the value of the parameter. We included a high degree of uncertainty in the potential effects that ARVs would have on increasing survival and reducing infectivity. Basing our parameters on U.S. and European experience, as well as key studies in other settings, we assumed that treatment with ARVs could: (i) increase the average survival time anywhere from 50% to 300% (i.e. three-fold), and (ii) induce anywhere from a two- to a one-hundred-fold reduction in per-partnership infectivity [4]. We modeled a differential treatment response to ARVs between drug-susceptible and ARV-resistant cases so that ARVs were less effective in decreasing disease progression rates and reducing infectiousness in ARV-resistant patients in comparison to drug-susceptible patients. We also included the assumption that anywhere from 1% to 25% of ARV-treated patients would give up ARVs annually. Since it is possible that what is often termed “risky behavior” (i.e., injection drug use or increased sexual activity without protective barrier methods such as condoms) could increase as a result of the introduction of ARVs, we included an uncertain degree of increase, ranging from no increase to a doubling of the average level of risky behavior.

We differentially modeled the biology and pathogenesis of ARV-resistant and drug-susceptible strains by allowing the strains to differ in their infectivity and disease progression rates. In order to conduct the uncertainty analysis, we
assumed that ARV-resistant strains could either be as virulent as the drug-susceptible strains or attenuated (to some uncertain degree) in comparison with drug-susceptible strains. We modeled the effect of viral attenuation in two ways. First, we assumed that individuals infected with ARV-resistant strains might be less infectious (i.e., their infecting viral strain would be less fit) than individuals infected with drug-susceptible strains, but we varied the reduction in infectivity due to attenuation from an insignificant 1% (i.e., so that the ARV-resistant strains had almost the same level of infectivity or "fitness" as the drug-susceptible strains) to 99% (i.e., so that the ARV-resistant strains were only 1% as infectious (fit) as the drug-susceptible strains). Second, we modeled the effect of viral attenuation by assuming that untreated individuals infected with ARV-resistant strains would, on average, survive longer (for some uncertain amount of time) than untreated individuals infected with drug-susceptible strains. In the model, we also allowed for the possibility that ARV-resistant individuals could transmit both ARV-resistant and drug-susceptible strains, as some individuals are co-infected with more than one strain of HIV. Our modeling assumptions about the biology and pathogenesis of drug-resistant HIV are based upon virological, immunological, and clinical studies [14-19].

Predictions: Transmitted Resistance, Prevalence of Resistance, and the % of HIV Infections Prevented

We predicted the impact on the transmission of ARV-resistant strains in developing countries of treating anywhere from 10% to 50% of HIV-infected cases, assuming that the rate of emergence of acquired resistance ($r$) varied from 20% to 70% of treated drug-susceptible cases per year. The predicted results of our uncertainty analysis, based upon 1,000 computer simulations, is shown in Figure 1A. The results are plotted as box plots, with the median value of each box plot shown as a horizontal line in the middle of the box and the interquartile range (IQR) specified by the box length. We predict that the likely value of transmitted resistance (in terms of the percentage of new HIV infections that are drug-resistant) will be low, even after 10 years of ARV usage; the median value of transmitted resistance is 5.9% and the IQR is 2.5% to 11.7%. Our results also reveal that, under certain conditions, an extremely high level of transmitted resistance could occur; the maximum value of transmitted resistance, after 10 years, is 41.1% (Figure 1A).

We then performed a multivariate sensitivity analysis in order to identify the key factors (as determined by the value of their Partial Rank Correlation Coefficient (PRCC)) in increasing the level of transmitted resistance after 10 and 20 years (Table 1). These sensitivity results show that the level of transmitted resistance increases substantially as: (i) the usage rate of ARVs increases (from 10% to 50%; graphical results from the uncertainty analysis are shown in Figure 1B), (ii) the relative fitness (i.e., the transmissibility) of the ARV-resistant strains increases (graphical results from the uncertainty analysis are shown in Figure 1C), (iii) the increase in risky behavior rises (from no increase to a doubling of risky behavior), and (iv) the rate of emergence of acquired resistance ($r$) increases (from 20% to 70%) (Table 1). Finally, ineffective treatment regimens that do not adequately suppress viral loads will lead to a high rate of transmitted resistance (Table 1).

![Fig. (1).](image-url) (A) Temporal evolution of transmitted resistance; treatment with ARVs begins at time zero. (B) Relationship between the % of cases that receive treatment and the new HIV infections that are ARV-resistant (after 10 years). (C) Relationship between the relative fitness of ARV-resistant strains and the new HIV infections that are ARV-resistant (after 10 years). Relative fitness of ARV-resistant strains is defined in terms of transmissibility/infectivity; thus, for example, 60% relative fitness means that ARV-resistant strains are 40% less transmissible that drug-susceptible strains. Our sensitivity results show that the level of transmitted resistance that will emerge in developing countries is a function of viral factors (viral fitness, viral mutation rate), host factors (risk behavior, adherence), and also drug-regimen factors (ARV-induced viral load reduction will vary from regimen to regimen, since some are more potent than others) (Table 1). Thus, to minimize transmitted resistance, it
will be necessary to treat patients with ARV-resistant HIV with effective “second-line” regimens, to prevent increases in risky behavior (acknowledging that such behavior is itself often linked to risk-generating social conditions of poverty and social inequality), and to ensure high levels of adherence to effective regimens. These interventions will help to diminish the transmission of drug-resistant HIV and should be a goal of sound health policy. If, however, very fit ARV-resistant strains emerge, our predictions show that high levels of transmitted resistance are to be expected (Figure 1C). Since the level of transmitted resistance is a direct function of the usage rate of ARVs (Figure 1B), then developing countries that utilize the highest level of ARVs can be expected to have the highest levels of transmitted resistance. However, since usage rates of ARVs in developing countries will be lower than in developed countries, the rates of transmission of ARV-resistant strains will be substantially less than the rates already observed in developed countries. Resistance can also be expected to be lower in developing countries because patients in these settings were rarely treated with the ineffective mono- or dual-drug combinations frequently prescribed in the United States and Europe in the early ARV era. In addition, lower wages in developing countries render labor-intensive adherence support models feasible, and such interventions can dramatically increase therapeutic adherence. Finally, it is possible to integrate HIV prevention and care much more closely than has been done in most developed countries. Experience in Haiti and elsewhere, suggests that improved HIV care, which necessarily includes ARVs, may have a salutary effect on HIV prevention efforts. Interest in voluntary counseling and testing, a cornerstone of effective prevention, is boosted and stigma reduced in settings in which quality AIDS care is available; clinicians with recourse to these tools are also able to devote more attention to secondary prevention, believed to be an important means of reducing risky behavior.

We also predicted the impact, over time, of ARVs on the relative prevalence of both drug-susceptible and drug-resistant cases (Figure 2). If a relatively small percentage (i.e., 10%) of those infected are treated, we predict that the prevalence of ARV-resistant cases will remain low, but will

Table 1: Key Factors Increasing the Transmission of ARV-resistance. If PRCC > 0 then increasing the value of the key factor increases transmission of ARV-resistance, conversely if PRCC < 0 then increasing the value of the key factor decreases transmission of ARV-resistance.

<table>
<thead>
<tr>
<th>Key factor</th>
<th>Value of PRCC (at year 10)</th>
<th>Value of PRCC (at year 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of cases treated (10-50%)</td>
<td>0.88</td>
<td>0.88</td>
</tr>
<tr>
<td>Increase in risky behavior (0-double)</td>
<td>0.57</td>
<td>0.51</td>
</tr>
<tr>
<td>% of treated cases developing acquired resistance per year (20-70%)</td>
<td>0.51</td>
<td>0.39</td>
</tr>
<tr>
<td>ARV-induced reduction in transmissibility (due to reduced viral load) in ARV-resistant cases (50-99%)</td>
<td>-0.90</td>
<td>-0.86</td>
</tr>
<tr>
<td>Relative fitness of ARV-resistant strains (in terms of reduced transmissibility in comparison with drug-susceptible strains) (1-99%)</td>
<td>0.68</td>
<td>0.81</td>
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Fig. (2). Temporal relationship between the % of cases receiving treatment and the increase in prevalence of ARV-resistant strains (red data) and the decrease in prevalence of ARV-resistant strains (black data), after 1 year (A), 5 years (B), and 10 years (C). Prevalence of ARV-resistance: median 0.8% (IQR 0.5-1.3%) (after 1 year), median 9.8% (IQR 5.8-14.7%) (after 5 years), median 20.1% (IQR 12.5-29.6%) (after 10 years).
rise slowly over time (Figure 2, red data; minimum value is 4% after 10 years). If, however, 50% of those living with HIV receive ARVs, then we predict that the prevalence of ARV-resistant cases will reach high levels (Figure 2, red data; maximum value is 53% after 10 years). Table 2 lists the key factors (identified by the value of their PRCC) that increase the prevalence of ARV resistance and decrease the prevalence of drug-susceptible strains of HIV. These sensitivity results suggest that, unsurprisingly, increases in risky behavior will lead to increases in both the prevalence of ARV-resistant and drug-susceptible strains. The prevalence of ARV-resistant strains of HIV will also rise as the relative fitness of ARV-resistant strains increases and the effectiveness of ARV regimens in suppressing viral load decreases (Table 2). However, increasing the ARV usage rate and/or the rate of acquired resistance (r) increases the prevalence of ARV-resistance but decreases the prevalence of drug-susceptible strains (Figure 2 and Table 2). These results demonstrate that designing optimal ARV-based strategies to control HIV epidemics is extremely complex, as increasing ARV usage has both beneficial and detrimental epidemic-level effects. Therefore, control strategies should be based upon the overall impact on the epidemic and not simply upon the impact ARVs will have on the transmission and/or prevalence of ARV-resistant strains.

We also predicted (using uncertainty analysis) the percentage of HIV infections that would be prevented due to ARVs. In Figure 3A we show uncertainty analysis results for the cumulative percentage of HIV infections prevented in terms of the usage rate of ARVs after 5 years (blue data: median value 6.1%, minimum 0.3%, maximum 20%) and after 10 years (red data: median value 8.5%, minimum -5.1%, maximum 31.5%). The key factors that substantially increase the cumulative percentage of HIV infections prevented are shown in Table 3. The greater the usage rate of ARVs, the greater the reduction in the transmission of HIV (i.e., the greater the number of HIV infections prevented) (Table 3 and Figure 3A). Also, the more effective drug regimens are in suppressing viral load (and hence reducing infectivity) in both drug-susceptible cases and ARV-resistant cases, the greater the impact that ARVs will have on

Table 2: Key Factors Increasing the Prevalence of ARV-resistant Strains and Drug-susceptible Strains. If PRCC > 0 then increasing the value of the key factor increases the prevalence of ARV-resistant strains or drug-susceptible strains, conversely if PRCC < 0 then increasing the value of the key factor decreases the prevalence of ARV-resistant strains or drug-susceptible strains.

<table>
<thead>
<tr>
<th>Key factor</th>
<th>Key factors increasing the prevalence of ARV-resistant strains</th>
<th>Key factors increasing the prevalence of drug-susceptible strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of cases treated (10-50%)</td>
<td>0.98</td>
<td>0.96</td>
</tr>
<tr>
<td>Increase in risky behavior (0-double)</td>
<td>0.83</td>
<td>0.85</td>
</tr>
<tr>
<td>% of treated cases developing acquired resistance per year (20-70%)</td>
<td>0.77</td>
<td>0.50</td>
</tr>
<tr>
<td>ARV-induced reduction in transmissibility (due to reduced viral load)</td>
<td>-0.55</td>
<td>-0.58</td>
</tr>
<tr>
<td>Relative fitness of ARV-resistant strains (in terms of reduced transmissibility in comparison with drug-susceptible strains) (1-99%)</td>
<td>0.24</td>
<td>0.50</td>
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</table>
example, more than half of all sequentially diagnosed AIDS and HIV incidence is increasing rapidly. In rural Haiti, for even more true in poorer countries in which TB is endemic HIV-associated TB epidemics have been documented; it is urban North America and in Europe, where hundreds of tuberculosis and perhaps more significantly, HIV and rate at which acquired drug resistance occurs. Furthermore, and TB, good case holding and effective regimens lessen the of mutant strains, it stands to reason that, with both AIDS Although there is ongoing debate about the “relative fitness” resistance and resistance can be transmitted in both diseases. chemotherapy. In both AIDS and active TB, monotherapy mycobacterial disease, both are treated with combination and hope of radical cure distinguish retroviral and resource-poor settings [20]. Although mode of transmission this insight has informed certain AIDS treatment programs in AIDS TREATMENT PROGRAMS IN RESOURCE-POOR SETTINGS

From the outset of the ARV era, AIDS was noted to resemble another chronic infectious disease, tuberculosis; this insight has informed certain AIDS treatment programs in resource-poor settings [20]. Although mode of transmission and hope of radical cure distinguish retroviral and mycobacterial disease, both are treated with combination chemotherapy. In both AIDS and active TB, monotherapy (or otherwise weak therapy) leads rapidly to acquired drug resistance and resistance can be transmitted in both diseases. Although there is ongoing debate about the “relative fitness” of mutant strains, it stands to reason that, with both AIDS and TB, good case holding and effective regimens lessen the rate at which acquired drug resistance occurs. Furthermore, and perhaps more significantly, HIV and Mycobacterium tuberculosis afflict overlapping populations. This is true in urban North America and in Europe, where hundreds of HIV-associated TB epidemics have been documented; it is even more true in poorer countries in which TB is endemic and HIV incidence is increasing rapidly. In rural Haiti, for example, more than half of all sequentially diagnosed AIDS patients have been discovered to have active tuberculosis [21]. Even higher rates of co-infection and disease have been documented in urban Haiti, where HIV fanned an already smoldering TB epidemic [22]. Although better TB case finding can diminish the burden of HIV-associated TB [23], emerging data from Haiti and South Africa suggest that, without ARVs, it will be difficult to control HIV-associated TB epidemics, which also afflict, if less mortally, HIV-negative contacts [24-27]. In spite of their similarities, TB and AIDS have been viewed in radically different ways by those setting policy for resource-poor settings; while the treatment of AIDS is still not widely viewed as cost-effective, the treatment of TB with directly observed short-course chemotherapy (DOTS) has been declared one of the most cost-effective interventions in public health [28]. But TB offers, to all those interested in AIDS, an important precedent in the community-based management of a chronic infectious disease: TB programs reporting the highest cure rates are often those relying on non-physician community-based providers.

In Haiti, one of the world’s poorest and most HIV-affected nations, we launched a small but mature integrated prevention-and-care project that first incorporated community-based ARV use in 1998; we have described this project in detail elsewhere [20,29,30]. Our experience in central Haiti, where most AIDS patients are co-infected with M. tuberculosis and where TB is treated effectively, led us to base our model of HIV care on an established DOTS program [20,29]. A number of key elements contributed to the AIDS program’s success. First, HIV care, including ARVs, was free of charge to the patient. Second, HIV care was largely community-based, and closely monitored by outreach workers called “accompagnateurs.” The village-based accompagnateurs (some of whom are themselves living with HIV) are not so much providing directly reducing transmission (Table 3 and Figure 3B). Increases in risky behavior (and also “risk-generating” social conditions) will lead to increases in the transmission rate (PRCC < 0). Accordingly (as we have shown previously [4,10]), substantial increases in risky behavior, whatever their causes, could mask the effect of ARV-induced reduction in transmission (Table 3). It is of note, however, that integrated HIV prevention and care offers clinicians greater opportunities to emphasize prevention messages, including the need to avoid risky behavior (“secondary prevention”). This salutary preventive impact of improved care has yet to be modeled. It is noteworthy that our uncertainty analysis reveals that it is possible (although very unlikely) that usage of ARVs in developing countries could lead to slight increases in the incidence rate. In 1.4% of our predictions we found that incidence rates had increased slightly after 10 years of ARV usage (red data, Figure 3A). This effect occurred in the simulations where the efficacy of the drug regimens in reducing viral load (and hence reducing infectivity) was relatively low.

### Table 3: Key Factors Increasing the Number of HIV Infections Prevented

<table>
<thead>
<tr>
<th>Key factor</th>
<th>Value of PRCC (at year 10)</th>
<th>Value of PRCC (at year 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of cases treated (10-50%)</td>
<td>0.92</td>
<td>0.79</td>
</tr>
<tr>
<td>Increase in risky behavior (0-double)</td>
<td>-0.41</td>
<td>-0.52</td>
</tr>
<tr>
<td>ARV-induced reduction in transmissibility (due to reduced viral load) in drug-susceptible cases (50-99%)</td>
<td>0.64</td>
<td>0.46</td>
</tr>
<tr>
<td>ARV-induced reduction in transmissibility (due to reduced viral load) in ARV-resistant cases (50-99%)</td>
<td>0.59</td>
<td>0.55</td>
</tr>
</tbody>
</table>

In Haiti, increasing the number of HIV infections prevented, conversely if PRCC < 0 then increasing the value of the key factor decreases the number of HIV infections prevented.
with AIDS program goals. This approach to enhancing adherence, deemed overly ambitious by some and “comprehensive” by others [32], led to excellent clinical outcomes and negligible rates of abandonment. Finally, the treatment component of the program was linked tightly to AIDS prevention efforts, many of them spearheaded by people living with HIV. Secondary prevention, whereby patients enrolled in the treatment program were encouraged to avoid risky behaviors and to help program staff promote AIDS prevention, has been central to the Haiti program. The integrated prevention-and-care project in central Haiti project has been notable for its clinical and social success - lowered mortality [33] and decreased stigma - and also for its low costs. With the advent of generic ARVs and adequate funding, this integrated-AIDS-prevention-and-care project is now being scaled-up throughout the forbidding terrain of central Haiti, which is without electricity or paved roads [30]. Similar efforts have been launched in urban Haiti. Although Haiti remains saddled with the hemisphere’s worst AIDS epidemic, seroprevalence surveys suggest that the Haitian epidemic is contracting rather than growing [34].

Although Brazil cannot be described as “resource-poor” when compared to Haiti or sub-Saharan African countries, it offers an important example for those attempting to formulate sound AIDS policy. Early in the ARV era, Brazil became one of the first nations in the world to mandate that access to HIV care be universal and free of charge to the patient. In Brazil, AIDS was transformed from a private problem, one affecting individuals and their families, into a public one. By passing innovative legislation, Brazil was able to build up Latin America’s largest and best-functioning AIDS treatment program. The impact of this program on prevention efforts was profound. Indeed, many feel that, as in central Haiti, improved access to ARVs has helped destigmatize AIDS and thereby increased demand for voluntary counseling and testing. Although such claims are hard to prove, what is clear is that projections made over a decade ago, when it was predicted that Brazil would have a rapidly expanding epidemic, have not come to pass. Epidemiological surveillance data released in 2002 shows that HIV incidence in Brazil has declined in recent years: only 7,361 new cases of HIV disease were registered in the first nine months of 2001, compared to the 17,504 cases registered in 2000 [35]. Furthermore, widespread ARV use has reduced hospitalizations and led to a substantial reduction in the incidence of TB and other opportunistic infections. The Brazilian Ministry of Health estimates that cost savings for reduced hospital admissions and treatment of opportunistic infections between 1997 and 2001 have been close to $1.1 billion.

DESIGNING HEALTH POLICIES FOR ARVS IN DEVELOPING COUNTRIES

Health policies will have profound effects on both the course of the global HIV pandemic and on the fates of those already living with HIV. Policies that fail to promote access to ARVs for those living with both poverty and AIDS will mean that millions will continue to die each year of a disease that could be managed effectively with already-existing tools. At the same time, the increased use of ARVs, and of most other antibiotics, will mean increased rates of acquired resistance. This conundrum stands as one of many reasons that effective AIDS care has been almost absent in the resource-poor settings in which AIDS has becoming the leading infectious cause of adult death. Although demand for ARVs in such settings is enormous, it is not overtly felt because most of the afflicted are unable to pay for their therapy. There have been, to date, few effective and coordinated strategies to use these treatment agents wisely. A properly biosocial analysis of the AIDS epidemic and responses to it will draw not only on conventional epidemiology, but also on all quantitative and qualitative methodologies that might inform our understanding of AIDS and of effective health policies. As our modeling results quantitatively show AIDS-control strategies should be based upon an intervention’s overall impact on the epidemic and not simply upon the impact ARVs will have on the transmission and/or prevalence of ARV-resistant strains. Policy makers will be faced with difficult decisions in deciding how best to balance different aspects of the fight against HIV/AIDS. Integrated AIDS prevention and care must be the primary desideratum of sound and innovative AIDS policy for resource-poor settings.

To date, policy regarding ARV use in such settings has been faltering at best. Indeed, many have not hesitated to declare that ARVs are not cost-effective in the poorest and most heavily HIV-burdened countries [36,37]. However, conventional cost-effectiveness analyses have sharp limitations, particularly in developing countries where ARV prices are in great flux. Rigid economic models may have little validity or predictive value, especially when such models are not grounded in properly biosocial analyses that bring into relief the health-seeking behavior of the afflicted: most cost-effectiveness analyses fail to note that ARVs are widely available on the market in even the poorest countries of sub-Saharan Africa and Latin America. What is lacking, of course, are sound national AIDS programs that might ensure that ARVs are used wisely. All this may change in the next few years, but the degree to which change is positive and effective will depend upon many variables. Sound health policy must seek to control rather than prevent the use of ARVs in precisely those settings in which they are needed most. It is only within the past year that widespread donor-supported therapy for ARVs, such as that agreed upon a decade ago by stakeholders involved in international TB control, has gained support among policy makers and those who control funding for health budgets in resource-poor settings. Some are now asserting that HIV prevention and care, like TB control, should be considered a “public good” [38,39]. In the course of the past year, for example, the Global Fund to Fight AIDS, Tuberculosis and Malaria has made important sums available for a broad variety of programs designed to prevent or alleviate the suffering caused by the world’s leading infectious causes of adult and pediatric death. Each of these three plagues is unique in important ways, but in each instance the pathogen is vulnerable to antibiotics; in each case, acquired and primary drug resistance occur; in no case is a reliable vaccine available.

Uncertainty analysis can be a useful health policy tool for robust decision-making, since the outcome variable of interest can be examined as many variables are
simultaneously varied. The first step in designing useful ARV policies for developing countries is to decide upon the goal or goals that the policy is meant to achieve, and then to decide upon the time-frame for achieving the specified goals. Our modeling has shown that increased availability of ARVs will decrease the HIV transmission rate; thus, the higher the usage of ARVs the greater the number of HIV infections that will be prevented. However, our modeling also suggests that the higher the usage of ARVs, the greater the ensuing prevalence and the transmission of ARV-resistant strains. Thus our mathematical modeling has shown that certain goals are incompatible. It would be impossible, for example, to maximize the reduction in the transmission rate and also to minimize the transmission and prevalence of ARV-resistance. At the same time, it is impossible - and ethically undesirable - to limit access to ARVs among populations living in poverty. Every resource-poor country needs an integrated AIDS-prevention-and-control program. And each developing country in which ARVs become readily available will need to weigh the relative importance of preventing HIV infections and minimizing ARV-resistance. Given variations in modes of transmission and in local health infrastructures, it seems likely that optimal AIDS-control strategies will be country-specific, with some countries electing treatment strategies focused on reducing transmission rates and other countries choosing strategies that are focused on minimizing ARV-resistance. Specifying the usage rate of ARVs (i.e., the % of cases to receive treatment) will determine the reduction in HIV transmission; the highest usage rate (50%) will induce the maximum reduction in transmission (Figure 3A).

To determine how to minimize ARV-resistance (Figure 4, yellow data), policy makers will need to consider both the treatment rate (Figure 4, x-axis) and the rate of acquired resistance (r) (Figure 4, y-axis); Figure 4 shows the relative sensitivity of these two factors to achieving any specified level of ARV-resistance. In terms of generating ARV-resistance, the rate of acquired resistance is trivial at low usage rates of ARVs; but as usage rates increase, the rate of acquired resistance becomes increasingly important. Therefore, treatment strategies in developing countries will need to be specified both in terms of the usage rate of ARVs and in terms of a defined “acceptable” rate of acquired resistance.

There are other reasons to seek improvements in AIDS prevention-and-care policies. In the absence of an effective vaccine, it is important to note that current prevention methods are of limited efficacy. Even more troubling is the fact that existing prevention methods are only poorly studied. After two decades of relying solely on information and education as the primary tools in HIV prevention, there have been, until very recently, no careful studies of the efficacy of these interventions. One metanalysis of information and education campaigns concluded that, “somewhat surprisingly, towards the end of the second decade of the AIDS pandemic, we still have no good evidence that primary prevention works” [40]. It is important to draw sound conclusions from such reviews, since there are obvious policy implications. Information and education campaigns are necessary but insufficient; the efficacy of such campaigns, which are designed to lessen risky comportments, is related to local social conditions. Poorer outcomes - a lack of reduction in risky behaviors - have been documented in the poorest and most heavily HIV-burdened settings. Social conditions, rather than ignorance about HIV and its modes of transmission, are the primary determinants of risk in many of the poorest parts of the world. Furthermore, it is difficult to categorically class on-the-ground activities as contributing to “prevention” versus “treatment.” For example, most policy makers would class the prevention of mother-to-child transmission of HIV (pMTCT) as a prevention activity. But implementing pMTCT programs often leads to improved prenatal care. Similarly, as noted, improving HIV care helps to destigmatize AIDS and leads to increased interest in voluntary counseling and testing, a cornerstone of effective HIV prevention and care [20,29]. Improving HIV care, which necessarily means making ARVs available to those with advanced HIV disease, leads to a marked decreased in the number of opportunistic infections (including TB) suffered by persons with advanced AIDS. Clinic time that, prior to the usage of ARVs, had been dedicated to the management of thrush or diarrhea can instead be spent imparting important secondary prevention information. Therefore, ARVs can help to afford clinicians (whether doctors or nurses or community health workers) more time to reinforce prevention messages.

In previous work, we have attempted to move beyond sterile debates regarding prevention versus care and catalogued the mechanisms by which increased access to quality HIV care can strengthen prevention efforts, seeking to assess the likely impact of ARVs on the future of the epidemic in developing countries [10]. In this paper, we seek to show how mathematical models can be married to program experience and to a properly biosocial analysis in order to predict the potential impact that even low to moderate usage rates of ARVs might have on HIV epidemics in developing countries. We have determined the relationship between the specific usage rate of ARVs (in terms of the percentage of cases that receive treatment) and: (i) the prevalence of drug-resistant HIV that will arise, (ii) the future transmission rate of drug-resistant strains of HIV, and (iii) the cumulative number of HIV infections that will be prevented. We have shown that designing optimal control strategies is difficult and that optimal control strategies are

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**Fig. (4).** Relationship between % of cases receiving ARVs (x-axis) and rate of acquired resistance (y-axis) in increasing the prevalence of ARV-resistance (after 5 years of ARV usage). Prevalence of ARV-resistance: yellow data 0.7-2.8%, blue data 2.8-4.8%, orange data 4.8-6.9%, green data 6.9-9.0%, and red data 9.0-11.0%.
likely to vary between countries. We must act swiftly to use ARVs prudently in settings in which health infrastructures are weak and now weakened further by the advent of AIDS. It is urgent that all those concerned to slow the AIDS pandemic - whether policymakers or clinicians or those who study the pandemic - seek to formulate sound policies designed to lessen the terrible suffering caused by HIV. Mathematical modelling (if carefully done) should be used to inform the design and implementation of integrated AIDS-prevention-and-care strategies in developing countries.

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ABBREVIATIONS
AIDS = Acquired Immunodeficiency Syndrome
HIV = Human Immunodeficiency Virus
ARV = Antiretroviral
TB = Tuberculosis
PDF = Probability Density Function
IQR = Interquartile Range
PRCC = Partial Rank Correlation Coefficient
DOTS = Directly Observed Short Course Chemotherapy
PMCTC = Prevention of Mother to Child Transmission Chain

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