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ANTIBIOTIC RESISTANCE AMONG THE AIDS-IMMUNOCOMPROMISED: A MODEL OF ITS INFLUENCE ON MICROBIAL EVOLUTION

By

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ABSTRACT OF THE DISSERTATION

Antibiotic Resistance Among the AIDS-immunocompromised:

A Model of Its Influence on Microbial Evolution

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First recognized in 1981, the AIDS pandemic has had a tremendous impact on global public health. Despite the development of highly active anti-retroviral therapy, which significantly slows the progression of HIV, HIV/AIDS continues to pose a significant health concern; its effects on the immune system leave individuals with active AIDS at increased risk for colonization by opportunistic pathogens. To address this, AIDS patients have traditionally relied upon curative and prophylactic antibiotics to treat and prevent infection, respectively. However, the use of antibiotics exerts a selective pressure against drug-sensitive microbial strains, thus bolstering the evolutionary fitness of drug-resistant strains by allowing them to persist without competition. When this occurs, resistant strain dominance can threaten the efficacy of both targeted and prophylactic antimicrobials, thereby creating health risk for both immunocompetent and immunocompromised hosts.

Although mathematical modeling has been used to study the emergence of antibiotic resistance in a variety of settings, the question of how the microbial evolutionary landscape is changed by a highly immunocompromised host population has not been addressed. My research uses compartmental epidemiological modeling to

examine the evolutionary effects of changes in the prevalence and fitness of drug-sensitive and drug-resistant pathogens due to antibiotic use in highly AIDS-affected regions. I apply an SEIR model to study the means by which collective host immunosuppression creates a novel environment for the emergence and maintenance of drug-resistant bacterial pathogens. Broadly, I address three questions.÷ First, I examine the immune status-based differences in relative contribution to the emergence of antibiotic resistance when curative antibiotic adherence is varied among the actively AIDS-immunocompromised. Second, holding HIV/AIDS prevalence constant, and varying percent antibiotic prophylaxis treatment among HIV/AIDS patients, I analyze the risks and benefits of prophylaxis use. (Although prophylactic use prevents opportunistic infection, it potentially selects for the emergence of antibiotic resistance at the same time.) Third, I vary the prevalence of prophylactic antibiotic and resistant strain fitness to analyze the condition-dependent differences in the evolutionary success of drug-resistant and drug-sensitive pathogen strains.

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INTRODUCTION

A Brief Overview of Behavioral Epidemiology

Though there continues to be debate in the primary literature as to how to define the field of behavioral epidemiology, Sallis, et al. [1], have devised a five-point framework that provides the basic tenets of the field. Their paradigm includes the following phases: "1) establish links between behaviors and health; 2) develop measures of the behavior; 3) identify influences on the behavior; 4) evaluate interventions to change the behavior; and 5) translate research into practice [1]."

Behavioral epidemiological modelers must consider each of these phases during the design and parameterization of their models. For example, there is ample evidence that the failure to prescribe (on the part of the health professional) or use (on the part of the patient) antibiotics appropriately selects for the emergence of drug-resistant pathogen strains [2-5]. Thus, in modeling the expected emergence attributable to a particular patient demographic, it is helpful to include a parameter representing the probability that antibiotics will be prescribed and/or used in accordance with dosing instructions. In assigning that probability, it is also necessary to take into account the myriad of factors, including, but not limited to, diagnostic difficulties, patient age and socioeconomic status and the side-effect profile of the drug [2, 6], that can influence the decision to prescribe and/or consume antibiotics. Just as understanding behavioral drivers is important in other epidemiological fields such as addiction and obesity research [7, 8], the inclusion of behavior-associated parameters in infectious disease models can enhance their value with regard to shaping public health policy.

The HIV/AIDS Pandemic

First recognized in 1981[9], the HIV/AIDS pandemic has had a tremendous impact on global public health. Research into the progression from HIV to AIDS [10-12] has enabled the development a highly active anti-retroviral therapy (HAART) regime. HAART suppresses viral replication, thereby significantly slowing the progression of HIV and enabling affected individuals to live considerably longer than was once possible [13-15]. Nevertheless, HIV/AIDS continues to pose a significant health concern – especially in developing countries [16, 17] – with the World Health Organization estimating that as many as 34 million people worldwide may currently be HIV-positive [18].

Once HIV progresses to AIDS, the immune system loses function and is unable to effectively ward off pathogens. As a consequence, individuals with active AIDS are considerably more susceptible to opportunistic infections than their fully immunocompetent counterparts [15, 19-21]. To minimize morbidity and mortality associated with antibiotic-sensitive opportunistic pathogens, the AIDS-immunocompromised have traditionally relied upon regimens of targeted or prophylactic antibiotics [22-24]. Yet, the use of antibiotics – even in an appropriate manner – carries the risk selection for drug resistance [25-27]. Emergence of resistance can be particularly problematic in an AIDS-prevalent host population due to the twofold health risk associated with suppressed immune function and a lack of effective antibiotic treatment.

A number of factors characteristic of AIDS-prevalent geographical regions – especially within the developing world – can compromise appropriate antibiotic use [28-32], with the unintended result being that targeted and prophylactic antibiotic regimens

actually contribute to the emergence of antibiotic resistance in these locations [22, 24, 33, 34]. In developing countries, the risk of community-acquired infection is high [35], yet community access to medical care is limited. This lack of access undermines efforts to implement and enforce antimicrobial use policies [28]. Moreover, in the absence of highly trained medical professionals, antibiotic distribution may be left to pharmacists who have limited knowledge of appropriate antibiotic use [36, 37]. Those seeking treatment may therefore be ill-informed with respect to proper dosing protocols, or they may simply be unable to sustain these protocols for practical/economic reasons. Either way, the ultimate result is an increased probability of the emergence of antibiotic resistance. Both immunocompromised and immunocompetent individuals may, therefore, be at greater risk of infection by resistant pathogens as resistant strains selected for in AIDS patients are transmitted throughout the population as a whole.

Biological and Behavioral Components of Antibiotic Resistance

The emergence of antimicrobial resistance represents an interaction between biology and behavior wherein host healthcare decisions act as a catalyst for the biological changes that contribute to the selection for antibiotic-resistant organisms [29, 38-40]. Behaviorally, antibiotic resistance is primarily attributable to inappropriate use of antimicrobials [4, 41-43]. Within the context of a patient-practitioner relationship, antibiotic misuse can refer to the prescription of antibiotics in the absence of a treatable bacterial infection, the failure to finish a prescription as directed, and the use or prescription of antibiotics such that they circulate within the host's system in a subtherapeutic dose, thereby diminishing efficacy [2, 44, 45].

Patients fail to complete appropriately prescribed antibiotic regimens for a variety of reasons, but one important factor which is known to affect their decision-making process regarding adherence is availability of medical and financial resources [46, 47]. Especially within the developing world, which is the focus of my research, resource availability has the potential to become critical to behavioral motivation if HIV/AIDS patients with limited monetary resources elect to direct those resources toward HAART, rather than curative and/or prophylactic antibiotics.

Biologically, within bacterial colonies, the persistence of resistance genes – which generally initially arise due to genetic mutations [48, 49] – is attributable to the sharing of DNA via conjugation [48, 50-53]. Subsequent selective pressures against antibiotic-sensitive microbes also contribute to the persistence of antibiotic resistance (discussed in more detail below).

The Evolutionary Impact of Antimicrobial Resistance within AIDS-prevalent Populations

Although the goal of antimicrobial therapy is to select against the active target infection, even appropriately prescribed antibiotics can select against other drug-sensitive members of the host's microbiome (*i.e.,* the microbes which have colonized, but are not actively infecting, the host) [54]. The result of this side-effect is selection for antibiotic-resistant microorganisms, which occurs in two ways: First, if preexisting resistant organisms are present within a host, antibiotic use will eliminate only their antibiotic-sensitive commensals, thereby leaving the host vulnerable to increased colonization by the resistant strain [45]. Second, antibiotic-induced elimination of normal host flora permits the invasion by resistant microbes, which, even if they are not yet pathogenic, can still flourish in the absence of competition for host resources [45].

While, initially, the presence of benign microbes may not pose an infection risk to the host, these microbes have the potential to mutate and become pathogenic under the selective pressure of antibiotic treatment. Strains that, in a healthy host, might exist solely as benign background pathogens can result in infections needing treatment among the immunocompromised. Under this circumstance, it may be necessary to eliminate the entire pathogen burden via antibiotic use. Unfortunately, this strategy not only has the potential to disrupt normal physiological function, it can allow for strain replacement by antibiotic-resistant pathogens, since the clearing of the original strains eliminates antibiotic-sensitive competitors [55].

Moreover, even if these "background" microbial strains mutate in the presence of antibiotics to become pathogenic, in the average host general immunocompetence limits their ability to cause active disease [56, 57]. Among the AIDS-immunocompromised, however, this is not the case. Instead, a limited – or completely non-functional – immune system fails to curtail replication among the same drug-resistant pathogens that antibiotics fail to target [58]. So, when antibiotics are misused and there is selection for resistant strains among the host's background pathogen load, AIDS-positive (AIDS+) hosts become reservoirs for the emergence of new variants [59]. Therefore, it is clear that the burden of infectious disease can be further complicated by the interaction between a high prevalence of HIV/AIDS and the presence and emergence of multi-drug resistant pathogen strains commonly isolated from HIV-infected individuals [35, 60, 61].

The novel environment created by an AIDS-prevalent host population may decrease – or effectively eliminate – the pathogen fitness penalty that can accompany resistance [62], such that the resistance gene actually becomes beneficial. If suppressed

host immunity allows for successful pathogen replication, despite any maladaptive traits that may accompany the resistance gene, high AIDS prevalence communities may actually be more conducive to resistant pathogen persistence. Under these conditions, the new strain has time to accrue traits that would allow further success in immunocompetent hosts. With this potential boost to the relative fitness of the resistant pathogen comes the potential for increased health risks to both immunocompetent and immunocompromised individuals, since both are vulnerable to pathogens unresponsive to antibiotic treatment. My research examines the epidemiological risk of heightened emergence of antibiotic resistance, and the changes in infection risk and potential pathogen evolution that result from the disrupted ecosystem created by a highly AIDS-immunocompromised host population.

Modeling

Although mathematical modeling has been used to study the emergence of antibiotic resistance in a variety of settings [45, 63-69], including with respect to cases of immunosuppression due to AIDS- [70], no one has asked how the evolutionary landscape is changed by the relationship between resistant pathogens and the host population in areas with high HIV/AIDS prevalence. My dissertation research consists of the application of an SEIR epidemiological model to study the population-level impact on groups of people whose collective immunosuppression creates a novel environment for drug-resistant pathogens.

First detailed by Kermack and McKendrick [71, 72], and extensively discussed by Anderson and May [73], compartmental modeling has proven to be a valuable tool with respect to predicting epidemiological trends. Compartmental models divide the population being studied into discrete categories, or compartments, that reflect the health

status – susceptible (S), infectious (I) or recovered (R) – of the individuals within the group. Infection-specific compartments can also be added to the model when necessary. For example, having parameterized my models based on data specific to tuberculosis, it was necessary that I account for the latent period characteristic of TB [74]. To address this, I included a category within which individuals that have been exposed (E) could be counted. When individuals are exposed, *i.e.*, no longer susceptible, the rate of transmission by random contact between infected individuals with the rest of the population is reduced. However, exposed individuals do not yet contribute to the number of infectious individuals themselves. Given these conditions, the inclusion of the exposed within the S or I compartments is not appropriate).

Because the portion of the population that corresponds to each category may change over time – especially during an epidemic – each compartment is set forth as a function of time. In its simplest form, the SIR model is represented by the series of ordinary differential equations that are explained below. Also included in the model are two common parameters, β and γ, which represent the composite probability of susceptible-infective contact and infection transmission, and the rate of recovery, respectively.

In a basic SIR model, the following equation denotes a change in the number of individuals susceptible to infection over time:

$$\frac{dS}{dt} = -\beta SI$$

Eqn. 1

Susceptibles who contract the infection transition into the infective category at a rate traditionally represented by β. Assuming a closed system, changes in the size of the

infectious population over time are attributable to the entry of new infectives and departure of those who recover at a rate of γ. Equation 2 is used to represent these transitions.

$$\frac{dI}{dt} = \beta SI - \gamma I$$

Eqn. 2

When we assume that immune memory loss is instantaneous, the third equation is used to determine the return rate from recovered to susceptible.

$$\frac{dR}{dt} = \gamma I$$

Eqn. 3

Though further detail regarding the extension of the above equations (including the differential equations added to capture the change in the size of the "exposed" subpopulation) to address my research questions will be provided below, I note that I do not include HIV/AIDS as an epidemiological process. While the members of my study populations are characterized by both immune and bacterial infection status, I assume no seroconversion over the 180-day duration of the model [75]. The "compartments," therefore, refer to bacterial infection status alone (*i.e.* "S" signifies susceptibility to bacterial infection, regardless of HIV status), with the model being parameterized to account for immune status-specific factors such as the presumed increased susceptibility of the AIDS-immunocompromised to pathogen infection.

Research Questions

The SEIR model I developed is applied (with modifications as appropriate) to three broad research questions, each of which is further discussed in its own designated chapter. I first examine the potential magnitude of the effect that antibiotic use in highly AIDS-immunocompromised populations may have on the emergence of antibiotic resistance by quantifying the relative emergence attributable to each of three immune status-based categories. I then present a risk-benefit analysis of the use of antibiotic prophylaxis, given its propensity to select for antibiotic resistance, while at the same time protecting the AIDS-immunocompromised from opportunistic bacterial pathogens. Finally, I model the condition-dependent differences in drug-sensitive and resistant strain dominance when prophylactic antibiotic use and relative pathogen strain fitness are varied within the host population.

A Global Health Threat from a Novel Environment:

Emergence of Antibiotic Resistance in Immunocompromised Host Populations

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Abstract

The evolution of antibiotic resistance is far outpacing the development of new antibiotics; and, with this, comes a global public health concern, wherein emerging infections may be unresponsive to antimicrobials. This risk is magnified in highly AIDS-immunocompromised populations for two reasons. First, widespread, population-level immunoincompetence creates a novel host environment with disrupted selective pressures. Second, within AIDS-prevalent populations, the recommendation that antibiotics be taken to treat and prevent opportunistic infection raises the risk of selection

for drug-resistant pathogens. To assess impact of HIV/AIDS on the emergence of antibiotic resistance – specifically in the developing world – we present an SEIR epidemiological model of bacterial infection, and parameterize it to capture HIV/AIDS-attributable emergence under conditions of both high and low HIV/AIDS prevalence. We demonstrate that HIV/AIDS-immunocompromised hosts could be responsible for a disproportionately greater contribution to emergence of resistance than would be expected based on population-wide HIV/AIDS prevalence alone. As such, the AIDS-immunocompromised have the potential become wellsprings of novel, resistant, opportunistic pathogen strains that can propagate into the broader global community.

Introduction

The rapid emergence of antibiotic resistant microbes represents a worldwide health risk since development of antibiotics is being outpaced by the evolution of resistance [76]. Factors contributing to resistance include prescribing habits of health professionals, antibiotic policy-making decisions, drug availability, and sociocultural beliefs regarding the necessity of antibiotics [5]. Regardless of the drivers of emergence, the result is the same: antibiotic-resistant infections. We have seen the dangers of drug resistance exemplified in bacterial pathogens such as *Escherichia coli*, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, *Clostridium difficile*, and *Staphylococcus aureus*, each of which includes strains unresponsive to at least one antimicrobial agent [5, 77].

We expect the risk of emergence to be magnified in regions where selection for drug-resistant pathogens is particularly high. Thus, we consider the potential for AIDS-prevalent populations to serve as hotbeds of emerging resistance. One of the most

important tools in opportunistic infection management among the AIDS-immunocompromised is a constant regimen of antibiotics [19]. However, the use of antibiotics – even appropriately – exerts a strong selective pressure upon drug-sensitive pathogens [2]. Therefore, in highly HIV/AIDS-prevalent populations (>25% prevalence) [78], resistance develops and proliferates quickly [79], as constant use of antibiotics advances the emergence and maintenance of drug-resistant microbes [80]. This effect is compounded under conditions of limited drug availability and/or non-adherence to antibiotic protocols [2]. Under these circumstances partially resistant strains benefit from increased probability of survival, which also increases their chance of evolving greater resistance. Further, while antibiotics usually act in concert with the host's immune system to combat infection [81], AIDS-immunocompromised hosts lack the additional selective pressure imposed by immunocompetence against all pathogen replication. Even usually antibiotic-sensitive strains may therefore be able to survive 'normal' antibiotic doses longer in these patients. This effect can bolster their potential to survive long enough to increase resistance by mutation or horizontal gene transfer [3, 82].

For these reasons, populations with a high prevalence of active AIDS cases represent novel environments with unique selective pressures leading to potentially drastically different probabilities of emergence of antibiotic resistance, relative to those expected in an immunocompetent population. This is particularly concerning in resource-poor regions, where access to full courses of antibiotics may be limited by drug availability and economic constraints [83]. (We note that antibiotic adherence can also be undermined – and selection for resistance increased – by excessive availability of antimicrobials that can often be purchased without a prescription [84].) If AIDS-prevalent

regions are serving as wellsprings of drug resistance, emergence of resistance is not limited to just those areas. The movement of hosts who are either actively infective or harboring resistant, but currently benign, microbial strains can create a global health threat [85]. As the debate continues over how to allocate antibiotics so as to minimize the emergence and propagation of resistance [3], policy decisions must account for resistant microbial strains spreading from one region to another via host migration [86].

To demonstrate the potential impact of AIDS prevalence on the likelihood of emergence of antibiotic resistance in the developing world, we present an SEIR compartmental model [71]. We parameterize this model to reflect conditions in two resource-limited communities, one with 27.4% -HIV/AIDS prevalence (Swaziland) [78], and one with 0.46% HIV/AIDS prevalence (Indonesia)[87]. In addition to the potential for non-adherence that is created by resource limitations, we have chosen to focus on the developing world for two reasons. First, despite the growing availability of antiretrovirals, developing nations remain at risk for an increase in the prevalence of HIV/AIDS (and, therefore, AIDS-defining illnesses) [17]. Second, the growing incidence of nosocomial infections indicates that resistance will arise rapidly within hospital settings in these regions [2]. The combination of these factors suggests that AIDS-prevalent host populations in the developing world may ultimately be responsible for a disproportionate number of resistant infections, which presents a significant worldwide health risk to both immunocompetent and AIDS-immunocompromised individuals.

Fully and functionally immunocompetent hosts can still contribute to antibiotic resistance. Thus, we use our model to quantify the relative contribution to the emergence of resistance from both fully immunocompetent and HIV/AIDS patients receiving highly

active antiretroviral treatment (HIV/AIDS+, HAART +) hosts. We also compare the actual contribution to emergence attributable to AIDS-immunocompromised hosts to that which would be expected based on AIDS prevalence alone. We do so by computationally reducing HIV/AIDS prevalence to zero in both countries and then measuring the magnitude of the corresponding decreases in infection prevalence and total emergence. Finally, holding antibiotic adherence constant among infectives, we calculate total emergence as a function of gradually increasing HIV/AIDS prevalence.

Mathematical Model

Our model examines the relative rate of emergence of antibiotic resistance in populations whose collective immunosuppression and prescribed antibiotic use patterns disrupt the selective pressures typically exerted on bacterial pathogens by host immune function and medically recommended antibiotic-taking behavior. The vast difference in HIV/AIDS prevalence that exists between Indonesia (0.46%) and Swaziland (27.4%) [78, 87] suggests that there is a significant difference in the proportion of each population that is actively recommended to be taking antibiotics at any time.

We defined our population according to four descriptors: immune (HIV/AIDS) status, HAART adherence, bacterial infection status, and antibiotic adherence. We denote immune and HAART status by $^{\text{superscript}}$, and bacterial infection status and adherence to antibiotics by $_{\text{subscript.}}$ (All possible super/sub-script combinations appear in Appendix 1.) Using tuberculosis (TB) as an example of a pathogen affecting both immunocompromised and immunocompetent individuals, the model follows the progression of bacterial infection throughout an HIV/AIDS-stratified population, including the impact of antibiotic treatment with different levels of adherence (Figure 1).

We describe this scenario using a system of ordinary differential equations that appear in Appendix 1, along with a detailed list of parameters, their condition dependencies, values used, and the reference from which they were estimated.

Methods

Considerable variability in antibiotic adherence – and in the prevalence of TB and HIV/AIDS – exists worldwide. The model was therefore run under all combinations of tuberculosis prevalence, host immune status, and antibiotic adherence under parameters representing the HIV/AIDS prevalence in both countries.

In both Indonesia and Swaziland, and under conditions of both high and low TB prevalence (as informed by the World Health Organization's Global Tuberculosis Report, 2012 [88]), we calculated the projected total number of bacterial infections contracted over 180 days. We then used that calculation to quantify the relative emergence of antibiotic resistance attributable to AIDS-immunocompromised hosts versus those who are HAART-adherent or fully immunocompetent. This analysis required that we establish a relative probability of emergence corresponding to each immune status/antibiotic adherence category. We accomplished this by multiplying the number of bacterial infections predicted by our model for each subpopulation by: (1) the per-cell per-bacterial generation mutation rate, (2) the expected total number of infected cells per host, (3) the expected number of bacterial generations per infection duration, and (4) the relative success of the mutant strain (see Appendix 1) [58, 89-91].

To quantify the impact of AIDS-immunocompromised hosts on overall TB prevalence, as well as total emergence, we conducted a trial in which HIV/AIDS prevalence was computationally reduced to zero for each population. We thus calculated the total emergence and total bacterial infections contracted in a fully immunocompetent population without changing the overall host population size or prevalence of infectives. Comparing these two parameters between HIV/AIDS-absent and HIV/AIDS-prevalent populations provided the expected AIDS-attributable increase in emergence. We used this increase to test the neutral assumption that the percentage of emergence associated with each type of infective host should be equivalent to the prevalence of that host category within the total population. For example, in Swaziland, 27.4% of the population is HIV/AIDS+ [78]. Of that proportion, we assumed, as an initial condition, that 7% is actively AIDS-immunocompromised [92]. We compared the model projections for the emergence of resistance against the assumption that emergence attributable to actively AIDS-immunocompromised hosts should mirror the prevalence of AIDS-immunocompromised hosts within the population, with the remaining emergent infections originating from those who are fully immunocompetent or HAART-adherent.

Finally, to investigate the full range of AIDS-attributable potential impacts on antibiotic resistance emergence~~,~~ we conducted a trial in which we varied HIV/AIDS prevalence in 5% increments ranging from zero to 30.0%. (At 27.4%, Swaziland's adult HIV/AIDS prevalence is the currently highest in the world [78]. Based on the nearly 1% increase in prevalence that has occurred in Swaziland since 2013[78], we expect that 30% of Swaziland's population could be HIV/AIDS+ within the next few years.) We recognize that considerable variability in TB prevalence can exist between host

populations; however, for purposes of illustration, we chose our initial prevalence based on the example of Swaziland's low infection condition [88].

Results

Relative Emergence

The relative contribution to total emergence attributable to fully immunocompetent and HAART-adherent hosts, versus those immunocompromised by active AIDS, shows that AIDS-immunocompromised infectives are responsible for 0.09 to 7.52% of emergence, depending on the combination of population-wide HIV/AIDS prevalence and bacterial infection prevalence (detailed in Table 1 and visualized in Figures 2a and 2b).

While these percentages might initially suggest that fully immunocompetent and HAART-adherent hosts pose the greatest health risk with respect to their relative responsibility for emergence, it is important to keep in mind that such hosts represent a much greater portion of the population. In Indonesia, actively AIDS-immunocompromised infectives comprise less than 0.03% of the entire adult population, In contrast, the AIDS-immunocompromised infectives account for less than 4% of all adult Swazilanders [92]. Consequently, a significantly larger proportion of the susceptible population in each country was fully or functionally immunocompetent at the outset of the model.

In analyzing the relative contribution to emergence attributable to each immune status, our results demonstrate that, at the very least, AIDS-immunocompromised infectives are individually responsible for nearly twice as many antibiotic-resistant infections as their comparators (Table 1). This result, which occurs despite our

conservative assumption of 20% antibiotic adherence [93], is troubling in light of the large body of research suggesting that full adherence to dosing instructions is rare in the developing world[2].

Moreover, the neutral assumption would be that the proportion of drug-resistant TB attributable to AIDS-immunocompromised hosts should be roughly equivalent to the proportion of AIDS-immunocompromised infectives in the population as a whole. Therefore assuming a neutral impact, in Indonesia, we would expect approximately 0.03% of resistant infections to be AIDS-attributable; and, in Swaziland, we would expect approximately 4% of resistant infections to arise in AIDS-immunocompromised hosts. However, this is not the case in either country. As seen in Figures 2a and b, which provide a side-by-side comparison of population-wide immune status and mean contribution to total emergence, AIDS-attributable emergence is considerably greater than would be expected based on neutral impact from population AIDS-prevalence alone. In Indonesia, AIDS-immunocompromised hosts are responsible for an average of 0.09 to 0.14% of emergence, depending on bacterial infection prevalence. In Swaziland, AIDS-attributable emergence accounts for an average of 7.32 to 7.52% of total emergence, despite the AIDS-immunocompromised being a smaller portion of the total infective population.

Knock-out Trials

The impact of HIV/AIDS on the emergence of antimicrobial resistance is even clearer when we calculate projected emergence after having reduced HIV/AIDS prevalence to zero. Having used TB data to inform bacterial infection prevalence, and recognizing that HIV-incident TB is common (especially in Swaziland, where an

estimated 77% of those with TB are also HIV+ [88]), we expected that computationally reducing HIV/AIDS prevalence to zero would greatly decrease the expected number of new bacterial infections. Figures 3a and b illustrate the difference in total expected infection incidence, as well as the shifts in health-status based infections, when HIV/AIDS+ hosts are absent. In both countries, the presence of HIV/AIDS+ hosts results in a disproportionate increase in TB incidence, relative to the percentages of such hosts present in the population. This effect is particularly pronounced in Indonesia where, despite the low initial prevalence of both TB and HIV/AIDS, the continuous availability of susceptibles permits for TB persistence [87, 88].

Variation in HIV/AIDS Prevalence

When we explored the full range of potential impacts of HIV/AIDS prevalence on emergence of antibiotic resistance, we found that as prevalence increases, we also see a near-linear increase in expected population-wide emergence (Figure 4). This result, which occurs even if infectives are assumed to adhere to dosing instructions an idealized 95% of the time, demonstrates the importance of the relationship between HIV/AIDS and antibiotic emergence. Even with near-perfect adherence – which is particularly rare within the developing world[32] – emergence of antibiotic resistance increases in response to increased HIV/AIDS prevalence. The relative impact of HIV/AIDS on emergence, versus that of adherence to dosing protocols, is further illustrated in Figure 5, wherein we demonstrate that emergence remains nearly unchanged as antibiotic adherence increases.

Discussion

Highly AIDS-prevalent populations represent a novel pathogen environment due to the combination of widespread immunoincompetence and antibiotic use. In such populations, antibiotics are used more frequently, and for longer periods of time, to treat and guard against opportunistic infections affecting the AIDS-immunocompromised [94]. This treatment scenario raises the risk of a global public health threat as these populations, following standard antibiotic protocols, may become wellsprings of novel resistant pathogen strains that can propagate into the broader global community. (Note that, while this work is focused specifically upon TB as a particular bacterial pathogen, many bacterial pathogens of accrue antibiotic resistance, and viral and parasitic infections can also be treatment-resistant, presenting additional health concerns to already at-risk populations [95]).

In consideration of these circumstances, as well as the high degree of antibiotic misuse that is characteristic of the developing world [83], we expected that increased HIV/AIDS prevalence would rapidly accelerate the emergence of antibiotic resistance among circulating bacterial infections. This expectation proved true in both Swaziland and Indonesia where the AIDS-immunocompromised were found to be individually responsible for a 1.82 to 5.35-fold increase in emergent resistant infections than would be expected based on HIV/AIDS prevalence alone.

Despite the considerable difference in HIV/AIDS prevalence that exists between Indonesia and Swaziland, the effect of HIV/AIDS on emergence in Indonesia was still concerning – especially in light of our assumption that only 7% of those with HIV/AIDS are actively immunocompromised due to lack of HAART treatment [92]. Despite this

small percentage of AIDS-immunocompromised hosts, we observe at best a nearly two-fold increase over our AIDS prevalence-based expectation of emergence.

Swaziland's HIV/AIDS prevalence is currently the highest in the world [78], yet, HIV/AIDS+ Swazilanders still comprise a minority of the population, especially assuming that only 7% of the HIV/AIDS+ population is actively immunocompromised[92]. Despite its size, that portion of the population is responsible for a disproportionate number of emerging drug-resistant infections. This result is particularly troubling when we consider the transmission of resistant strains. For purposes of simplicity, we have modeled emergence as a percentage of total infections only, *i.e.*, without including parameters for intra-host strain competition or secondary resistant infections arising out of host-to-host or horizontal transmission. We therefore recognize that our results represent a conservative estimate of emergence. Accordingly, future work will address the propagation of resistance that occurs when susceptibles are exposed to resistant infections.

The increased likelihood of resistance emergence that occurs within AIDS-prevalent host populations represents a previously unrecognized global health risk that can be entirely ascribed to the novel environment created by the presence of widespread, population-level immunosuppression. We must begin to consider cross-disease implications for long-term treatments, since emergence of resistance is not solely limited to target bacteria, but also occurs within the greater host microbiome due to both selective pressure and horizontal gene transfer [96]. This type of emergence can result in the replacement of antibiotic-sensitive strains with resistant ones [97]. As exemplified by

both viral and bacterial pathogens, the eventual result of these processes is compromised efficacy among previously successful treatment regimens [97, 98].

We demonstrated that a significant proportion of antibiotic resistance is attributable to AIDS-immunocompromised hosts. Therefore, we must also consider the associated impact – and potential tradeoff between individual and public health – that arises in the context of antibiotic regulation and policy recommendations for treating infection in the developing world. Even discounting the health behavioral choices made by AIDS-immunocompromised individuals, limited and/or excessive access to antibiotics, coupled with the potential for distribution by medical professionals unfamiliar with optimal administration protocols [32, 84], ensures the continuing risk of rapid emergence of antibiotic resistance. To foster best medical practices, it is necessary that antibiotic cycling recommendations balance the ethical considerations associated with both personal medicine and public health, such that an active, purposeful, consideration of public health is inherent in antibiotic policy decisions. That said, changes to dosing regulations that may involve the withholding of antibiotics from those unlikely to adhere to prescribing instructions are not without their own set of ethical considerations. The ethical questions surrounding the withholding of potentially life-sustaining treatments – especially among those whose access to antibiotics is already limited by economic constraints – are equally complex, and remain the subject of considerable debate [99]. However, considering the disproportionate increase in drug-resistance that accompanies the presence of HIV/AIDS-affected hosts in an otherwise healthy population, a greater population-level health risk than that imposed by AIDS may occur in the presence of strong selection for antibiotic-resistant microbes.

Acknowledgements

We thank Drs. Julie Lockwood and Yana Bromberg for very helpful comments on the initial design of the research. We also thank Drs. Eva Top, Jeffrey Townsend, Bradford Greening, Jr., and Kellen Myers, for their expertise and generosity in providing feedback.

Figure Legends

Figure 1 a-b. SEIR Transmission Dynamics

1a shows a basic SEIR model (assuming a closed system), wherein health status changes from susceptible to exposed at a rate of β, from exposed to infectious at a rate of ζ, and infectious to recovered at a rate of γ. The super- and subscripts “i” and “a" are used generically to demonstrate that there are many possible host health outcomes, depending on the combination of immune status and antibiotic-taking behavior. The flowchart seen in 1b depicts transmission dynamics specific to our model; we note all possible progressions for an HIV/AIDS- host that contracts a bacterial pathogen.

Figure 2. Immune Status-based Contributions to Emergence

In both Indonesia and Swaziland, and under conditions of both high (H) and low (L) TB prevalence, AIDS-immunocompromised hosts are individually responsible for considerably more emergence that would be expected given their prevalence in each country. (We have made the simplifying assumption that HIV/AIDS+, HAART+ hosts are functionally immunocompetent except with respect to loss of immune memory.)

Figure 3 a-b. Population Infectivity with and without HIV/AIDS

Under conditions of high (H) and low (L) TB prevalence, we compare health status-based TB incidence in Indonesia (Figure 3a) and Swaziland (Figure 3b), visualizing conditions of both actual and zero HIV/AIDS prevalence. In both countries, AIDS increases total incidence. In Swaziland, when TB prevalence is low, we observe a an increase in incidence of 9.6%, relative to the AIDS-absent condition; when TB prevalence is high, the relative increase in incidence is 9.9%. In Indonesia, the changes in TB incidence are much more pronounced, with an observed 167.9% increase when TB prevalence is low and a 167.12% increase when TB prevalence is high. Immunocompetent. (We assume 20% adherence to antibiotics, except where specifically noted [93].)

Figure 4. Emergence as a Function of Increasing HIV/AIDS Prevalence

Using Swaziland's low TB condition as an example, and assuming 95% antibiotic adherence [93], we found that, as HIV/AIDS prevalence increases from zero to 30%, we observe a corresponding increase in expected population-wide emergence of antibiotic resistance. Our conservative estimate of 20% antibiotic adherence represents a best-case scenario in terms of expected emergence; however, the likelihood of emergence becomes greater as adherence decreases [32].

Figure 5. Adherence-based Contributions to Relative Emergence

Within the developing world, economic, medical and social barriers can limit antibiotic adherence [32]. To measure the impact of antibiotic adherence on emerging resistance within HIV/AIDS prevalent environments, we varied the probability of complete adherence (represented as C_1 in the model) from 0-100%, while maintaining the original adherence ratios reported in the literature [93, 100] (Appendix 1). We use Swaziland's

low TB condition for purposes of illustration, however, we note that the results for Swaziland's high TB, as well as both the low and high TB conditions in Indonesia, mirror the results presented: antibiotic adherence has very little impact on the emergence of resistance in HIV/AIDS-immunocompromised host populations, relative to the impact of HIV/AIDS prevalence.

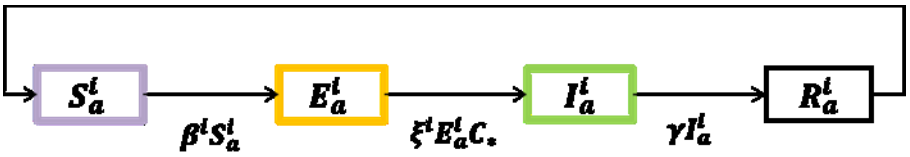

Figure 1a.

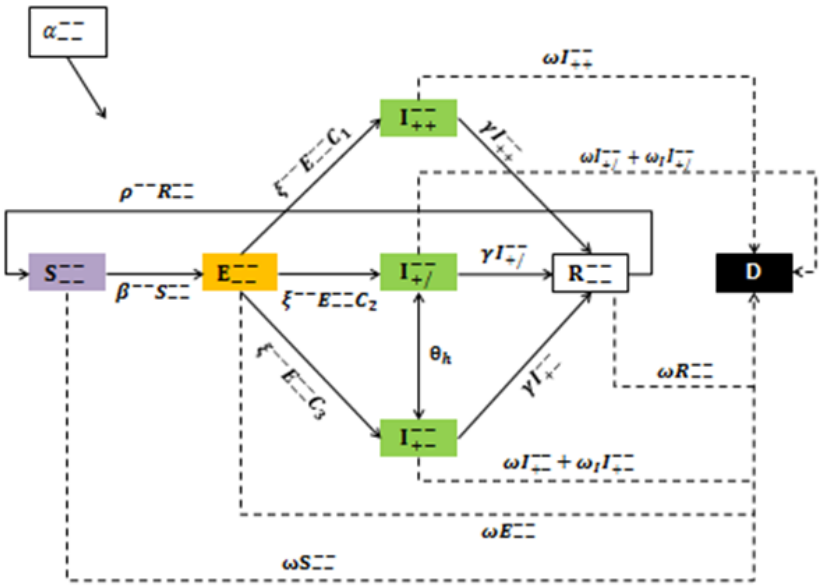

Figure 1b.

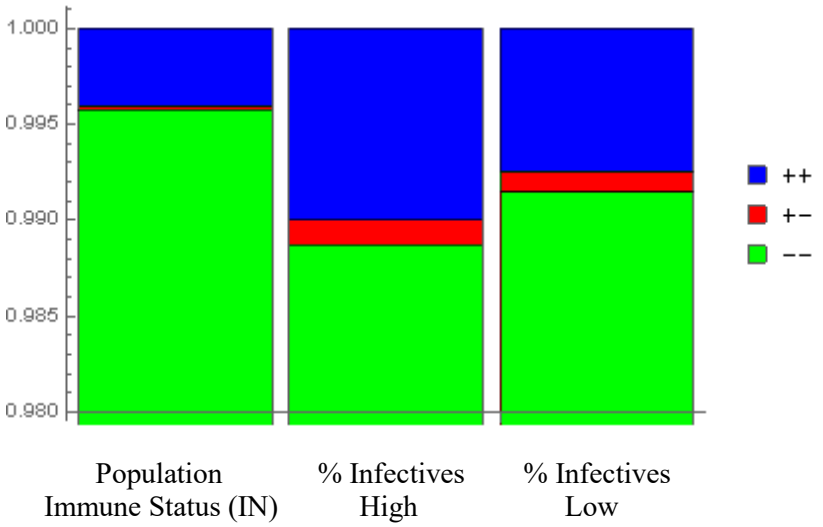
1.000
0.995
0.990
0.985
0.980
++
+−
−−
Population Immune Status (IN)
% Infectives High
% Infectives Low

Figure 2a.

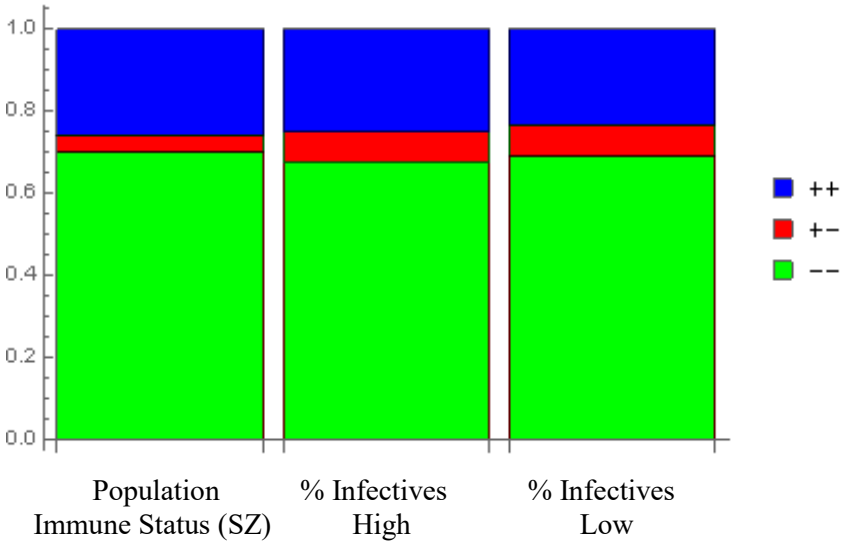
1.0
0.8
0.6
0.4
0.2
0.0
++
+−
−−
Population Immune Status (SZ)
% Infectives High
% Infectives Low

Fig 2b.

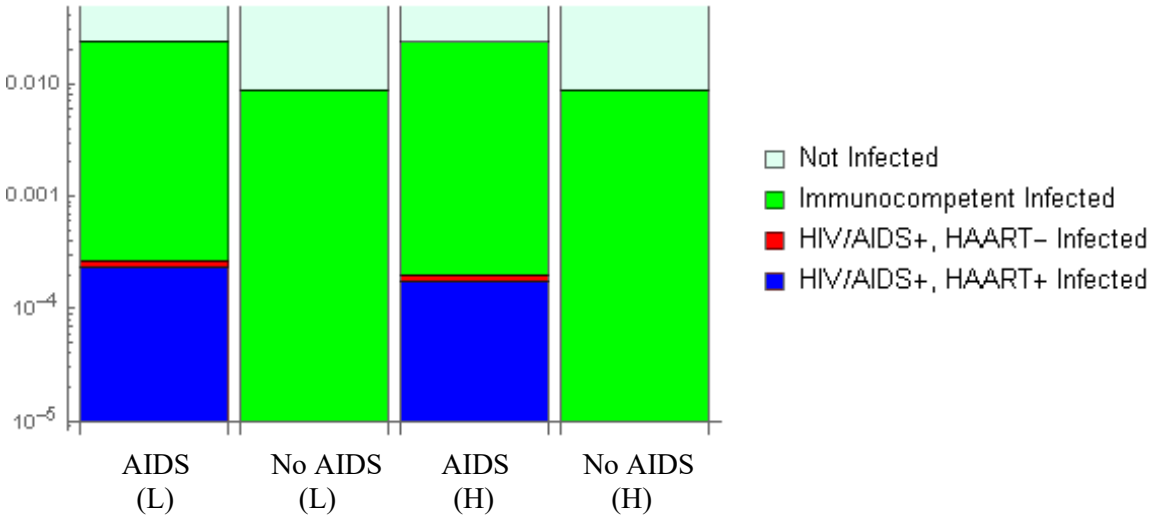

Figure 3a.

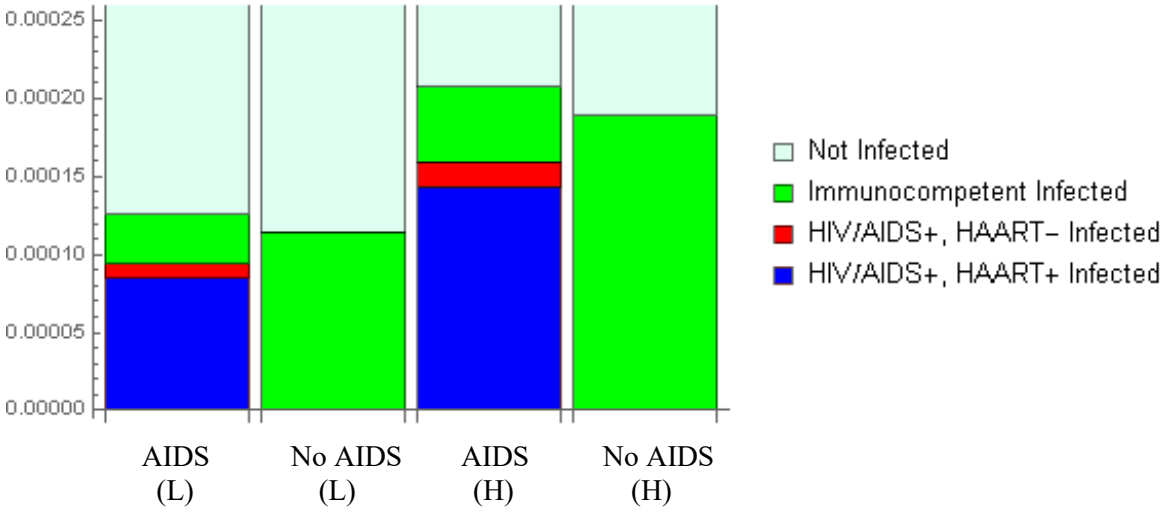

Figure 3b.

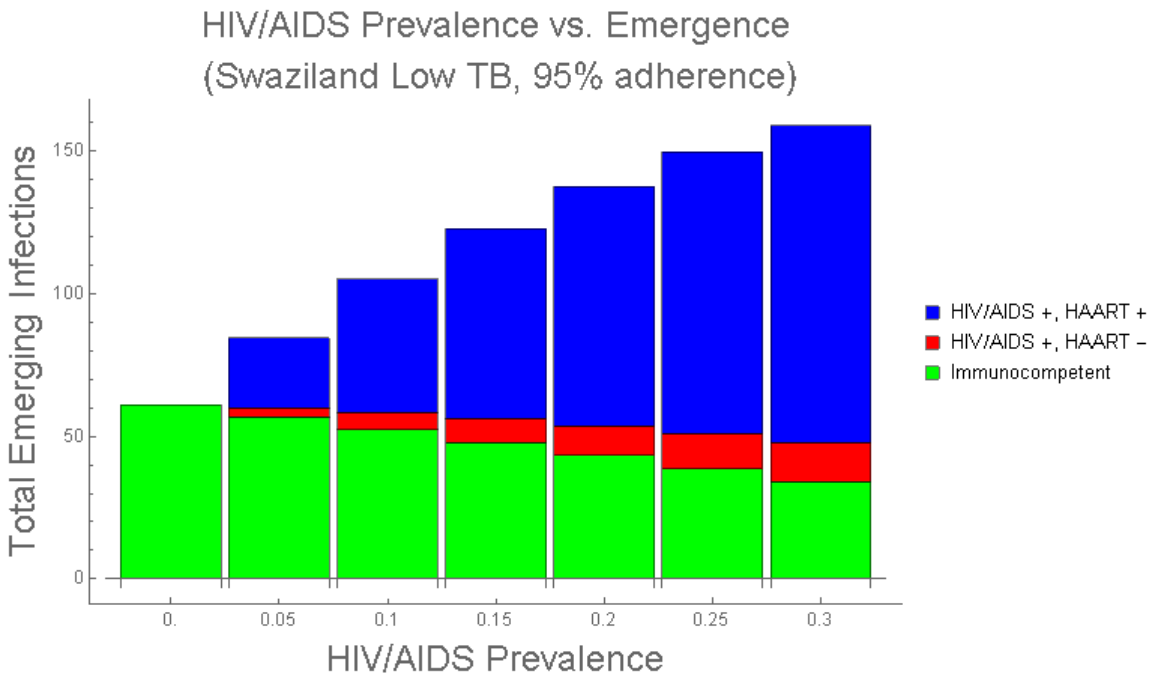
HIV/AIDS Prevalence vs. Emergence
(Swaziland Low TB, 95% adherence)
Total Emerging Infections
150
100
50
0
0.
0.05
0.1
0.15
0.2
0.25
0.3
HIV/AIDS Prevalence
HIV/AIDS +, HAART +
HIV/AIDS +, HAART –
Immunocompetent

Figure 4.

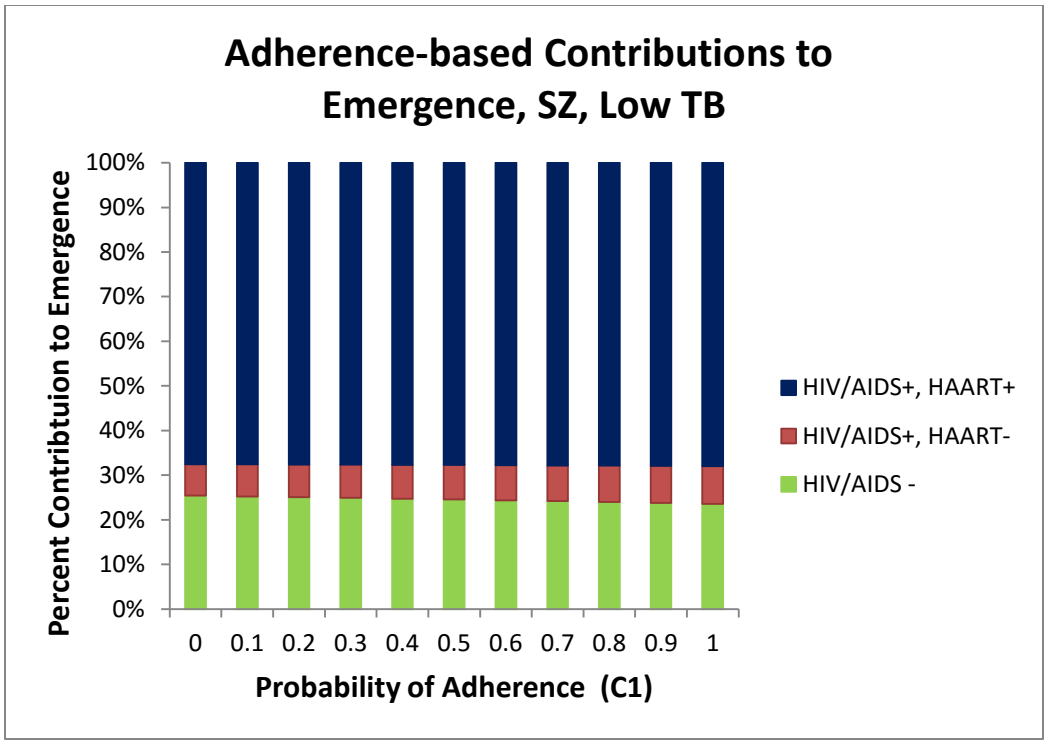
Adherence-based Contributions to Emergence, SZ, Low TB
Percent Contribtuion to Emergence
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
Probability of Adherence (C1)
HIV/AIDS+, HAART+
HIV/AIDS+, HAART-
HIV/AIDS -

Figure 5.

Tables and Legends

Table 1. AIDS-attributable Factor Increases in Antibiotic-resistant Infection

Having separated the infective populations in Indonesia and Swaziland by immune status, we calculated the factor contribution to emergence by dividing the number of emergent infections associated with each class by the mean percentage of individuals appearing in that class over a 180-day period. While the effect is most pronounced in Indonesia, we note that in both countries, under high and low TB conditions, actively AIDS-immunocompromised infectives are responsible for a disproportionately greater number of emergent infections than would be expected based on their prevalence within the population. Despite the conservative assumption of 20% antibiotic adherence [93], at best, AIDS-immunocompromised infectives are associated with a 1.82-fold increase in emergence.

Population	TB Prevalence	Immune Status	Mean Infective Immune Percentage	Percent Contribution to Emergence	Factor Contribution to Emergence
IN	Low	--	99.57%	98.9%	0.99
		+-	0.03%	0.14%	5.35
		++	0.40%	0.99%	2.49
	High	--	99.57%	99.2%	0.99
		+-	0.03%	0.09%	3.92
		++	0.40%	0.75%	1.86
SZ	Low	--	70.28%	67.57%	0.96
		+-	3.89%	7.33%	1.82
		++	25.81%	25.10%	0.97
	High	--	70.28%	69.24%	0.99
		+-	3.89%	7.52%	1.93
		++	25.81%	23.24%	0.90

Impact of Prophylaxis Policy for AIDS-immunocompromised Patients on Emergence of Bacterial Resistance

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Abstract

Antibiotic prophylaxis is a long relied-upon means of opportunistic infection management among HIV/AIDS patients, but its use represents an evolutionary tradeoff: Despite the benefits of prophylaxis, widespread use of antibiotics creates a selective advantage for drug-resistant bacterial strains. Especially in the developing world, with combined resource limitations, antibiotic misuse, and often-poor infection control, the emergence of antibiotic resistance may pose a critical health risk. Having demonstrated that this risk is further heightened when a significant proportion of the population is HIV/AIDS-immunocompromised, we now extend our earlier work to address the relationship between HIV/AIDS patients' use of antibiotic prophylaxis and the emergence of resistance. We apply an SEIR compartmental model, parameterized to reflect varying percentages of prophylaxis use among HIV/AIDS+ patients in a resource-limited setting, to investigate the magnitude of the risk of prophylaxis-associated emergence versus the individual-level benefits it is presumed to provide. The results from

this model suggest that, while still providing tangible benefits to the individual, prophylaxis is associated with negligible decreases in population-wide morbidity and mortality from bacterial infection, and may also fail to provide assumed efficacy in reduction of TB prevalence.

Introduction

The use of antibiotic prophylaxis has long been relied upon to reduce morbidity and mortality due to opportunistic infection among the HIV/AIDS-immunosuppressed – especially when access to antiretrovirals is limited [94, 101-105]. However, the use of antibiotic prophylaxis among HIV/AIDS-immunocompromised patients represents an evolutionary tradeoff, wherein the success of antibiotic prophylaxis must be weighed against its potential to contribute to antimicrobial resistance by selecting for drug-resistant bacterial strains.

The rapidity with which antibiotic resistance can develop represents a worldwide threat to infection prevention and treatment. The risk of emergence is magnified in the developing world, where resource constraints limit both infection management and resistance monitoring, and where antimicrobial misuse is rampant due to factors such as inconsistent availability and poor drug quality [2, 35, 106, 107]. Moreover, HIV/AIDS incidence and prevalence, worldwide, are highest within developing nations [108-111]. We recently demonstrated that, in HIV/AIDS-prevalent settings, the disrupted selective pressures associated with widespread population-level immunoincompetence (as compared to those usually applied by the combination of antibiotic therapy and immune activation [81]) further contribute to the emergence of antibiotic-resistant bacterial infections (DeNegre, Galvani, Ndeffo Mbah and Fefferman, in prep). Having chosen

Swaziland and Indonesia – which, respectively, represent upper and lower bounds of HIV/AIDS prevalence within the developing world in 2013[78, 87] – as sample populations, we now examine the effects of antimicrobial prophylaxis use by the HIV/AIDS-immunocompromised on the probability of emergence.

Our previous study relied on the simplifying assumption that antibiotic use referred specifically to targeted antimicrobials, since the high prevalence of bacterial infections that is characteristic of the developing world necessitates frequent use of the use of curative antibiotics [5, 88, 112, 113]. However, as exemplified by pathogens such as *Mycobacterium tuberculosis* and *Staphylococcus aureus*, the incidence of bacterial infections, despite the use of broad-spectrum prophylaxis to combat them, is indicative of the emergence of resistance [26, 103, 114-116]. (While it is outside the scope of this paper, we note that chemoprophylaxis prescriptions for the HIV/AIDS-immunocompromised also include antiviral and antiparasitic agents, which can select for resistant viral and parasite strains, respectively [94, 117-119].) Given that total, population-wide, emergence is the sum of the resistant infections attributable to curative antibiotic use and those arising due to the use of chemoprophylaxis, we now analyze the extent to which antibiotic prophylaxis affects the emergence of drug-resistant bacterial strains.

Even when antibiotics are used correctly, widespread antimicrobial use for the treatment of active infections selects for the emergence of resistance [2, 5]. Based on data specific to curative antibiotic use, we suspect that many factors, including financial constraints, sociocultural perspectives on medicine, patients' mental and physical health and drug regulation [35, 84, 106, 120-122], could lead to considerable variation in the use

and availability of prophylaxis. However, among the HIV/AIDS-immunocompromised, an additional economic barrier exists: Although HIV/AIDS prevalence varies greatly between Indonesia (0.46%) and Swaziland (27.4%) [78, 87], the widespread poverty common to both regions suggests that those with HIV/AIDS may, at some point, need to choose between purchasing chemoprophylaxis and purchasing highly active antiretroviral treatment (HAART) [123, 124]. This constraint could lead to variability in the proportion of HIV/AIDS+ susceptibles actively using prophylaxis at any given time, thereby also increasing variation in projected prophylaxis-attributable emergence.

There is ample evidence that the misuse of curative antibiotics, which includes overuse, self-medication, and inconsistent dosing, is the greatest predictor of emergence [5, 29, 37, 67, 76, 125-130]. However, the degree to which the use of chemoprophylaxis within HIV/AIDS-prevalent regions contributes to local and worldwide emergence is not readily available in the literature. Despite the potential health benefits of antibiotic prophylaxis to HIV/AIDS+ susceptibles, we cannot ignore the possibility that the risk of heightened emergence in HIV/AIDS-prevalent populations (DeNegre, et al., in prep) may be compounded by an increase in selection for resistant bacteria arising out of prophylaxis use. Drug-resistant infections are particularly problematic among HIV/AIDS-immunocompromised hosts, given their increased susceptibility to opportunistic pathogens, as well as the accelerated progression from HIV to active AIDS that occurs as a result of chronic, infection-mediated, immune activation [131-133]. Therefore, in an effort to promote antibiotic-prescribing decisions that minimize resistance arising out of the use of chemoprophylaxis, we present an SEIR compartmental model to quantify the relative contribution to total emergence that results from

chemoprophylaxis use in HIV/AIDS patients, given the many factors that may limit its availability in the developing world. We also analyze the risk-benefit relationship between prophylaxis-associated emergence, and the health advantages prophylaxis use is presumed to offer the HIV/AIDS-immunocompromised, by examining the factor change in morbidity and mortality among HIV/AIDS+ susceptibles as prophylaxis use is varied.

Model Parameterization

Holding HIV/AIDS prevalence constant at 0.46% and 27.4% for Indonesia and Swaziland [78, 87] respectively, we address the question of how the use of antibiotic prophylaxis contributes to the emergence of antibiotic resistance. In recognition of the need for curative antibiotics among the fully immunocompetent, and those with HIV/AIDS who are not prescribed prophylaxis, we include a parameter representing the probability of antibiotic adherence among those with active infections. We assume that HIV/AIDS+ infectives receiving targeted antibiotics are not simultaneously being treated with broad-spectrum prophylaxis.

Given the time-scale of interest for bacterial infections, we do not focus on host HIV/AIDS status as an epidemiological process. We note that susceptibles are categorized based on immune status as follows: those who are fully immunocompetent (i.e., HIV/AIDS-negative); those whose immune function is compromised by active AIDS; and those who are HIV or AIDS+, but whose consistent use of HAART enhances their immunocompetence such that their risk of succumbing to complications of AIDS-defining illness is low [75, 134, 135]. The rapid nature of bacterial evolution allows us to observe emergence of resistance over a relatively short time period – in this case 180

days – during which we assume HIV/AIDS status remains constant, with no seroconversion occurring [75].

Because we also describe hosts in terms of bacterial infection status and adherence to targeted antibiotics, we attach super- and subscripts to the variables associated with each compartment of the model. In keeping with our previous work, we use a ^{superscript} to dually describe HIV and HAART status; and we use a $_{subscript}$ to describe both bacterial infection status and adherence to antibiotics. In addition to the previously defined notational designations, we also adopt the subscript combination "+-" to describe infection-negative, prophylaxis-positive, susceptibles, thereby distinguishing them from hosts using antibiotics to treat active infection (all possible super- and subscript combinations appear in Table S1, in the methods appendix).

We also include the composite probability of emergence of and success of an antibiotic resistant infection among prophylactically-treated susceptibles (ϕ). Values for ϕ (Appendix 2) vary based on immune status and antibiotic adherence, and were determined based on (1) a combination of the per cell, per bacterial generation mutation rate; (2) the total number of infected cells per host; (3) the expected number of bacterial generations per infection duration; (4) the per category infection duration; and (5) the relative success of the mutant strain [58, 89-91].

We make two conservative assumptions: First, we assume that those susceptibles prescribed antibiotic prophylaxis are completely adherent to their dosing instructions. Second, we assume that those who develop resistant infections while using chemoprophylaxis are then also completely adherent to the targeted antibiotics used to treat the active infection. As such, all infectives who have previously been treated

prophylactically are assigned to either the I^{+-}_{++} or I^{++}_{++} categories, depending on HIV/HAART status. Consistent with these assumptions, we assign ϕ^{+-}_{-+} and ϕ^{++}_{-+} values equivalent to those assigned to fully antibiotic adherent AIDS+/HAART- and HIV/AIDS+/HAART+ hosts, respectively.

Using tuberculosis as a example pathogen, the model follows the progression of TB infection throughout a population separated by immune status (Figure 1a-b) and measures the combined impact of prophylactic and targeted antibiotic treatment (with different levels of adherence among the actively infective) on the emergence of antibiotic resistance. The entire system is described by a set of ordinary differential equations (Appendix 2), which also captures TB-specific mortality for all infectives. We assume zero mortality among fully immunocompetent and HAART+ infectives when antibiotic protocols are followed completely. (Table S5 contains a detailed list of parameters introduced in this chapter, including their condition dependencies, values used, and the reference(s) from which they were estimated; and Appendices 1 and 2 detail the methods by which parameter values were calculated.)

Methods

The significant difference in HIV/AIDS prevalence between Indonesia (0.46%) [87] and Swaziland (27.4%) [78] suggests that the proportion of HIV/AIDS+ susceptibles – regardless of HAART status – using antibiotic prophylaxis at any given time is likely to vary considerably between the two countries. This ensures their suitability as extremal comparators as we examine the impact of chemoprophylaxis use on the emergence of antibiotic resistance.

In surveying a subset of HIV+ Italians, Napoli, et al. [136] found that 40% had been treated prophylactically against *Pneumocystis carinii*. However, since this refers to a specific patient population (HIV+ susceptibles not yet considered AIDS-immunocompromised) from the developed world, we suspect that it is unlikely to be representative of treatment percentages within the developing world. We therefore investigated the impact on emergence of varying the percentage of HIV/AIDS+ susceptibles being treated prophylactically in 10% increments from 0-100%, with the trial in which prophylaxis is not used acting as a negative control. In the absence of any data regarding the prevalence of prophylaxis use in the developing world, we based this range on reported adherence to targeted antibiotics. Adherence varies based on factors such as age, socioeconomic status and the drug's side-effect profile [137-139]. We expect that similar factors will influence the use and availability of chemoprophylaxis, thereby also influencing the likelihood of treatment.

Prophylaxis-specific Emergence

When infections occur in HIV/AIDS+ susceptibles despite the intended effects of antibiotic prophylaxis, they likely arise out of drug-resistant mutations within the host. Within this initial exploration, we make the simplifying assumption that resistant strains do not circulate within the population, though follow-up efforts will explore competition between sensitive and resistant strains.

Probability of Emergence

To quantify the relative contributions of both broad-spectrum prophylaxis and targeted antibiotics to the emergence of resistance, we established a composite probability of the emergence of resistance for each possible combination of treatment and

immune status. The values for this parameter are informed by the TB literature, and are designated as ϕ^{i}_{rx} , where *"i*" and *"rx*" are used generically to designate immune and treatment status, respectively. (We note that ϕ^{i}_{rx} is calculated from the results of the ODE model; see Appendix 2). We multiply category-specific ϕ^{i}_{rx} values by the total number of infectives corresponding to each category to determine the expected number of resistant infections as percent prophylaxis treatment is varied. Finally, we calculate the prophylaxis-dependent relative emergence specifically attributable to each category of infective.

Results

Prophylaxis-Dependent Emergence

When we compared the expected emergence of antibiotic-resistant TB in Swaziland to that in Indonesia, we observed a drastic difference in the impact of prophylaxis. In Swaziland, irrespective of initial TB prevalence, there was a negligible difference in expected emergence among actively immunocompromised (HIV/AIDS+, HAART-) and HAART-treated patients (Figure 2). Given that we assumed no resistant strain circulation occurs, we would not expect antibiotic prophylaxis to have a significant effect on the number of drug-resistant infections arising among the fully immunocompetent since they were not provided prophylaxis. However, even when 100% of HIV/AIDS+, HAART- susceptibles received prophylaxis, there was a less than 1% decrease in the emergence of resistance (described in Table 1 and illustrated in Figure 2). The greatest observed impact occurred among HIV/HAART+ hosts, with a 2% reduction in emerging resistance when 100% prophylaxis use was assumed. This suggests that prophylaxis cannot be relied upon as a means of emergence control in Swaziland.

Contrary to the results from Swaziland, we note a sharp decline in risk of prophylaxis-associated emergence in Indonesia, where, among the actively AIDS-immunocompromised, we observed a nearly 60% reduction in risk when 100% of HIV/AIDS+ susceptibles are prophylactically treated. Among those who are HIV/AIDS+ and HAART-adherent, the impact was even greater; risk of emergence was reduced by approximately 80%. These results occurred irrespective of initial TB prevalence (described in Table 2 and visualized in Figure 2). Despite this result, when we analyzed per capita risk of emergence in HIV/AIDS patients we found that, in both Indonesia and Swaziland, drug-resistant TB infections are still approximately twice as likely to emerge among those with active AIDS than among those receiving HAART (Figure 3). This suggests that increased HAART access may be a valuable means of managing TB in HIV+ patients.

Recall that, in both Indonesia and Swaziland, we have made the conservative assumptions that prophylactically-treated susceptibles adhere completely to dosing instructions, and that they continue to do so once they become infected with a bacterial pathogen resistant to broad-spectrum prophylaxis and must change antibiotics to treat the infection. We may therefore be conservatively underestimating total emergence, but we do not expect that this will qualitatively impact the results of our model.

Influence of Prophylaxis on Infectivity and Mortality

Using expected TB incidence under conditions of 0% prophylaxis use as a baseline, we analyzed the factor change in population-wide infectivity that results from varying the percentage of HIV/AIDS+ susceptibles using antibiotic prophylaxis. While we did observe a decline in population-wide TB incidence Swaziland as prophylaxis use

was increased from 0-100%, it was not as pronounced as we might have expected, given the reliance upon antibiotic prophylaxis as a means of minimizing opportunistic infection risk among HIV/AIDS patients [140]. Under conditions of both low and high TB prevalence, we observed the greatest decline in infectivity among HIV/AIDS+, HAART+ individuals. However, incidence was reduced by only 2%, relative to the baseline, when 100% of HIV/AIDS+ susceptibles were prescribed prophylaxis.

We note that, when 100% of HIV/AIDS+ susceptibles are treated prophylactically, 27.4% of the population should be protected [78]. We would, therefore, expect a proportionate decrease in TB prevalence; however, this was not the case. We instead found that the benefits of prophylaxis are overwhelmed by the risk attributable to transmission by current infectives. Unfortunately, this effect mitigates the intended impact of prophylaxis.

Our mortality results mirrored those from the analysis of TB incidence in Swaziland. Again, despite a goal of prophylaxis being to reduce bacterial infection-related mortality among the HIV/AIDS-immunocompromised, the decline in mortality as percent prophylaxis treatment increased was nearly undetectable (<1%), irrespective of immune status or initial TB prevalence.

Consistent with our findings regarding emergence in Indonesia, we also observed a more noticeable effect of prophylaxis when we examined TB-incidence and TB-associated mortality among HIV/AIDS-affected individuals. As prophylaxis use among HIV/AIDS+ susceptibles increased from 0-100%, we observed a corresponding decline in TB incidence. Relative to the baseline, TB incidence among HIV/AIDS+, HAART-hosts is reduced by 60% when initial TB prevalence is low, and by 58%, when initial

prevalence is high. TB-attributable mortality among HIV/AIDS+, HAART+ hosts is reduced by 81% in the low TB condition, and by 78% in the high TB condition.

As would be expected given the decline in TB incidence, TB-associated mortality also decreased with increased prophylaxis treatment. When initial TB prevalence was low, and 100% of HIV/AIDS+ susceptibles were prophylactically treated, HIV/AIDS+, HAART- hosts benefitted from a 60% reduction in mortality; and mortality in HIV/HAART+ hosts declined by 80%. Under the high TB condition, mortality was reduced by 55% among the actively AIDS-immunocompromised, and by 74% among those receiving HAART. We note, however, that our analysis of per capita mortality among HIV/AIDS patients demonstrated that those with active AIDS experience twice the risk of TB-associated mortality as those who are HAART-treated (Figure 4).

Discussion

Swaziland

Antibiotic prophylaxis has long been considered to be a valuable infection management strategy among the HIV/AIDS-immunocompromised [140]. Despite the selective pressure favoring the emergence of resistance that is associated with its use [129], antibiotic prophylaxis is presumed to have had a net beneficial effect on opportunistic infection related morbidity and mortality. However, our model has demonstrated that this may not always be the case – especially within the developing world, where resource limitations and sociocultural factors such as nonbelief in the usefulness of antibiotics further complicate the health behavioral component of antimicrobial resistance [141-144]. For these reasons, both individual and population-level health remain crucial considerations to be addressed during the development of medical policy recommendations.

Given that 27.4% of Swaziland's adult population is HIV/AIDS+, (making Swaziland the current world leader in HIV/AIDS prevalence) [78], we were hopeful that prophylaxis could be counted upon to manage TB within that region. However, irrespective of the percentage of HIV/AIDS+ susceptibles receiving prophylaxis, we observed a negligible factor reduction in TB-associated infectivity and mortality, as compared to the baseline condition of zero prophylaxis use. These findings suggest that the use of antibiotic prophylaxis under conditions similar to those in Swaziland may not be benefitting HIV/AIDS patients to the extent expected. Moreover, we found that the effects of prophylaxis can be overwhelmed by the presence of current infectives within the population. Our model indicates that even when 100% of HIV/AIDS+ susceptibles receive prophylaxis, we observe only a negligible reduction in population-wide infectivity. The proportion of current infectives in the population, as well as those entering the infective category immediately via vertical transmission (thereby bypassing the susceptible phase, during which they would receive prophylaxis), reduce the benefits of prophylaxis use.

The results of our initial work on the relationship between HIV/AIDS-prevalent host populations and antibiotic resistance demonstrated the potential for heightened emergence (DeNegre, et al, in prep). Due to this finding, we expected that the current model would reveal that prophylaxis could further compound the risk of emergence – a catastrophic result, considering the protective benefits attributable to antibiotic prophylaxis. Fortunately, despite the results of our previous work, we found that increased used of prophylaxis by HIV/AIDS patients did not strongly select for drug resistance. Therefore, while prophylaxis may fail to manage infection as effectively as

expected in Swaziland, it is still provides some benefit to HIV/AIDS patients, without risking population-level public health by selecting for emergence of resistance.

Indonesia

Among HIV/AIDS+ patients in Indonesia, the benefits of antibiotic prophylaxis were much more noticeable, with category-specific TB incidence declining by as much as 80% when 100% of HIV/AIDS+ susceptibles are treated. Given this decrease in observed incidence, we also noted a corresponding decrease in emergence of resistance and TB-associated mortality. These findings reflect the characteristics of the population: While pathogen persistence is typically constrained by the availability of susceptibles (as seen in Swaziland) [88, 145], Indonesia's population of greater than 250 million, of whom less than 1% are TB infected [88], represents an effectively limitless reserve of susceptibles. Considering these conditions, a high rate of contact and transmission is expected [146], especially in the absence of any mitigating host conditions. A decline in transmission, as would be expected due to the implementation of prophylaxis regimens for HIV/AIDS patients, would, therefore, be impactful.

Despite these positive findings for HIV/AIDS patients, we must acknowledge that, contrary to Swaziland**,** the majority of TB cases in Indonesia occur among otherwise immunocompetent hosts[88]. This result is a necessary consideration when assessing TB-associated risk in Indonesia. Again, while prophylaxis does provide observable benefits to those affected by HIV/AIDS, it may not be an effective means of infection control for the Indonesian population as a whole. Rather, the combination of prophylaxis availability to the majority – ideally, 100% – of HIV/AIDS+ susceptibles, coupled with an early

detection and treatment program such as DOTS [147] for those with active TB infections, may have the greatest impact on TB reduction under conditions similar to those in Indonesia.

Conclusions

Having examined the risk of prophylaxis-associated emergence, versus the protective benefits it provides, we determined that the magnitude of its impact as an infection control measure varies depending on the prevalence of HIV/AIDS+ susceptibles within the population. In Swaziland, where more than a quarter of the population is HIV/AIDS+, and where 77% of TB cases occur in HIV/AIDS+ hosts [78, 88], the prevalence of current infectives compromises the intended effects of antibiotic prophylaxis. Even though TB transmission may be slightly curtailed as percent prophylaxis treatment is increased, those who are already actively infective perpetuate transmission to the extent that only a negligible decrease in infectivity is observed – even when 100% of HIV/AIDS+ susceptibles are given prophylaxis. Conversely, in Indonesia, where a significantly smaller percentage (0.46%) of the population is HIV/AIDS+[87], and the majority of TB cases occur among the fully immunocompetent, the prophylaxis-associated benefits to HIV/AIDS+ susceptibles are observably greater.

These findings suggest that policy decisions regarding TB infection management should take into account the prevalence of both HIV/AIDS and HIV-incident TB in the target population, since the effectiveness of antibiotic prophylaxis is affected by both of these conditions. We also emphasize that, while antibiotic prophylaxis initially appears

not to be contributing significantly to the rate of emergence of novel resistance, our follow up work will evaluate the impact of strain competition using a longer-term model.

Acknowledgements

The authors are grateful to Drs. Yana Bromberg, Alison Galvani, Julie Lockwood, Bradford Greening, Jr., Jeffery Townsend and Eva Top for their expertise and guidance with regard to the design of the research question.

Figure Legends

Figure 1 a-b. SEIR Transmission Dynamics

1a shows a basic SEIR model (assuming a closed system), wherein health status changes from susceptible to exposed at a rate of β, from exposed to infectious at a rate of ζ, and infectious to recovered at a rate of γ. The super- and subscripts "i" and "a" are used generically to demonstrate that there are many possible host health outcomes, depending on the combination of immune status and antibiotic-taking behavior. The flowchart seen in 1b depicts transmission dynamics specific to our model; we note all possible progressions for a prophylactically-treated HIV/AIDS+, HAART- host.

Figure 2a-d. Effect of Prophylaxis on Expected Emergence

The impact of antibiotic prophylaxis on emergence of resistance varied considerably between Swaziland (Figures 2a and 2b) and Indonesia (Figures 2c and 2d). While prophylaxis use does not actively contribute to the emergence of resistance in SZ, its neutral effect on emergence suggests that prophylaxis may not be managing TB incidence effectively. Conversely, use of prophylaxis in Indonesia dramatically reduces the incidence of drug-resistant TB in HIV/AIDS patients.

Figure 3. Expected Per Capita Emergence

When we examined the per capita risk of emergence associated with both HAART+ and HAART- patients, we found that drug-resistant TB infections are twice as likely to arise

in those who do not receive HAART (*i.e.*, those with active AIDS). We observed this result in both Indonesia and Swaziland, irrespective of both initial TB prevalence and percent prophylaxis treatment.

Figure 4. Expected Per Capita TB-Associated Mortality

Our analysis indicates that HIV/AIDS patients not receiving HAART are, individually, twice as at risk of TB-related mortality as those who are HAART treated. This result occurred in both Indonesia and Swaziland, regardless of both initial TB prevalence and the proportion of HIV/AIDS patients receiving antibiotic prophylaxis.

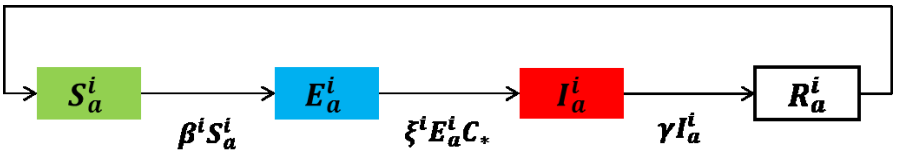


Figure 1a.

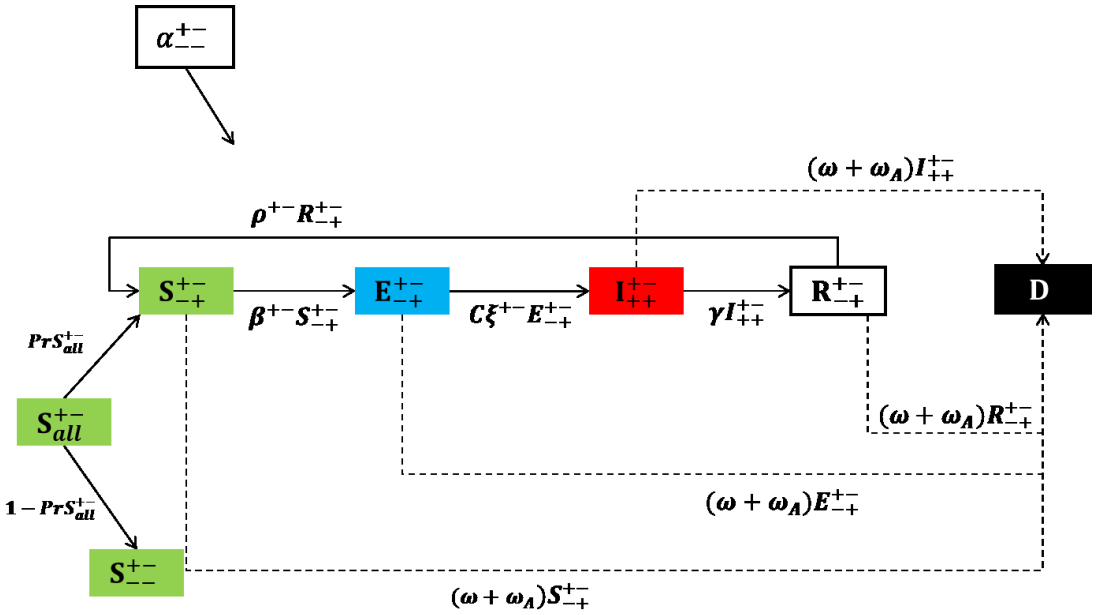


Figure 1b.

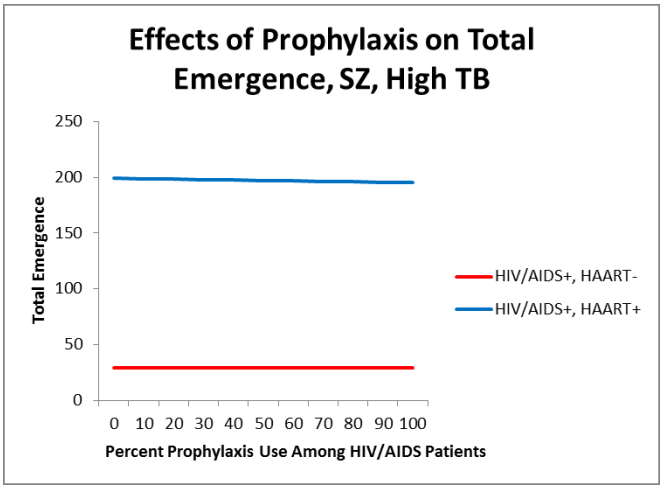
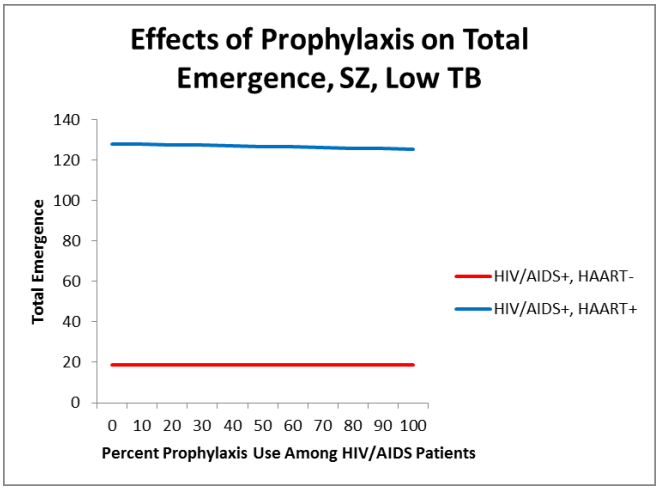


Figure 2a.



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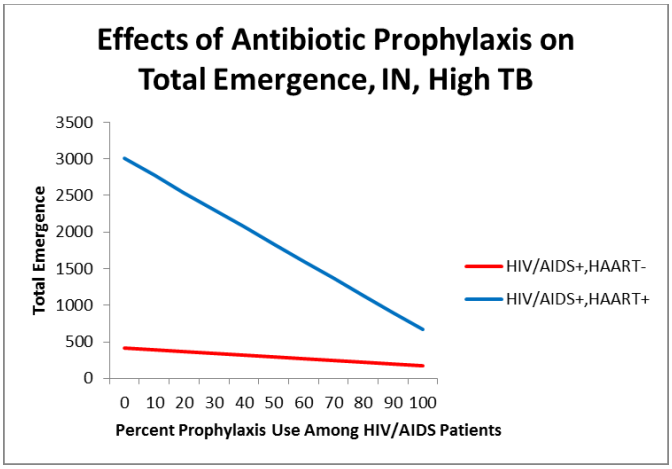

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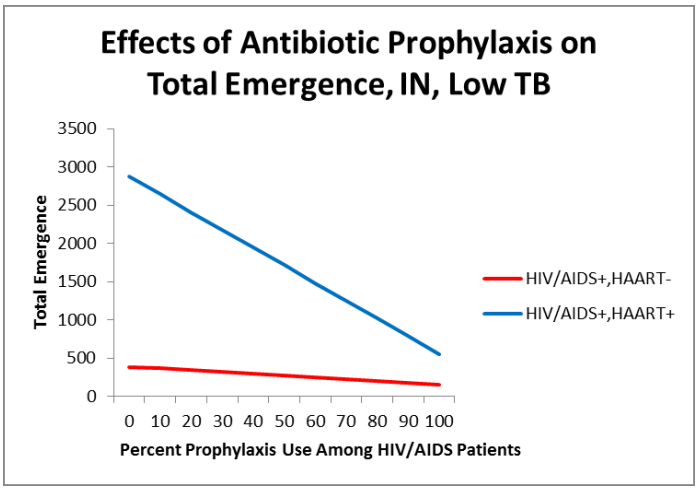

Effects of Antibiotic Prophylaxis on Total Emergence, IN, Low TB
Total Emergence
3500
3000
2500
2000
1500
1000
500
0
0 10 20 30 40 50 60 70 80 90 100
Percent Prophylaxis Use Among HIV/AIDS Patients
HIV/AIDS+,HAART-
HIV/AIDS+,HAART+

Figure 2d.

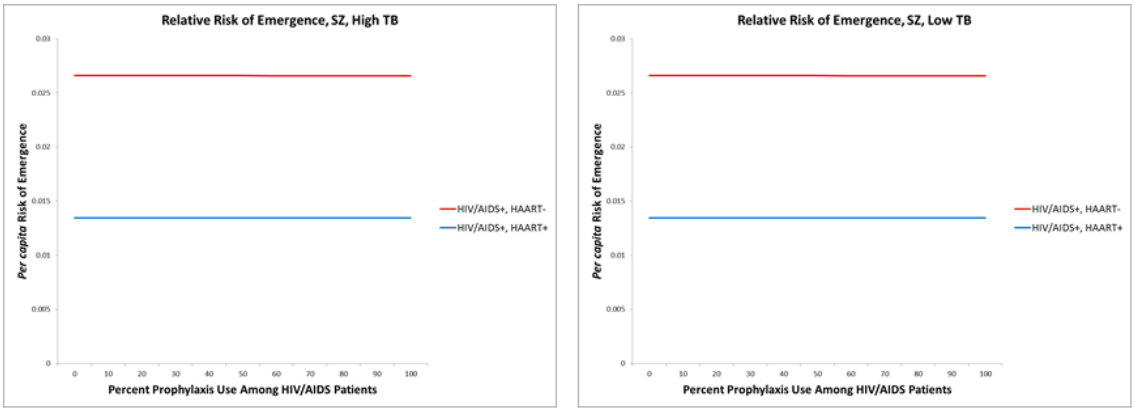
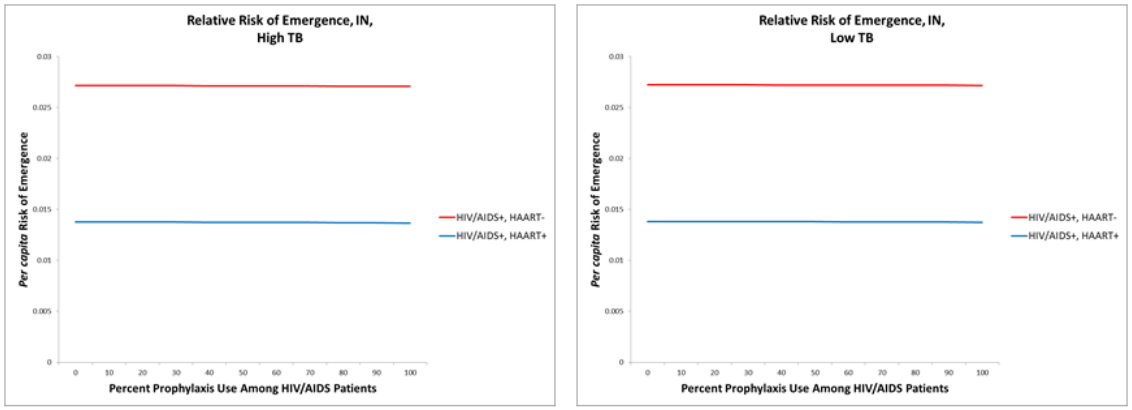


Figure 3a.



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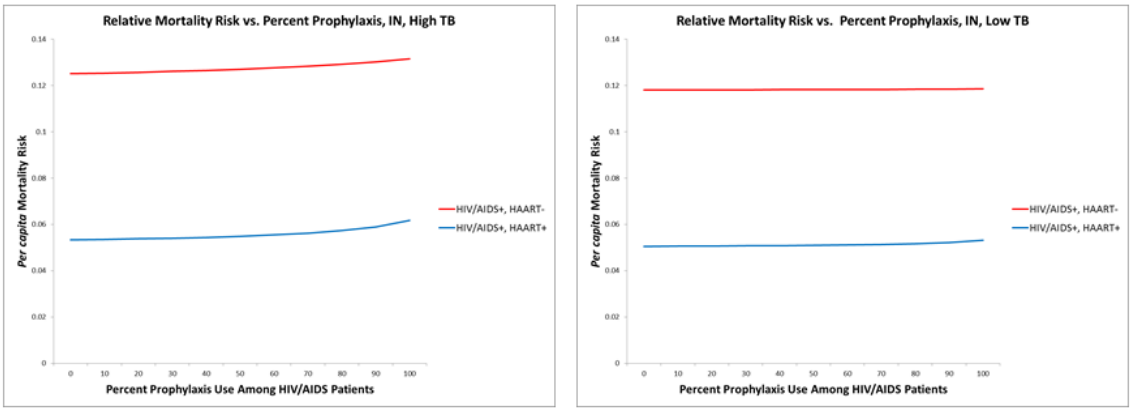

Figure 4a.

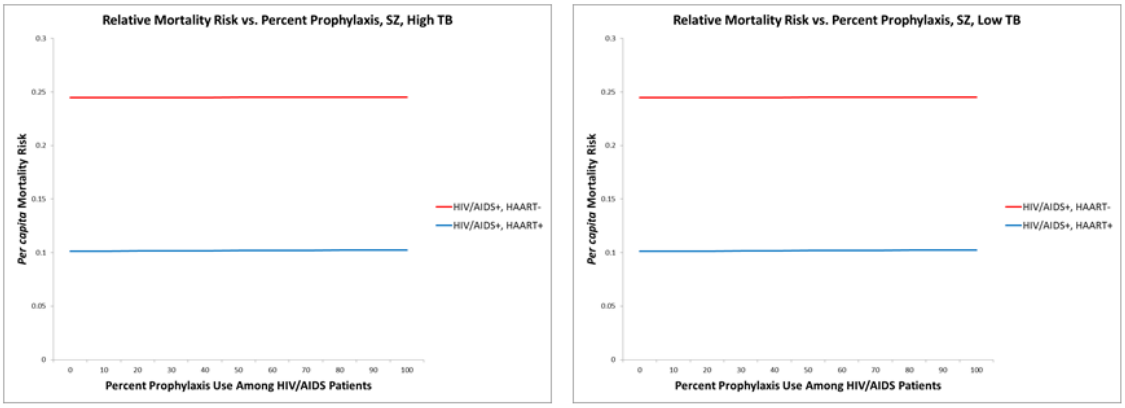

Figure 4b.

Tables and Legends

Table 1. Factor Changes in Emergence, Swaziland

Using 0% prophylaxis treatment as a baseline, we calculated the factor differences in cases of emerging antibiotic-resistant TB, occurring in HIV/AIDS+ hosts, as percent prophylaxis use was varied in 10% increments. Given that increasing prophylaxis use had a negligible effect on the emergence of resistance in Swaziland, we have included only the 0, 50 and 100% prophylaxis conditions for purposes of illustration. We note that we use "*" to represent all possible TB/curative antibiotic combinations that can occur with a particular immune status.

Population	TB Prevalence	Immune Status	Percent Prophylaxis Use (HIV/AIDS+)	Expected Emergence (Total Cases)	Factor Difference in Emergence
SZ	Low	I_*^{+-}	0%	18.68	-
			50%	18.65	0.99
			100%	18.62	0.99
		I_*^{++}	0%	128.07	-
			50%	126.74	0.99
			100%	125.40	0.98
	High	I_*^{+-}	0%	29.07	-
			50%	29.03	0.99
			100%	28.99	0.99
		I_*^{++}	0%	199.2	-
			50%	197.2	0.99
			100%	195.17	0.98

Table 2. Factor Changes in Emergence, Indonesia

The impact of antibiotic prophylaxis on emergence in Indonesia varied considerably, relative to Swaziland. Again using 0% prophylaxis treatment as a baseline, we found that risk of emergence could be reduced by approximately 60% among HIV+/AIDS+, HAART-infectives, and by approximately 80% among HIV/AIDS+, HAART+ infectives.

Population	TB Prevalence	Immune Status	Percent Prophylaxis Use (HIV/AIDS+)	Expected Emergence (Total Cases)	Factor Difference in Emergence
IN	Low	I_*^{+-}	0%	390.17	-
			50%	273.41	0.70
			100%	156.72	0.40
		I_*^{++}	0%	2878.52	-
			50%	1717.98	0.60
			100%	557.62	0.19
	High	I_*^{+-}	0%	412.43	-
			50%	293.28	0.71
			100%	174.22	0.42
		I_*^{++}	0%	3006.82	-
			50%	1856.37	0.61
			100%	667.105	0.22

Impact of Strain Competition on Bacterial Resistance in Immunocompromised Populations

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Abstract

Despite the risk of emerging drug resistance that occurs with frequent use of antimicrobial agents, targeted and prophylactic antibiotics have been considered crucial to opportunistic infection management among the HIV/AIDS-immunocompromised. As we recently demonstrated, the disrupted selective pressures that occur in AIDS-prevalent host populations increase the probability of novel emergence. This effect is concerning, given that bacterial strains unresponsive to first-line antibiotics can be particularly dangerous to hosts whose immune response is insufficient to fight infection in the absence of antibiotic support. While greater host susceptibility within a highly immunocompromised population may offer a fitness advantage to drug-resistant bacterial strains, this advantage could be mitigated by increased morbidity and mortality among the AIDS-immunocompromised. Using an SEIR epidemiological model parameterized to reflect conditions in an AIDS-prevalent host population, we examine the evolutionary relationship between drug-sensitive and resistant strains of *Mycobacterium tuberculosis*.

We explored this relationship when fitness of the resistant strain is varied relative to that of the sensitive strain to investigate the likely long-term multi-strain dynamics of AIDS-mediated increased emergence in drug resistance.

Introduction

Among HIV/AIDS immunocompromised patients, frequent use of antibiotics is essential to the prevention and/or treatment of many opportunistic bacterial pathogens [148]. Yet, it is well-known that with increased antibiotic use comes the increased likelihood of selection favoring the emergence of antibiotic resistance [5, 39, 128]. Though this risk is markedly greater when antibiotics are used incorrectly – as in the cases of over-prescription or patient non-adherence to dosing instructions – resistance may still arise out of appropriate antibiotic use, especially in the case of chronic, prolonged illness [2, 149, 150].

We recently demonstrated that the disrupted selective pressures associated with an AIDS-prevalent host pool can drastically increase the probability of emergence of antibiotic resistance (DeNegre, Galvani, Ndeffo Mbah and Fefferman, in prep). Emerging resistance has the potential to be particularly devastating in HIV/AIDS-prevalent regions due to widespread host immunoincompetence. Pathogen nonresponse to one or more first-line antibiotics promotes the maintenance of resistant strains within a host population whose collective immunosuppression offers little to no defense against the spread of infection. Although morbidity and mortality associated with resistant infection may be higher among the AIDS-immunocompromised, emergence of resistance also poses a risk to immunocompetent susceptibles. Even in immunocompetent hosts, immune activation can sometimes be insufficient to effectively fight infection without the support

of antibiotics. However, when immune response alone fails to adequately clear an infection caused by an antibiotic-resistant pathogen strain, treatment options are critically limited [151].

In our previous work, we made the simplifying assumption that antibiotic-resistant infections, while originating via the emergence of drug-resistant mutations, increase in prevalence due solely to selective pressures within the host population. However, these same selective advantages can lead to resistant strain dominance, which in turn leads to a greater percentage of infectives harboring and transmitting pathogens nonresponsive to antibiotics [152]. Using *Mycobacterium tuberculosis* as a model pathogen, we now examine the impact of the emergence and maintenance of resistance via bacterial strain circulation and the potential for strain replacement.

We have chosen to focus on the developing world because, within resource-limited settings, poor sanitation and infection management enhance the burden of infectious disease, and economic constraints can hinder access to effective antibiotics [32]. Moreover, factors such as limited understanding of HIV transmission, high-risk sexual behavior (sometimes in conjunction with intravenous drug use), and inconsistent access to highly active antiretroviral therapy (HAART) once seropositive, currently place developing nations in danger of increasing HIV/AIDS prevalence [108, 153]. The combination of these factors enhances the risk of emergence of antibiotic resistance (DeNegre, et al., in prep), and this risk could be compounded by resistant strain circulation. To reflect these conditions accurately, we have chosen Swaziland as a model population. With 27.4% of its adult population being HIV/AIDS-positive (HIV/AIDS+)

in 2015 [78], Swaziland represents a worst-case scenario of host vulnerability to drug-resistant opportunistic infection.

To explore the evolutionary and epidemiological effects of the emergence and subsequent circulation of antibiotic-resistant pathogens within a highly immunocompromised host population, we present an SEIR model [154], and parameterize it to reflect conditions similar to those in Swaziland. We vary the percentage of HIV/AIDS+ susceptibles using antibiotic prophylaxis (thereby protecting themselves from drug-sensitive pathogens), and the probability of resistant strain transmission, including the potential for either increased or decreased fitness of the resistant strain, relative to that of the wild-type. We define successful strain fitness as successful transmission, whether due to altered rates of within-host replication yielding altered exposure per contact, or altered probability of successful transmission from the same level of bacterial exposure. By analyzing the condition-dependent differences in the evolutionary success of drug-sensitive and drug-resistant bacterial strains, we provide a framework for developing public health policy recommendations geared toward minimizing the emergence and proliferation of resistance.

Mathematical Model

Extending our previous work, we stratify our population based on immune status, including five categories of susceptibles: (1) those who are fully immunocompetent (*i.e.* HIV/AIDS-negative); (2) those who are HIV+ or AIDS+, but whose opportunistic infection risk is minimized by consistent use of HAART [75, 134, 135]; (3) those whose are AIDS-immunocompromised (*i.e.*, HAART-). We further divide the susceptible

HIV/AIDS+, HAART+, and AIDS+, HAART- subpopulations into those who, as an initial condition, receive antibiotic prophylaxis and those who do not (Appendices 1 and 2). We note that we have made the simplifying assumption that no seroconversion occurs during the duration of the model. However, we recognize that making this assumption limits the timeframe for our analysis. We therefore examine the evolutionary fitness of the resistant and wild-type strains during a one-year period, within which we may observe the emergence of antibiotic resistance [155] and assess the initial behavior of the system, without having to account for changes in host immune status [75]. Future work will explore the longer-term implications of bacterial strain competition under shifting conditions of HIV/AIDS.

Within each immune class, we further delineate our population based on the combination of bacterial infection and adherence to targeted antibiotics. The combined description of immune/HAART and infection/antibiotic status is depicted via super- and subscripts to the variables associated with each compartment of the model (Figure 1 and Appendices 1-3). $^{\text{Superscripts}}$ dually describe immune and HAART status, and $_{\text{subscripts}}$ are used to dually describe bacterial infection status and antibiotic adherence, such that $_{--}$ means infection negative (and, therefore, untreated); $_{*+}$ means infection-positive, completely adherent; $_{*/}$ means infection positive, nonadherent; and $_{*-}$ means infection-positive, untreated. For purposes of this description, we use "*" generically to represent the possibility of infection with either the drug-sensitive or drug-resistant bacterial strain. In the ODE model equations (Appendix 3), however, we use notation reflecting Hardy-Weinberg models [156], in which "p" represents the wild type allele, and "q" represents the mutant allele, to distinguish between the drug-sensitive (wild-type) and drug-resistant

(mutant) strains among actively infected hosts. (For example, whereas $_{p+}$ indicates that the host is infected with a wild-type strain, $_{q+}$ indicates that the host is infected with a mutant strain; in both cases the "+" designates complete antibiotic adherence.) Finally, we use the subscript $_{-+}$ to describe prophylactically-treated susceptibles.

For HIV/AIDS+ susceptibles initially prescribed antibiotic prophylaxis, we make two conservative assumptions: First, we assume that these susceptibles are completely adherent to their prophylaxis regimens. Second, we assume that those who contract drug-resistant infections while being prophylactically treated are then also completely adherent to the targeted antibiotics subsequently prescribed to treat the infection. Therefore, all infectives who have previously been treated prophylactically are assigned to either the I_{q+}^{+-} or I_{q+}^{++} categories, depending on HIV/HAART status.

Particularly in the developing world, many demographic and economic factors influence host antibiotic adherence [47, 120-122, 157, 158]. Therefore, using the constant "C," we divide infectives based on the probability that they will participate in each of three categories as follows: C_+ is the probability of immediate infection detection and complete treatment, as defined by DOTS protocol [159]; $C_/$ is the probability of partial adherence, wherein the host received antibiotics for some period of time during infectivity, but did not follow dosing instructions; and C_- is the probability that the host failed to seek treatment.

β_q^n (where "n" is used to represent any possible immune status) values are derived from the work of Cohen and Murray [160], who provide a transmission rate constant of $8.5x10^{-06}$ for drug resistant TB among immunocompetent hosts. We adjusted Cohen and

Murray's rate, which was based on an idealized population of one million, to account for the combination of Swaziland's total population, and the size of each immune status-based subpopulation, and converted it from an annual to a daily rate. In assigning β values associated with both the sensitive and resistant strains, we assume equivalent immune function for the fully immunocompetent and HAART+ categories. We also assume that the actively AIDS-immunocompromised are an arbitrary 10% more likely to contract TB following exposure to an infected individual.

Since data regarding the transmission probability of drug-sensitive TB was not immediately available in the literature, we assigned values to β_p^n using the combination of the comparative fitness results set forth by Cohen, et al. [161], and the drug-resistant TB transmission probability published by Cohen and Murray [160]. Details regarding the assignment of parameter values, including those for β_p^n , appear in Appendices 1-3.

We use ϕ to represent the composite probability of emergence of and success of an antibiotic resistant infection among prophylactically-treated susceptibles. Values for ϕ (see Appendix 1) were determined based on the per cell, per bacterial generation mutation rate; the total number of infected cells per host; the expected number of bacterial generations per infection duration; the per category infection duration; and the relative success of the mutant strain [58, 89-91]. We note that ϕ is used to represent the probability of resistance arising out of mutation only and does not represent the probability of contracting a resistant infection due to strain circulation.

Finally, we use ζ to represent the immune status-based transition rate from latent to active infection. Adapting our values from Cohen and Murray [160], who themselves rely upon Dye [162, 163], we chose an annualized, midrange transition rate of 0.88, and,

consistent with the other parameters used in this model, and adjusted it to reflect a daily transition probability. We assume that those with active AIDS progress from exposed to infective 10% faster than those who are HIV/AIDS- or HAART+, and that those who are HAART+ progress at the same rate as the fully immunocompetent. We also assume that ζ values are equivalent for the drug-sensitive and drug-resistant TB strains.

Our model follows the progression of both drug-sensitive and drug-resistant infections throughout a population stratified based on immune status (Figure 1). We use a set of ordinary differential equations to describe the system (Appendix 3), where the symbols $\hat{I}_p$ and $\hat{I}_q$ are used to represent the sum of all of those infected with drug-sensitive or drug-resistant infections, respectively, that can that infect susceptibles at a rate of β; β depends on both immune status, and strain type. We include three separate mortality rates: ω_I represents rate of death due to TB; ω_A represents AIDS-attributable rate of death; and ω represents all other cause-related rate of death. Other parameters used include α, which represents per capita birthrate; ρ, which represents the immune status-dependent rate of loss of immunity; γ, which represents the HIV/AIDS and antibiotic category dependent rate of recovery from bacterial infection; θ, which represents the rate of transition between the partially antibiotic adherent and untreated states; and ψ, which represents the HAART-dependent increase in infection-attributable death for patients with active AIDS. (Table S1 contains a detailed list of parameters, including their condition dependencies, values used, and the reference(s) from which they were estimated; where applicable, Appendix 1 details the methods by which parameter values were calculated.)

Methods

Using HIV/AIDS prevalence data from Swaziland, we address the question of evolutionary fitness in drug-resistant and drug-sensitive bacterial strains when prophylaxis use among the HIV/AIDS-immunocompromised and resistant strain transmission probability are varied. (We include a parameter corresponding to the probability of curative antibiotic adherence among the actively infective, but we assume that prophylactically-treated HIV/AIDS+ susceptibles who become infective cease treatment with broad-spectrum prophylaxis during the infectious period.)

Prophylaxis-attributable Emergence and Strain Circulation

Use of antibiotic prophylaxis has been heavily relied upon as a means of opportunistic infection management among the HIV/AIDS-immunocompromised [105]. Yet, despite its protective value to HIV/AIDS patients, use of broad-spectrum prophylaxis can select for the emergence of resistance [24]. With the expectation that the prevalence of prophylaxis use in the developing world may vary significantly based on factors such as drug availability, patient age and/or socioeconomic status and the drug's side-effect profile [137-139], we capture the combined impact of primary, prophylaxis-attributable emergence, and the secondary infections that occur due to emergent strain circulation, as percent prophylaxis treatment among HIV/AIDS+ susceptibles is increased incrementally from 0 to100%.

Host-Dependent Variation in Transmission Probability

Pathogen persistence relies upon the composite probability of host-to-host contact and infection transmission [72]. Host susceptibility increases the likelihood of pathogen success; with greater susceptibility – as would be the case in an AIDS-prevalent host

population – comes the potential for more widespread transmission [164]. Among immunocompromised hosts, however, transmission potential is mitigated by the increased likelihood of host mortality – especially in the absence of antibiotic treatment that can occur due to host nonadherence and/or drug resistance.

Cohen, et al. [161], found that the comparative fitness values of certain drug-resistant TB mutants ranged from 0.5 to 1.2, relative to their parent strains. We used this same range to analyzed fitness-based differences in the prevalence of drug-sensitive and drug-resistant TB over a one-year period.

Results

When we analyzed the evolutionary behavior of the resistant (q) strain over a one-year period, we observed an immediate and rapid increase emergence, such that, by day 365, greater than 90% of infections could be expected to be attributable to q-strain emergence (Figure 2). This result occurred irrespective of the percentage of HIV/AIDS+ susceptibles being prescribed antibiotic prophylaxis. However, we note that, as the comparative fitness of the q-strain (again, relative to that of the p-strain) is increased from 0.5 to 1.2 [161], we observed a corresponding increase in the percentage of infections associated with q-strain emergence.

As would be expected, due to both curative antibiotics and a decline in available hosts (whether due to immune memory, or mortality), we observed a decline in total infection prevalence over the 365-day duration of the model (Figures 3a and 3 b). Nevertheless, it is crucial to recognize the speed with which the resistant strain emerges and begins to outcompete the sensitive strain. Again, using the endpoint comparative fitness values of 0.5 and 1.2 for the resistant strain, the infection curves depicted in

Figures 3a and 3b demonstrate that, while nearly identical with regard to population-wide TB prevalence, over just a short time resistant strain cases account for a majority of all infectives. Even under the condition when the q-strain experiences the greatest fitness penalty (cf = 0.5), examining total TB prevalence, without analyzing the percentage of drug-resistant vs. drug-sensitive strains, would critically fail to capture overall risk; bacterial strains unresponsive to antibiotics have the potential to be particularly harmful to highly HIV/AIDS-immunocompromised populations. As further evidence of the health risk that arises due to the interplay between HIV/AIDS and emerging resistance, we found that, as HIV/AIDS prevalence increases, there is a corresponding increase in the proportion of q-strain infections; and this occurs irrespective of the relative fitness of the resistant strain (Figures 4a-d).

Finally, Figure 5 illustrates the combined impact of percent prophylaxis use and resistant strain fitness. Visualizing these effects using a heat map allows us to analyze the importance of both selective pressures at once. Even when q-strain fitness is at its presumed lowest (cf = 0.5) [161], the selective pressure applied by HIV/AIDS patients' use of prophylaxis increases q-strain emergence. While this effect is not as pronounced as the q-strain prevalence that we observe as its comparative fitness is increased, it is worth noting with respect to prophylaxis prescribing policies.

Discussion

Both the emergence of antibiotic resistance and the vulnerability of the HIV/AIDS-immunocompromised to opportunistic pathogens are well-documented medical crises [2, 40, 105, 110, 165-168]. In modeling the interplay between these two

health risks, we recently demonstrated that the disrupted selective pressures associated with an HIV/AIDS-related host immunosuppression create the potential for a drastic, AIDS-attributable, increase in the novel emergence of drug resistance (DeNegre, et al., in prep).

In our current SEIR model, we examined the evolutionary impact of resistant strain emergence and circulation within a highly HIV/AIDS-prevalent host population. The results of this model highlighted an additional reason why analyses of the probability of emergence of antibiotic resistance should include consideration of population-wide HIV/AIDS prevalence: widespread use of medically recommended antibiotic prophylaxis is a phenomenon specific to highly immunocompromised host populations [94]. Therefore, prophylaxis-attributable emergence of resistant microbial strains, as well as their subsequent circulation, is also directly related to population-level immunoincompetence. Our model demonstrated that, while the total number of infectives varied only slightly as prophylaxis use increased, the percentage of hosts infected within drug-resistant TB strains increased rapidly, thereby increasing the relative fitness of resistant TB strains.

The use of antibiotic prophylaxis is known to create an evolutionary tradeoff, wherein despite potential improvement of host health, a fitness benefit is conferred to resistant bacterial strains [26]. However, within the context of an HIV/AIDS-prevalent host pool, the elevation of resistant strain fitness that arises as an inevitable by-product of prophylaxis use may represent a considerably greater health risk – especially given the speed with which resistant bacterial strains become dominant. By the end of the 365-day duration of our model, we found that greater than 90% of TB infections could be

expected to be antibiotic-resistant, even when resistant strain fitness is comparatively low. While this percentage may seem high, Sanchez-Padilla, et al. [169], found that, in Swaziland, more than 50% of culture-positive TB patients harbored resistant strains, as of 2010.

In a population such as Swaziland, in which up to 27.4% of the adult population may be immunocompromised [78], this means that a large proportion of the host pool could become infected with bacterial strains that exhibit little, if any, response to targeted antibiotics. In the absence of both antibiotic treatment and sufficient immune response to fight infection, elevated morbidity and mortality among HIV/AIDS+ hosts is a likely outcome. (Though to a lesser degree, it is also possible that fully immunocompetent hosts will suffer the effects of resistant strain dominance, as emergence initially arising in response to the selective pressure imposed by antibiotic prophylaxis is maintained via host mixing and strain circulation.)

We note that, without violating our simplifying assumption that immune status remains unchanged over the duration of the model, we are limited in our ability to assess the long-term (> one year) behavior of this system. However, our initial findings suggest that surveillance efforts directed toward examining the prevalence of TB – or any other opportunistic pathogen – alone, without consideration for strain specificity, will fail to capture the impact of HIV/AIDS-related effects, such as the widespread use of antibiotic prophylaxis, on resistant strain emergence and maintenance. Moreover, it is likely that projections regarding TB-attributable morbidity and mortality will be underestimated, if the percentage of hosts infected with resistant bacterial strains is not taken into account. Given that these effects were visible within the one-year duration of this model, the

potential for long-term resistant strain dominance creates a public health threat that cannot be ignored.

Figure Legends

Figure 1. SEIR Transmission Dynamics

The model follows the progression of fully immunocompetent, HIV/AIDS+, HAART- and HIV+/HAART+ susceptibles who become infected with either drug-sensitive (p) or drug-resistant (q) TB strains. As an example, we include a diagram depicting this process for actively AIDS-immunocompromised (S^{+-}_{--}) susceptibles who have not previously received antibiotic prophylaxis.

Figure 2. Relative Emergence

Using the extremal comparators of resistant strain comparative fitness (cf) = 0.5 and 1.2, we analyzed the resulting changes to relative emergence. Even when its evolutionary fitness is low (0.5), q-strain dominance occurs immediately and rapidly; among all infections, 80-95% can be expected to be antibiotic resistant, irrespective of percent prophylaxis treatment among HIV/AIDS patients.

Figures 3a-b. Total Infectivity

Again using the lowest (cf = 0.5) and highest (cf = 1.2) resistant strain comparative fitness figures, we quantified the prevalence of the q-strain versus that of the p-strain for a one-year period. While there is a slight fitness-dependent change in the ratio of drug-sensitive to drug-resistant infections, the rapid q-strain dominance occurs even when its comparative fitness is low. Therefore, surveillance efforts that analyze total TB prevalence only, while failing to consider the percentage of resistant strain infectives within the population, could be critically flawed – especially when HIV/AIDS prevalence is high (DeNegre, et al., in prep).

Figure 4a-d. Ratios of Emergence as HIV/AIDS Prevalence Increases

We investigated the emergence and dominance of resistant strains as HIV/AIDS prevalence increased from 0-30%, and we present results for the entire population, and for HIV/AIDS+ hosts only. Irrespective of the initial fitness of the q-strain, we observe increasing q-strain success, as HIV/AIDS prevalence increases.

Figure 5. Combined Impact of Comparative Fitness and Percent Prophylaxis Use

Here, we present a heat map representing the change in q-strain prevalence that occurs due to prophylaxis use and changes in comparative fitness. We demonstrate that increased prophylaxis use, and increased comparative fitness, both benefit the resistant strain. While the magnitude of the effect of increased relative fitness is observably greater, even when the relative fitness of q is low, the selective pressure imposed by prophylaxis use increases q-strain prevalence overall. (We note that the lines appearing on the heat map are present for visual assistance only.)

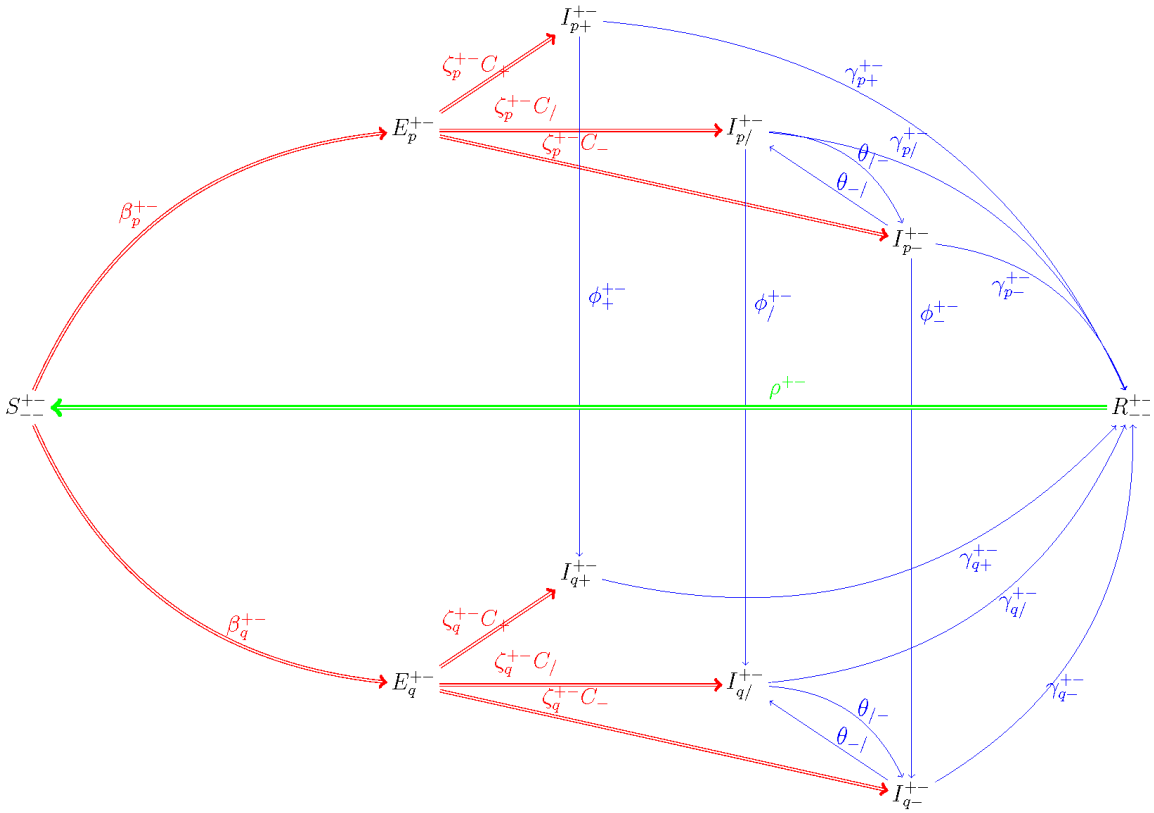

I_{p+}^{+-}
$\zeta_p^{+-}C_+$
γ_{p+}^{+-}
$\zeta_p^{+-}C_/$
E_p^{+-}
$I_{p/}^{+-}$
$\zeta_p^{+-}C_-$
$\gamma_{p/}^{+-}$
$\theta_{/-}$
$\theta_{-/}$
β_p^{+-}
I_{p-}^{+-}
ϕ_+^{+-}
$\phi_/^{+-}$
ϕ_-^{+-}
γ_{p-}^{+-}
ρ^{+-}
S_{--}^{+-}
R_{--}^{+-}
I_{q+}^{+-}
γ_{q+}^{+-}
$\gamma_{q/}^{+-}$
β_q^{+-}
$\zeta_q^{+-}C_+$
$\zeta_q^{+-}C_/$
E_q^{+-}
$I_{q/}^{+-}$
$\zeta_q^{+-}C_-$
γ_{q-}^{+-}
$\theta_{/-}$
$\theta_{-/}$
I_{q-}^{+-}

Figure 1.

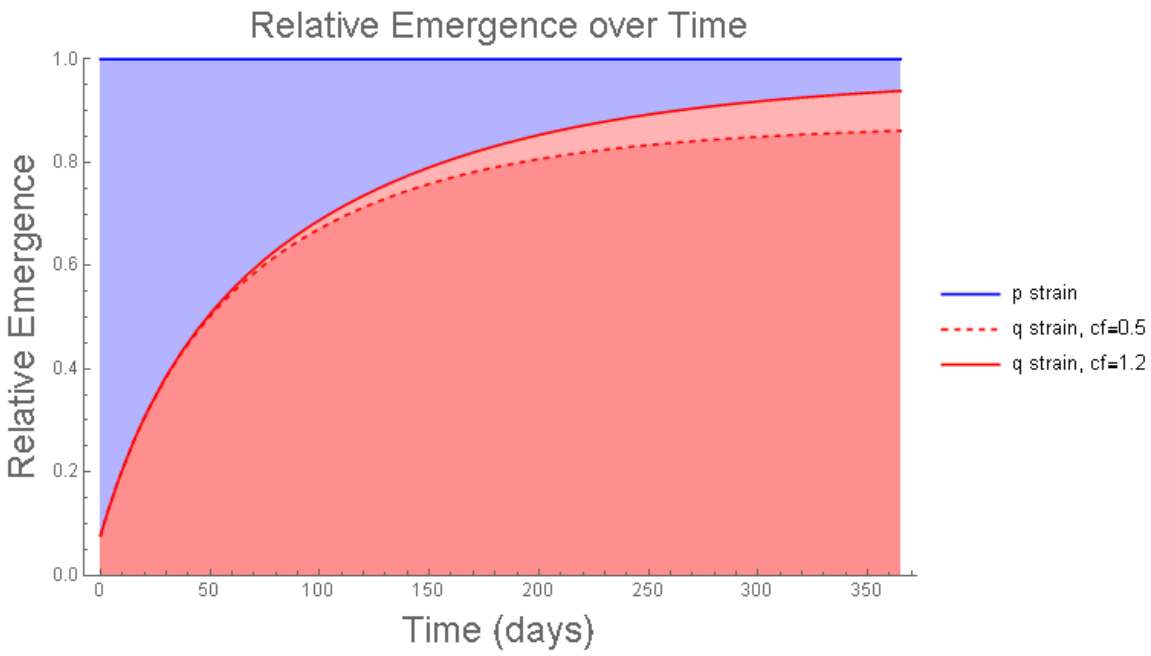

Relative Emergence over Time
Relative Emergence
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
300
350
Time (days)
p strain
q strain, cf=0.5
q strain, cf=1.2

Figure 2.

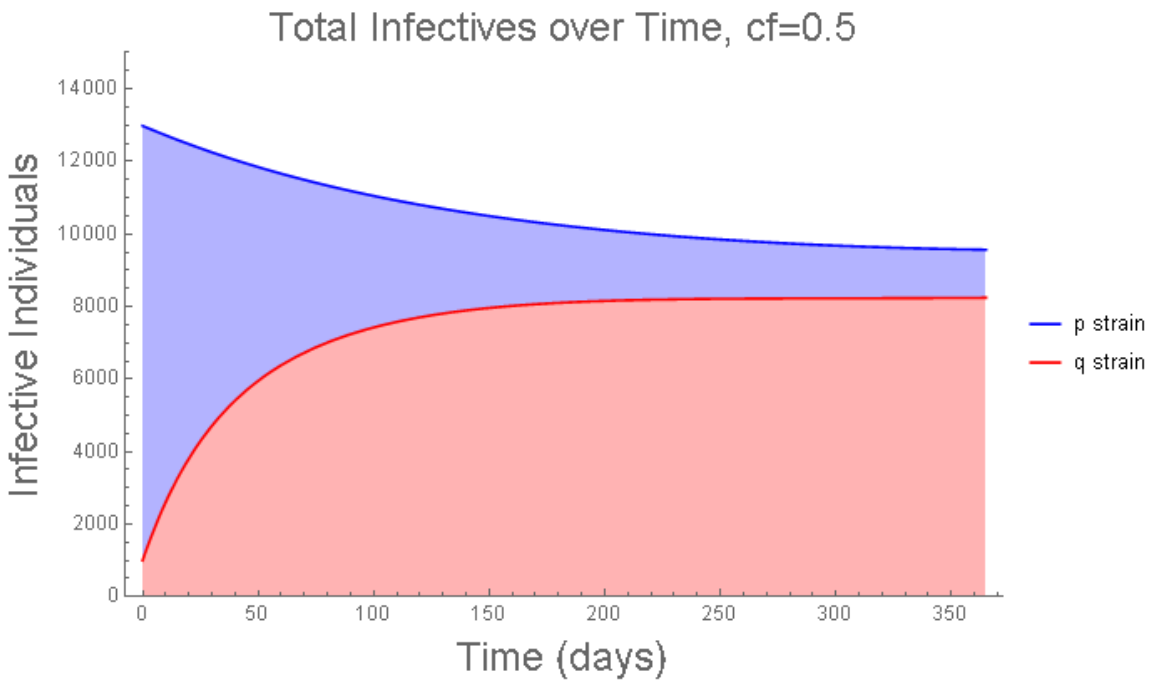


Figure 3a.

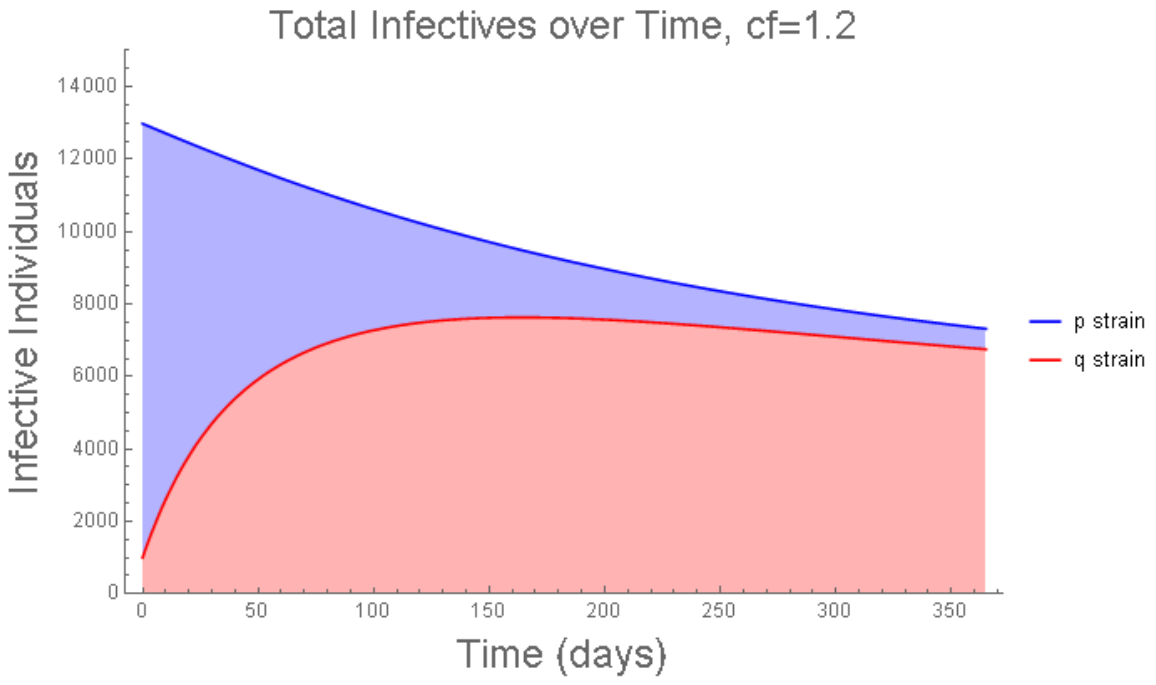
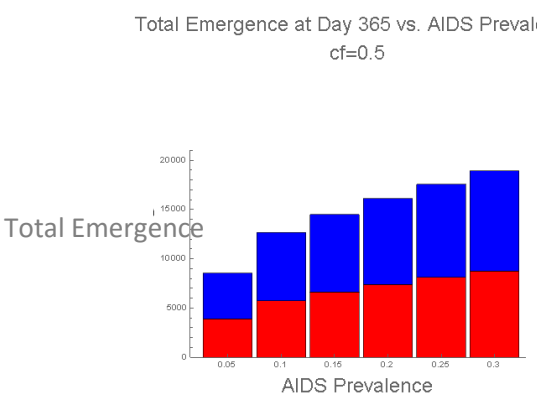


Figure 3b.



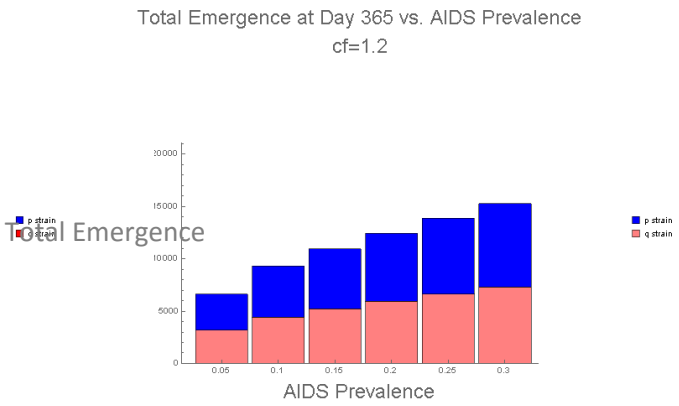
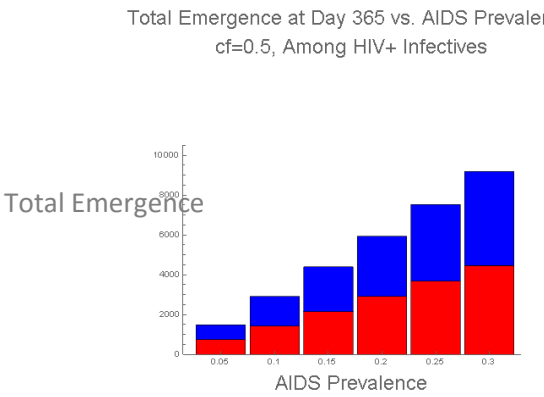


Figure 4a.



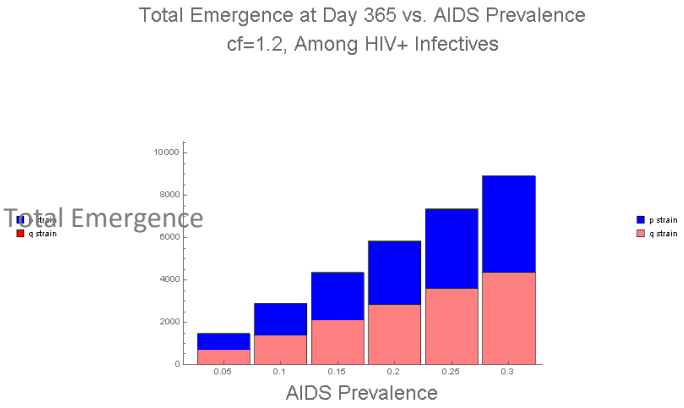


Figure 4b.

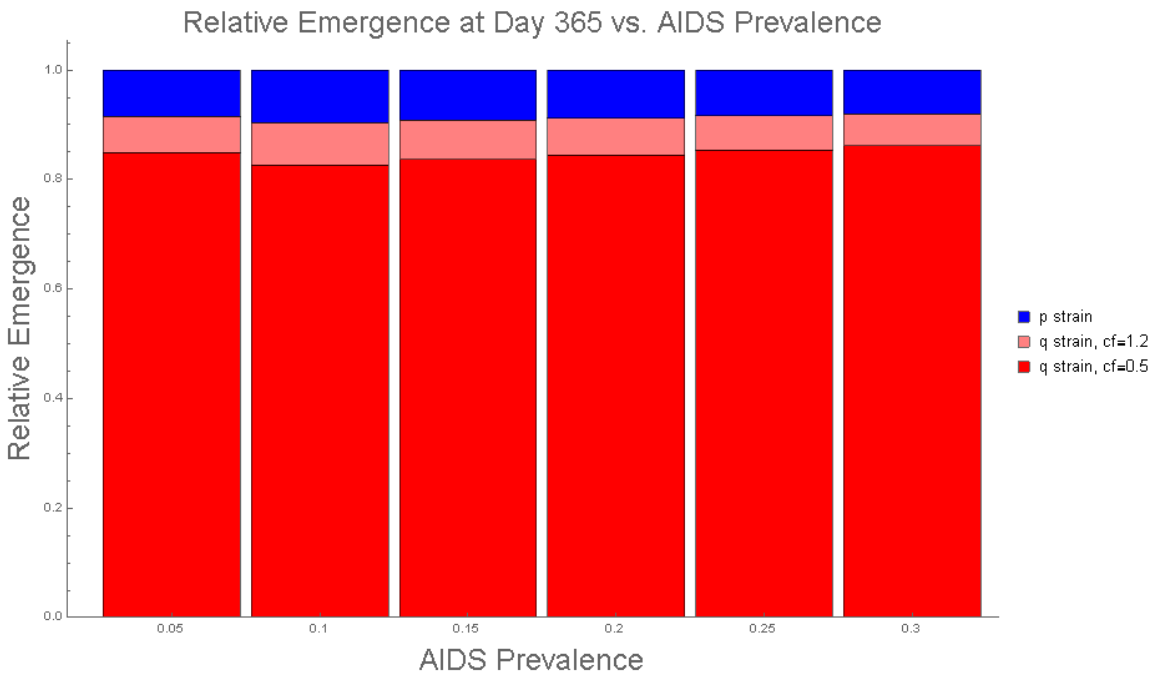


Figure 4c.

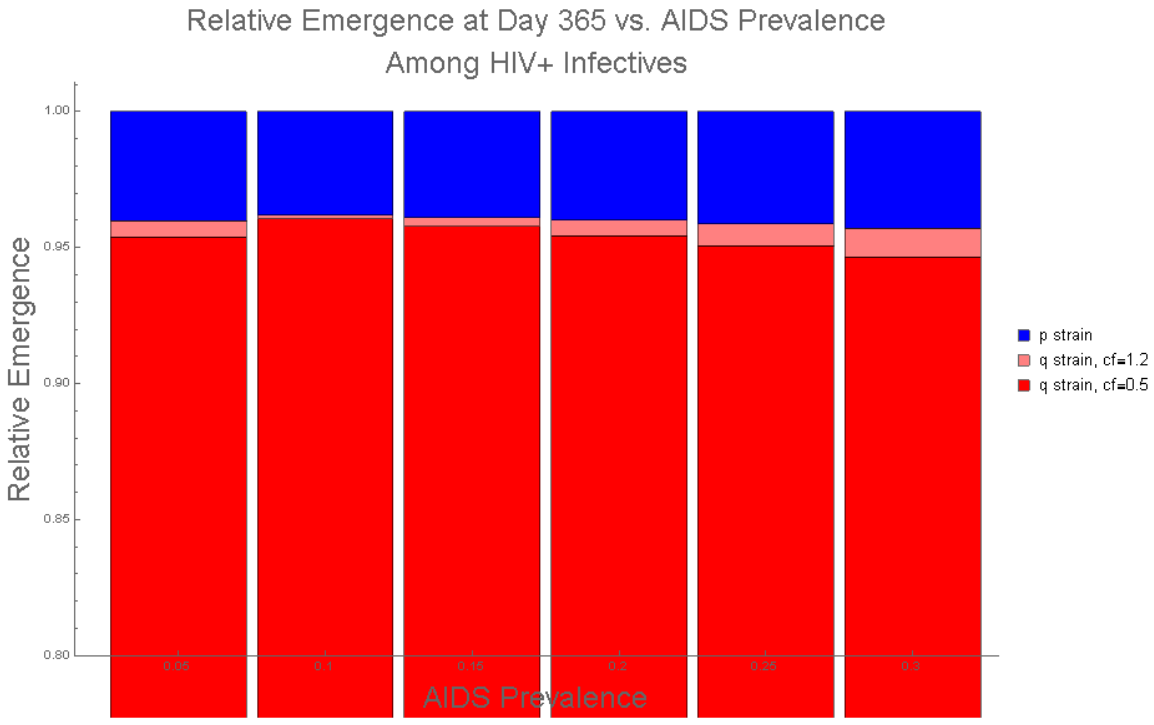


Figure 4d.

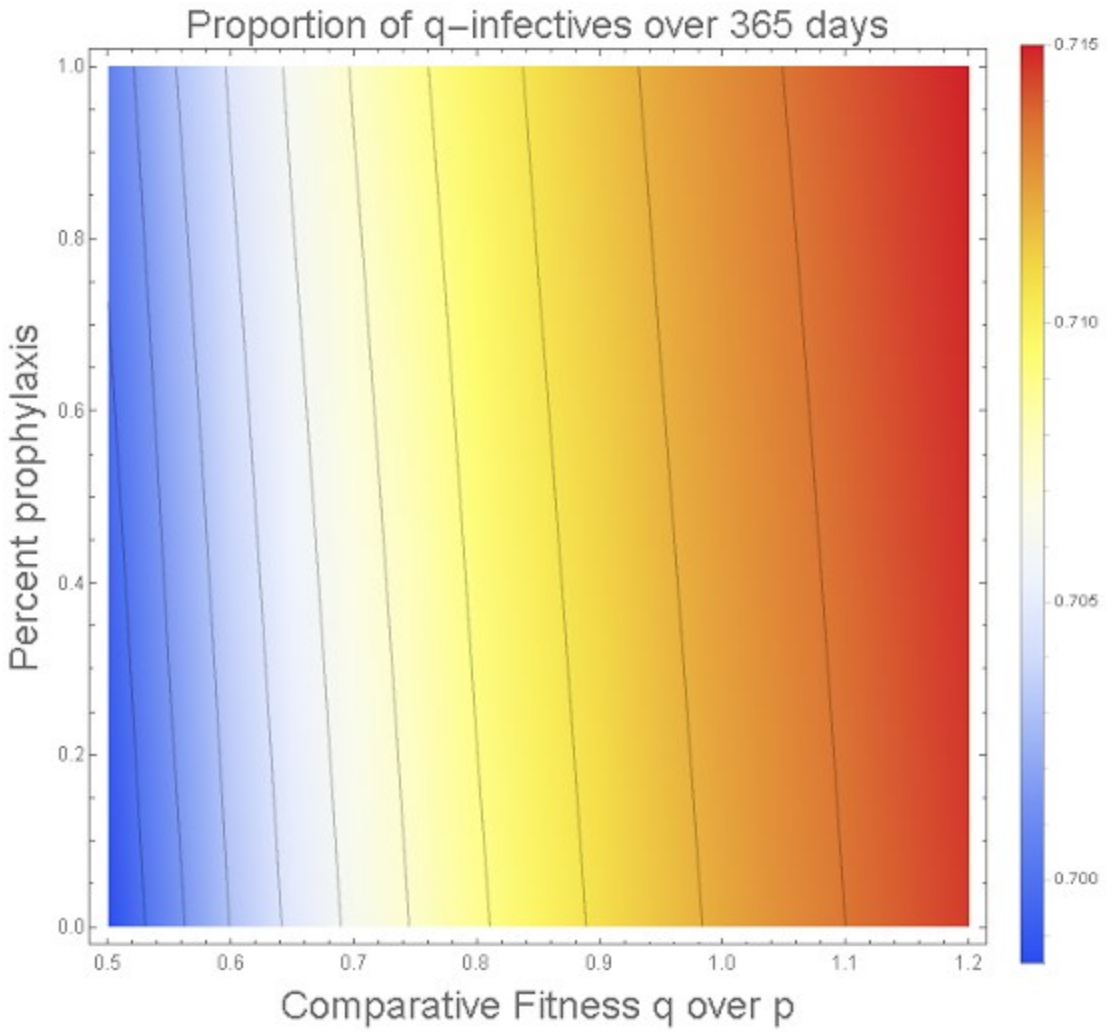

Proportion of q−infectives over 365 days
Percent prophylaxis
1.0
0.8
0.6
0.4
0.2
0.0
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
Comparative Fitness q over p
0.715
0.710
0.705
0.700

Figure 5.

GENERAL DISCUSSION AND CONCLUDING REMARKS

The emergence of antibiotic resistance is a worldwide health risk, as resistant organisms are evolving at a rate that far outpaces the development of new antimicrobials[170]. My dissertation research has demonstrated that this risk is disproportionately greater in AIDS-prevalent host populations where widespread immunoincompetence creates a novel evolutionary environment favoring selection for resistance. Within the developing world, AIDS-attributable risk of emergence is compounded by the combination of poor infection management, as well as the limitations upon economic and medical resources that can restrict patients' ability to adhere to antibiotic dosing instructions [32]. Even if AIDS-related emergence was solely limited to developing nations, it would represent a health crisis; however, migration of human hosts – and insect and animal vectors – has already proven to be a driver of transmission of antibiotic-resistant bacteria, thereby extending the risk of resistant pathogen persistence outside the origin of emergence [85, 171, 172].

Curtailing the emergence of antibiotic resistance is a complex process that requires a multidisciplinary approach. Inroads are being made toward the development of novel antimicrobials, but, given the speed with which resistance emerges [173, 174], this may only be a temporary solution – especially since the chemical composition of antibiotics recently brought to market tends to differ only slightly from those previously used [175]. Given this, it is imperative that antibiotic prescribing policy decisions take into account the behavioral and economic components associated with drug resistance, without relying upon the potential for novel drug development as the primary means of

reducing resistance; and, in doing so, it is necessary that liabilities associated with the patient-provider relationship be examined.

When drug resistance emerges in highly-immunocompromised host populations – such as hospitals [176] and regions plagued by HIV/AIDS – it is the result of the disruption to selection pressure that arises out of the combination of failed host immune activation and widespread use of antibiotics. In environments such as these, when pathogenic bacteria are prevalent, limiting the use of antibiotics (especially when they represent a life-sustaining treatment), while at the same time minimizing transmission of infection, may not possible.

Assuming that some resistance will emerge under the circumstances described above, it is all the more important that antibiotics be prescribed judiciously and used responsibly. This also extends to the use of antibiotic prophylaxis in HIV/AIDS+ patients. While prophylaxis use may benefit the individual patient, population-level morbidity and mortality appear virtually unchanged in prophylaxis-present versus prophylaxis-absent conditions; and, the effects of prophylaxis use can be overwhelmed by the presence of current HIV/AIDS+ infectives. Moreover, the rapid dominance that has the potential to occur when drug-resistant bacterial strains are introduced into highly immunocompromised host populations suggests that, should the selection for resistant strains that arises as a by-product of curative and prophylactic antibiotic misuse continue unchecked, large portions of the host pool are likely to harbor pathogens with no known treatment.

While specific to TB, the World Health Organization's Directly Observed Treatment, Short Course (DOTS), program has proven successful with regard to ensuring the quality and affordability of antibiotics provided to TB patients in resource-limited regions [147]. By regulating the dissemination and consumption of antibiotics, and identifying factors driving patient nonadherence, DOTS also aims to minimize resistance [147]. The fact that DOTS has been successful despite the many challenges associated with TB – namely the cost and duration of treatment – suggests that it might prove to be an appropriate model upon which to base future anti-resistance programs. As such, a future step might be to analyze the costs and benefits associated with the implementation of a similar program specific to highly-immunocompromised host populations. The value derived from reducing the emergence of resistance may prove considerably greater than the potential expenses associated with assuring the quality of both the antibiotic and the trained provider.

As a final comment, there is still much to determine regarding the system I have studied during my dissertation research. In designing my models, each of which was run over a duration of one year or less, I assumed that HIV/AIDS-driven immune status remained constant, with no seroconversion occurring. While this simplifying assumption was appropriate for addressing my research questions, which were designed to assess the initial behavior of the system, it is limited from being able to provide any insight into the relationship between HIV/AIDS and antimicrobial resistance beyond a one-year time period[92, 177]. Having, at this point, only scratched the surface of this topic, I note that future work should involve the interaction of two compartmental models – one to represent the transition from HIV susceptibility to viral infection (and progression to

active AIDS), with varying levels of HAART-dependent immunocompetence, and one to represent the transition from susceptibility to bacterial infection to antibiotic-dependent recovery. By simultaneously implementing both of these models, the long-term effects of this system can be analyzed.

METHODS APPENDIX

To follow are the parameters used in each chapter of the dissertation, their condition dependencies, values, and the sources from which they were obtained directly or, when necessary, estimated. Since parameters assigned in Chapter 1 are also used in Chapters 2 and 3, each section of the appendix includes only newly introduced parameters specific to the chapter being discussed.

Appendix 1: Chapter 1 Model Description, Equations and Parameters Used

Model Description

Our model examines the relative rate of emergence of antibiotic resistance in populations whose collective immunosuppression and prescribed antibiotic use patterns disrupt the selective pressures typically exerted on bacterial pathogens by host immune function and medically recommended antibiotic-taking behavior. We have chosen Indonesia and Swaziland as sample populations, since these countries represent the lower and upper extremes of HIV/AIDS prevalence within the developing world. The vast difference in HIV/AIDS prevalence that exists between the two countries (0.46% of the adult population in Indonesia is HIV/AIDS+, versus 27.4% in Swaziland [78, 87]) suggests that there is a significant difference in the proportion of each population that is actively recommended to be taking antibiotics to treat or prevent infection.

Based on immune function alone, we recognize three categories of susceptible host: (1) those who are fully immunocompetent; (2) those rendered immunocompromised by active AIDS, including those incompletely adhering to highly active antiretroviral therapy (HAART); and, (3) those who are HIV/AIDS-positive, but whose consistent use of HAART provides them with a level of immune function sufficient to greatly reduce

their risk of complications from AIDS-defining illness [75, 134]. Given the short-term nature of bacterial evolution (independent of the duration of infection), we chose to examine the emergence of antibiotic resistance over the course of 180 days. We therefore assume that no change in population description from seroconversion occurs [75]; immune status remains constant over time (though, future work will relax this assumption). Due to its high incidence in HIV/AIDS+ patients [88], we parameterized our model with values reflecting tuberculosis, though the model can represent any bacterial infection.

We defined our susceptible, infectious and recovered populations according to four descriptors: immune status, HAART adherence, TB status, and antibiotic adherence. We denote immune (HIV/AIDS) and HAART using $^{\text{superscripts}}$, and TB status and adherence to antibiotics using $_{\text{subscripts}}$ (Table S1). For example, the compartment S^{+-}_{--} is comprised of AIDS-immunocompromised, HAART-nonadherent hosts ($^{+-}$ in the superscript), who are susceptible to bacterial infection, but are thus far infection-negative, and therefore do not take antibiotics ($_{--}$ in the subscript).

In consideration of high HIV/TB co-infection prevalence – especially in the developing world [88, 178, 179] – we have chosen to use tuberculosis data to inform our parameter values, having derived those values directly from the literature whenever possible. We therefore use the work of Blower and Chou [93], who estimate that fewer than 20% of TB cases are treated worldwide and Trostle [100], who reports a failure rate of 40-60% with respect to antibiotic adherence, to establish a relationship between C values when adherence is varied. When C_1 is equal to 20%, we assume that C_2 is equal to 50%, the mean of Trostle's reported treatment failure rate. Under these

circumstances, C_3 is equal to 30%. In varying adherence, we maintain this initial ratio of probabilities by assuming that C_2 is equal to $0.625*(1 - C_1)$, and that C_3 is equal to $0.375*(1 - C_1)$.

We describe this scenario using the system of ordinary differential equations shown below, where the symbol Î is used to represent the sum of all infectives that can that infect susceptibles at a rate of β, where β depends on HIV/AIDS status of the susceptible, ζ represents the transition rate from exposed to actively infective, ω represents the HIV/AIDS excluded rate of death, ω_A represents the AIDS-attributable rate of death, ω_I represents the bacterial infection-attributable rate of death (as informed by tuberculosis), α represents per capita birthrate, ρ represents the HIV/AIDS status-dependent rate of loss of immunity, γ represents the HIV/AIDS and antibiotic category dependent rate of recovery from bacterial infection, θ represents the transition among antibiotic adherence states, and ψ represents the HAART-dependent increase in infection-attributable death for patients with active AIDS. We have made the simplifying assumptions that HIV/AIDS+, HAART+ individuals give birth to HIV/AIDS- offspring, and that the offspring of HIV/AIDS+, HAART- individuals are also HIV/AIDS+. We expect the effects of these assumptions to be minor, especially given the few births likely to take place during the 180-day duration of the model. For detailed list of parameters, their condition dependencies, values used, and the reference from which they were estimated, see Table S2.

$$\frac{dS_{--}^{--}}{dt} = -\beta^{--}S_{--}^{--}\hat{I} - \omega S_{--}^{--} + \alpha(S_{--}^{--} + S_{--}^{++} + E_{--}^{--} + E_{--}^{++} + I_{++}^{--} + I_{++}^{++} + R_{--}^{--} + R_{--}^{++}) + \rho^{--}R_{--}^{--}$$

$$\frac{dE_{--}^{--}}{dt} = \beta^{--}S_{--}^{--}\hat{I} - \omega E_{--}^{--} - \zeta^{--}E_{--}^{--}$$

$$\frac{d\,I_{++}^{--}}{dt} = \zeta^{--}E_{--}^{--}C_1 - \gamma_{++}^{--}I_{++}^{--} - \omega I_{++}^{--}$$

$$\frac{dI_{+/}^{--}}{dt} = \zeta^{--}E_{--}^{--}C_2 - \gamma_{+/}^{--}I_{+/}^{--} - I_{+/}^{--}(\omega + \omega_I) + \alpha I_{+/}^{--} + \theta_{+/}I_{+-}^{--} - \theta_{+-}I_{+/}^{--}$$

$$\frac{dI_{+-}^{--}}{dt} = \zeta^{--}E_{--}^{--}C_3 - \gamma_{+-}^{--}I_{+-}^{--} - I_{+-}^{--}(\omega + \omega_I) + \alpha I_{+-}^{--} - \theta_{+/}I_{+-}^{--} + \theta_{+-}I_{+/}^{--}$$

$$\frac{dR_{--}^{--}}{dt} = \gamma_{++}^{--}I_{++}^{--} + \gamma_{+/}^{--}I_{+/}^{--} + \gamma_{+-}^{--}I_{+-}^{--} - \rho^{--}R_{--}^{--}$$

$$\frac{dS_{--}^{+-}}{dt} = -\beta^{+-}S_{--}^{+-}\hat{I} - S_{--}^{+-}(\omega + \omega_A) + \alpha(S_{--}^{+-} + E_{--}^{+-} + I_{++}^{+-} + R_{--}^{+-}) + \rho^{+-}R_{--}^{+-}$$

$$\frac{dE_{--}^{+-}}{dt} = \beta^{+-}S_{--}^{+-}\hat{I} - E_{--}^{+-}(\omega_A + \omega_I) - \zeta^{+-}E_{--}^{+-}$$

$$\frac{d\,I_{++}^{+-}}{dt} = \zeta^{+-}E_{--}^{+-}C_1 - \gamma_{++}^{+-}I_{++}^{+-} - I_{++}^{+-}(\omega + \psi^{+-}\omega_I + \omega_A)$$

$$\frac{dI_{+/}^{+-}}{dt} = \zeta^{+-}E_{--}^{+-}C_2 - \gamma_{+/}^{+-}I_{+/}^{+-} - I_{+/}^{+-}(\omega + \psi^{+-}\omega_I + \omega_A) + \alpha I_{+/}^{+-} - \theta_{+-}I_{+/}^{+-} + \theta_{+/}I_{+-}^{+-}$$

$$\frac{dI_{+-}^{+-}}{dt} = \zeta^{+-}E_{--}^{+-}C_3 - \gamma_{+-}^{+-}I_{+-}^{+-} - I_{+-}^{+-}(\omega + \psi^{+-}\omega_I + \omega_A) + \alpha I_{+-}^{+-} - \theta_{+/}I_{+-}^{+-} + \theta_{+-}I_{+/}^{+-}$$

$$\frac{d\,R_{--}^{+-}}{dt} = \gamma_{++}^{+-}I_{++}^{+-} + \gamma_{+/}^{+-}I_{+/}^{+-} + \gamma_{+-}^{+-}I_{+-}^{+-} - R_{--}^{+-}(\omega + \omega_A) - \rho^{+-}R_{--}^{+-}$$

$$\frac{d\,S_{--}^{++}}{dt} = -\beta^{++}S_{--}^{++}\hat{I} - \omega S_{--}^{++} + \rho^{++}R_{--}^{++}$$

$$\frac{d\,E_{--}^{++}}{dt} = -\beta^{++}S_{--}^{++}\hat{I} - \omega E_{--}^{++} - \zeta^{++}E_{--}^{++}$$

$$\frac{dI_{++}^{++}}{dt} = \zeta^{++}E_{--}^{++}C_1 - \gamma_{++}^{++}I_{++}^{++} - \omega I_{++}^{++}$$

$$\frac{dI_{+/}^{++}}{dt} = \zeta^{++}E_{--}^{++}C_2 - \gamma_{+/}^{++}I_{+/}^{++} - I_{+/}^{++}(\omega + \psi^{++}\omega_I) + \alpha I_{+/}^{++} - \theta_{+-}I_{+/}^{++} + \theta_{+/}I_{+-}^{++}$$

$$\frac{dI_{+-}^{++}}{dt} = \zeta^{++}E_{--}^{++}C_3 - \gamma_{+-}^{++}I_{+-}^{++} - I_{+-}^{++}(\omega + \psi^{++}\omega_I) + \alpha I_{+-}^{++} + \theta_{+-}I_{+/}^{++} - \theta_{+/}I_{+-}^{++}$$

$$\frac{dR_{--}^{++}}{dt} = \gamma_{++}^{++}I_{++}^{++} + \gamma_{+/}^{++}I_{+/}^{++} + \gamma_{+-}^{++}I_{+-}^{++} - \omega R_{--}^{++} - \rho^{++}R_{--}^{++}$$

Calculation of Example Parameter Values

To reflect the entry and re-entry of new susceptibles into the population via birth and gradual loss of immune memory, respectively, as well as the departure, due to death, of individuals from all compartments (even just within the relatively short 180 day duration of the model), we defined several parameters (Table S2). (Where possible, the parameter values used in this model were taken from the existing literature; when we were unable to do this, values were assumed, or calculated using the models detailed in this section.) Mortality-associated parameter values include separate rates for HIV-excluded, bacterial infection-related, and other-cause AIDS-related death. We also use the parameters ρ and θ, which represent the differing rate of immune memory loss for each HIV status, and the rate of transition between antibiotic adherence categories, respectively. We note that ρ, β and ζ (the transition rate from exposed to infective) depend on immune status only, and do not vary based on antibiotic adherence; the opposite is true for the parameter θ, which varies based on antibiotic adherence alone. Parameters such as these, whose values are assigned based on either HIV/AIDS status or antibiotic adherence, but not both, are singly indexed using the applicable sub- or superscript.

Although we use ρ to represent the rate at which immune memory is lost during recovery from a bacterial infection, we recognize that it is difficult, if not impossible, to assign a value to a parameter that essentially equates to the number of T-cells lost per

day[180]. Because we cannot ignore the difference in immune memory that exists between immunocompetent and AIDS-immunocompromised hosts[181], we assigned an arbitrary value of 0.001 to represent rate of immune memory loss among the immunocompetent. We assume that immune memory is lost twice as fast in HIV/AIDS+, HAART-treated hosts[1][182], and ten times as fast in those with active AIDS. Though these particular values are chosen arbitrarily, the qualitative outcome of the model will be unaffected so long as the values remain monotonically increasing.

Due to financial constraints, people in developing countries may forgo antibiotic treatment [31, 183, 184] (possibly in favor of purchasing HAART), but, we found no data indicating the frequency with which they alternate between partially adherent and untreated. However, using the work of Kaona, et al.[185], we were able to establish a mean duration of adherence to antibiotic treatment in TB+ hosts by taking a weighted mean of the points at which patients ceased treatment prior to finishing their antibiotic regimens. We use the inverse of that 95.1-day duration to represent the rate at which infectives transition between the partially adherent and untreated states.

We use the symbol ζ to represent the rate of transition from exposure to active infectivity. Cohen and Murray [160] provide an annual transition rate, which we convert to reflect a daily value, and use as a baseline for fully immunocompetent and HAART+ hosts. We assume that those with active AIDS transition ten-percent more quickly once exposed.

[1] In assigning parameter values to HIV/AIDS+, HAART-adherent hosts, we assume their immunocompetence to be equivalent to that HIV/AIDS- hosts in all instances except with regard to loss of immune memory.

In keeping with the primary literature on compartmental modeling, we use the parameter β to represent the between-host bacterial transmission rate; and we use γ to represent the rate of recovery once a bacterial infection is contracted[71, 72]. We assume that β is equivalent for HIV- and HIV/AIDS+, HAART-adherent individuals, whereas the β value for AIDS+, HAART-nonadherent individuals was assumed to be ten-percent higher than that of their fully immunocompetent and HAART-adherent comparators. In all cases, we rely on the work of Cohen and Murray[160], who assigned an arbitrary annual transmission rate of 8.50×10^{-6} to their study population of one million. However, we converted this annual transmission rate to a daily transmission rate, and adjusted it to account for differing population sizes in Indonesia and Swaziland, and differing subpopulation sizes among immune classes.

Values for γ were assigned based on previously published TB infection duration data. Dye, et al.[186], report that in fully treated, immunocompetent hosts, TB infection lasts approximately 292 days; whereas, with partial treatment, approximate infection duration is 547.5 days. Tiemersma, et al.[187], estimate an infection duration of 1095 days in the complete absence of antibiotic treatment. We use the inverse of these three durations to establish baseline rates of recovery in fully immunocompetent hosts.

For HIV/AIDS+, HAART+ hosts, we assume that each antibiotic-dependent value of γ is equivalent to 50% of the one corresponding to fully immunocompetent hosts of the same antibiotic status. We made this assumption to reflect the potential immune complications that can arise within this subpopulation, despite HAART treatment, and to reflect a more reasonable steady state for the ratio of β to γ. In all cases, these values are reflective of initial values used in Cohen [160] and Dye [162, 163].

For AIDS-immunocompromised hosts, we the use the tuberculosis case fatality rates (CFRs) set forth by Corbett, et al.[188], to modify estimated rates of recovery[2] in hosts lacking immune function. Corbett reports a mean CFR ratio of 1.5 for HIV/AIDS+ versus immunocompetent hosts with full (DOTS) antibiotic treatment [159, 188]. We apply the inverse of that ratio, two-thirds, to γ_{++}^{--} - with the assumption that being 1.5 times more likely to succumb to tuberculosis is the equivalent of being 0.67 times as likely to recover – in order to define a recovery rate for fully antibiotic adherent, HIV/AIDS+, HAART- hosts. Similarly, we apply the inverse of 1.27 [188] to $\gamma_{+/}^{--}$ to adjust for immunoincompetence in partially treated (non-DOTS), HIV/AIDS+, HAART- hosts; and, in the complete absence of antibiotic treatment, we apply the inverse of 3.3[188] to γ_{+-}^{--}, to calculate a rate of recovery in AIDS-immunocompromised hosts.

We apply the multiplier ψ to the parameter ω_I to account for the increased probability of infection-attributable mortality affecting HIV/AIDS+, non-HAART-adherent hosts. We again refer to Corbett, et al.[188], and assume a worst-case scenario, in which infection-attributable mortality is 3.3 times greater than it is in fully immunocompetent and HAART-treated hosts. Accordingly, we set ψ^{+-} equal to 3.3 for those AIDS+ infectives not receiving HAART. We assume that immunocompetence and/or HAART is largely protective against death from opportunistic infection in antibiotic-adherent infectives, so we assign a value of one to ψ^{++}. (Values for ψ are based on HIV status alone.)

[2] Corbett's work separates CFRs according to smear-negative and smear-positive samples. However, since our work does not address smear- vs. smear+ TB, we apply a mean of the smear- and smear+ CFRs to our baseline γ values to adjust for immunoincompetence due to active AIDS.

Antibiotic Adherence

The literature reports ranges of antibiotic adherence from 5-95%, depending on factors such as age, socioeconomic status and medication side-effects [137-139]. We investigated the impact of adherence on emergence using a range of 0-100% adherence. When comparing projected emergence both with and without HIV/AIDS in the population, we also included a trial in which we assumed all categories of hosts were 20% adherent to reflect the best-case scenario of adherence reported by Blower and Chou [93].

Per Host Category Relative Emergence Calculations

Determining the relative emergence attributable to each host category required that we include estimates of the per cell, per bacterial generation mutation rate; the total number of infected cells per host; the expected number of bacterial generations per infection duration; the per category infection duration; and the relative success of the mutant strain (Table S3).

Per cell, Per Bacterial Generation Mutation Rate

To estimate this parameter value, we relied upon the work Billington, et al.[89], who report a range of 2.0×10^{-10} to 4.0×10^{-10} mutations per cell, per generation, in *Mycobacterium tuberculosis* (MTB) in the presence of Rifampin. Using the mean of that range, we establish a baseline mutation rate of 3.0×10^{-10} for fully immunocompetent (and HAART+), antibiotic-adherent hosts. In the absence of the selective pressure applied by antibiotic use[128], we assume mutations to develop 50% less frequently in immunocompetent and HAART+, antibiotic-negative hosts, as compared to the baseline. Finally, among partially-treated hosts, we expect that some selective pressure will be

exerted by the intermittent use of antibiotics; however, we do not expect that mutations will arise as frequently as they do in fully-adherent hosts. (Rather, we expect that drug-resistant strains already present within the host microbiome will gain a competitive advantage under this condition.) We therefore use the mean of the mutation rates for fully-adherent and untreated hosts to establish a mutation rate of 2.25×10^{-10} for partially-treated HIV/AIDS- and HIV/AIDS+, HAART+, hosts.

Among AIDS-immunocompromised hosts, the selective pressure typically applied by a functional immune response is absent [189, 190]. While this might suggest that fewer mutations would occur, bacterial replication occurs more rapidly in immunocompromised hosts[191], thereby presumably increasing the probability of random mutation. Therefore, for each antibiotic adherence category, we assume an arbitrary 10% increase in the per bacterium mutation rate of AIDS-immunocompromised hosts, relative to their fully immunocompetent and HAART+ comparators.

Total Infected Cells per Host

To calculate an expected number of infected cells for each host category, we referenced Stone, et al.[90], and Dormans, et al.[91], who provide estimates for the total number of alveolar cells in the mouse and human lung, and the number of MTB colony-forming units (CFUs) found in a mouse model, respectively. In examining strain-specific MTB colonization within the lungs of a mouse host, Dormans, et al., found a range of approximately 10^5-10^9 CFUs [91]. Assuming that MTB resides solely in the cells of alveolar region, and assuming a best-case bacillary load of 10^5 CFUs, we divided 10^5 by the total number of alveolar cells present in the mouse [90] to establish a percentage of infected cells. We then multiplied that same percentage by the total number of alveoli

present in human lungs [90] to correct for the large difference in total alveolar cells that exists between the mouse and human. This process produced a baseline of $4.15x10^5$ infected alveoli in fully immunocompetent and HAART-adherent hosts. We assumed that, among fully-treated hosts, 50% fewer infective alveoli would be found; and we used the mean number of infective alveoli found in fully-treated and untreated hosts to estimate infective alveoli in those who are partially-treated. Finally, among the AIDS-immunocompromised, we assumed a 25% increase in infected alveoli in fully and untreated hosts, relative to their immunocompetent counterparts. We then used the mean infective alveoli form those host categories to establish an estimate for partially treated hosts. (While we recognize that this process only provides us with a rough estimate of the number of infected alveoli, we do not expect it to significantly affect our results, nor do we expect it to compromise our ability to determine relative emergence attributable to each category of infective host.)

Bacterial Generations per Infection Duration

The expected number of bacterial generations per infection duration for each host category was estimated using Gill et al.[58], who report that MTB doubling time ranges from 18-54h. Accordingly, we assume an average doubling time of 36 h. For each adherence category, we apply that doubling time in the equation $(1/\gamma*24h/1d)/36h$, wherein $1/\gamma$ represents the per category infection duration.

Relative Probability of Mutant Success

Based on the combination of HIV/AIDS status and antibiotic adherence, each category of infective was assigned a value representing the relative probability that an antibiotic-resistant mutant would arise and successfully compete for host resources.

These probability values were assumed based on the selective pressures associated with each host category. For example, emergence of antibiotic resistance is less likely in immunocompetent, antibiotic adherent hosts, but those mutations that do arise face little host resource competition[38], since the combination of host immune function and appropriate antibiotic use exerts a twofold selective pressure against drug-sensitive strains[81]. The probability of evolutionary success of a drug-resistant mutant is, therefore, presumed to be high for the host category I^{--}_{++}. Accordingly, the probability value assigned to that host category is 0.95. Conversely, antibiotic-untreated, AIDS-immunocompromised, hosts lack the selective pressures typically applied by immune function and antibiotic adherence against drug-sensitive pathogens; drug-resistant strains are, therefore, unlikely to arise by means other than random mutation and horizontal transfer from antibiotic-resistant microbes already present within the host microbiome[192].

AIDS-attributable Mortality Adjustments

In order to accurately estimate a death rate due to attributable AIDS, it was necessary to divide the reported HIV/AIDS prevalence for each population into two separate groups: those who are HIV+, but whose disease has not yet progressed to AIDS, and those who are AIDS+. Morgan, et al.[92], report a median progression time from HIV seroconversion to active AIDS of 3431 days, and a median survival time from AIDS to death of 276 days in the rural Africa during the pre-HAART era; the total post-seroconversion survival time is 3707 days, 276 days of which are spent in the AIDS+ category. That is, of the total post-seroconversion survival time, 93% is spent with HIV

only, and 7% is spent with active AIDS. Accordingly, we estimate that of the HIV/AIDS+ hosts present in each country, 93% are HIV+, and 7% have active AIDS.

Since our model reflects the current state of HAART availability, it was necessary to adjust AIDS-attributable death to account for the longer post-seroconversion lifespans made possible by the introduction of antiretrovirals[193]. However, an updated estimate of post-activation of AIDS survival time in HAART-treated hosts was not readily available in the literature. We therefore adjust for the additional total post-seroconversion survival time afforded by HAART availability, while assuming that the same percentages apply to time spent in each category as were estimated using Morgan[92]; we expect that this assumption may change the outcome of the model slightly, but not significantly.

The model below, the parameter symbols for which appear in Table S4, was used to calculate the attributable AIDS death rate for Swaziland:

$$1/ ST_{ASZ} = (1/ LE_{SZ} – 1/ LE_{HESZ}*IC_{PSZ})/A_{PSZ}$$

Solving for ST_{ASZ}, and taking its inverse provides an annual AIDS-attributable death rate, and we divide that number by 365 to determine ω_A, the daily rate.

In Indonesia, calculating the AIDS-attributable death rate required that we adjust for the fact that population life expectancy is now greater than it was prior to the introduction of HIV/AIDS. (This phenomenon, actually the result of medical advances unrelated to HIV/AIDS[194], masks the impact of HIV/AIDS on life expectancy.) We use the model described below to adjust for increased Indonesian life expectancy in the post-HIV/AIDS era. Parameter values and symbols are found in Tables S4 and S5.

Using the equation $1/ST_{ASZ'} = (1/ LE_{SZ} - (1/LE_{SZ80}* IC_{PSZ}))/A_{PSZ}$, we solve for an adjusted survival time with active AIDS in Swaziland and apply its inverse to the ratio of

pre-AIDS life expectancies in Swaziland and Indonesia to determine HIV-excluded life expectancy in Indonesia as follows:

$$1/LE_{HEIN} = (1/LE_{IN} - 1/ST_{ASZ'}*(LE_{SZ80}/LE_{IN80}) *(A_{PIN}))/ IC_{PIN}$$

Finally, to calculate death due to AIDS in Indonesia, we apply $1/LE_{HEIN}$ to the ratio LE_{SZ80}/LE_{IN80}, and divide the product by 365 to assess daily AIDS-related mortality.

We note that this model relies upon two assumptions: First, we assume that the post-AIDS life expectancy ratio in Indonesia and Swaziland is equivalent to the pre-AIDS life expectancy ratio; and, second, we assume that life expectancy among the immunocompetent in Swaziland hasn't changed between the current and pre-AIDS era.

Table S1. Key to Super- and Subscripts Used in the Model

Within the ODE model, we describe variables using a combination of super- and subscripts reflecting immune and antibiotic treatment status. All possible combinations are shown below.

	Symbols	Definitions
Superscripts	--	HIV/AIDS-, HAART-
	+-	HIV/AIDS+, HAART-
	++	HIV/AIDS+, HAART+
Subscripts	--	Infection-, untreated
	++	Infection+, fully treated
	+/	Infection+, partially treated
	+-	Infection+ , untreated
	-+	Infection-, prophylaxis

.

Table S2. SEIR Model Parameter Values.

Table S2 defines the values for each parameter used in the model; some parameter values were readily available in the literature, while others were calculated using known values, with the formulas corresponding to these calculations appearing in the appendix. Where applicable, we assume equivalent immune function in HIV/AIDS- and HIV/AIDS+, HAART+ hosts. We note that, rather than the annual figures typically reported in the literature, parameter values for this model have been converted into per person, per day probabilities to reflect the duration of the model.

Parameter Symbol	Description	Population	Value/Source
N_{IN}	Total population	Indonesia	253,609,643[87]
N_{SZ}	Total population	Swaziland	1,419,623[78]
HA	HIV/AIDS prevalence	Indonesia	0.46%[87]
		Swaziland	27.4%[78]
α	Daily birth rate	Indonesia	$4.67x10^{-05}$ [87]
		Swaziland	$6.90x10^{-05}$ [78]
LE_A	Current population life expectancy at birth	Swaziland	32 y[78]
LE_{HE}	HIV-excluded life expectancy at birth	Swaziland	61.5y[78, 92]
ω	Daily HIV-excluded death rate	Indonesia	$3.69x10^{-05}$ 1
		Swaziland	$4.45x10^{-05}$ [78, 92]
$ω_A$	Daily death rate, attributable AIDS	Indonesia	$4.32x10^{-05}$
		Swaziland	$2.0x10^{-03}$ 2

ω_I	Daily tuberculosis-attributable death rate	Both	8.22×10^{-04} [160]
β^{--}	Between-host bacterial transmission rate for fully immunocompetent hosts	Indonesia	2.21×10^{-05} [160, 162]
		Swaziland	7.9×10^{-09} [160, 162]
β^{+-}	Between-host bacterial transmission rate for HIV/AIDS+, HAART-	Indonesia	1.72×10^{-09}; assumed.
		Swaziland	4.64×10^{-10}; assumed.
β^{++}	Between-host bacterial transmission rate for HIV/AIDS+, HAART+ hosts	Indonesia	9.49×10^{-08} [160, 162]
		Swaziland	2.76×10^{-09} [160, 162]
ζ^{--}	Rate of transition from exposed to infective, fully immunocompetent	Both	3.10×10^{-07}[160]
ζ^{+-}	Rate of transition from exposed to infective, HIV/AIDS+, HAART-	Both	3.41×10^{-07}; assumed.
ζ^{++}	Rate of transition from exposed to infective, HIV/AIDS+, HAART+	Both	3.10×10^{-07}; assumed.
ρ^{--}	Rate of immune memory loss in fully immunocompetent hosts	Both	$1{\cdot}0 \times 10^{-03}$; assumed.
ρ^{+-}	Rate of immune	Both	$1{\cdot}0 \times 10^{-02}$; assumed.

	memory loss in HIV/AIDS+, HAART- hosts		
ρ^{++}	Rate of immune memory loss in HIV/AIDS+, HAART+ hosts	Both	$2.0x10^{-03}$; assumed.
$\theta_{+/}$	Transition rate from untreated to partially antibiotic adherent	Both	$1.05x10^{-02}$ [185]
θ_{+-}	Transition rate from partially antibiotic adherent to untreated	Both	$1.05x10^{-02}$[185]
γ_{++}^{--}	TB recovery rate in HIV/AIDS-, DOTS-treated hosts	Both	$3.0x10^{-03}$ [162, 163, 187]
$\gamma_{+/}^{--}$	TB recovery rate in HIV/AIDS-, non-DOTS-treated hosts	Both	$2.0x10^{-03}$ [162, 163, 187]
$\gamma_{\pm-}^{--}$	TB recovery rate in HIV/AIDS-, untreated hosts	Both	$9.13x10^{-04}$ [162, 163, 187]
γ_{++}^{+-}	TB recovery rate in HIV/AIDS+, HAART-, DOTS-treated hosts	Both	$2.0x10^{-03}$ [162, 163, 187]
$\gamma_{+/}^{+-}$	TB recovery rate in HIV/AIDS+, HAART-, non-DOTS-treated hosts	Both	$1.5x10^{-03}$ [162, 163, 187]
γ_{+-}^{+-}	TB recovery rate in HIV/AIDS+, HAART-, untreated hosts	Both	$3.0x10^{-04}$ [162, 163, 187]

γ_{++}^{++}	TB recovery rate in HIV/AIDS+, HAART+, DOTS-treated hosts	Both	$1.50x10^{-4}$; assumed.
$\gamma_{+/}^{++}$	TB recovery rate in HIV/AIDS+, HAART+, non-DOTS-treated hosts	Both	$1.0x10^{-3}$; assumed.
γ_{+-}^{++}	TB recovery rate in HIV/AIDS+, HAART+, untreated hosts	Both	$4.57x10^{-4}$; assumed.
C_1	Probability of early TB detection and complete (DOTS) treatment	Both	Varied, depending on percent complete adherence[93]
C_2	Probability of incomplete (non-DOTS) TB treatment	Both	$0.625* (1-C_1)$[100]
C_3	Probability that no treatment was ever sought	Both	$0.375* (1-C_1)$; assumed.
ψ^{+-}	Multiplier representing increased risk of infection death in HIV/AIDS+, HAART- infectives	Both	3.3[188]
ψ^{++}	Factor of increase for infection-attributable death in HIV/AIDS+, HAART+ patients	Both	1 (placeholder only).

[1] HIV-excluded and AIDS-attributable mortality in Indonesia were adjusted using current and past mortality rates for Swaziland. The models used for this process appear in the appendix to this paper. [2] The model used to separate AIDS-attributable mortality from all-cause mortality is located in the appendix.

Table S3. Projected emergence parameters.

To calculate relative projected emergence attributable to each host category, we estimated relevant bacteriological rates. Generations per infection duration were estimated based on the work of Gill [58], and previously discussed γ values [186-188]; whereas the relative success of mutations was arbitrarily assigned based on selective pressures exerted by host health behavior and immune function [38, 81, 192].

Infective Category	Per cell, Per Generation, Mutation Rate	Total Infected Cells per Host	Per Category Infection Duration (Days)	Generations Per Infection Duration	Relative Success of Mutant
I^{--}_{++}	$3.00x10^{-10}$[89]	$2.08x10^{5}$	292	194.67	0.95
$I^{--}_{+/}$	$2.25x10^{-10}$	$3.11x10^{5}$	547	365	0.95
I^{--}_{+-}	$1.50x10^{-10}$	$4.15x10^{5}$[90, 91]	1095	730	0.05
I^{+-}_{++}	$3.30x10^{-10}$	$2.59x10^{5}$	438	292	0.95
$I^{+-}_{+/}$	$2.48x10^{-10}$	$3.89x10^{5}$	695	463	0.95
I^{+-}_{+-}	$1.65x10^{-10}$	$5.19x10^{5}$	3613	2409	0.05
I^{++}_{++}	$3.00x10^{-10}$[89]	$2.08x10^{5}$	292	194	0.95
$I^{++}_{+/}$	$2.25x10^{-10}$	$3.11x10^{5}$	547	365	0.95
I^{++}_{+-}	$1.50x10^{-10}$	$4.15x10^{5}$[90, 91]	1095	730	0.05

Table S4. AIDS-attributable mortality estimates, SZ

The parameters detailed above were used to estimate an AIDS-attributable mortality rate which applies only to those Swazilanders with active AIDS. We assume that HIV/AIDS+, HAART-adherent, hosts are susceptible only to HIV-excluded and infection-related death.

Parameter Symbol	Description	Value/Source
N_{SZ}	Total population, Swaziland	1,419,623[78]
HA_{SZ}	HIV/AIDS prevalence	26.5%[78]
LE_{SZ}	Current population life expectancy at birth	32 y[195]
LE_{HESZ}	HIV-excluded life expectancy at birth	61.5 y[193]
ω_{ASZ}	AIDS attributable death rate (d)	$(1/ ST_{ASZ})/365$
P_{HIV}	Proportion of HIV/AIDS+ hosts with HIV only	0.93[92]
P_{AIDS}	Proportion of HIV/AIDS+ hosts with active AIDS	0.07[92]
A_{POPSZ}	People living with active AIDS, Swaziland	N_{SZ}* HA_{SZ} * P_{AIDS}
IC_{POPSZ}	People who are fully immunocompetent or HAART treated, Swaziland	N_{SZ} - A_{POPSZ}
IC_{PSZ}	Percent of population that is fully immunocompetent or HAART treated, Swaziland	IC_{POPSZ}/NSZ
A_{PSZ}	Percent of population that with active AIDS, Swaziland	A_{POPSZ}/NSZ

Table S5. AIDS-attributable mortality, IN

AIDS-attributable mortality for Indonesia was calculated based on an adjusted life expectancy for Swaziland. This allowed us to avoid the appearance that HIV/AIDS is adding life-years to population life expectancy when, in fact, medical advances unrelated to HIV/AIDS are the reason for longer lifespans.

Parameter Symbol	Description	Value/Source
N_{SZ}	Total population, Swaziland	1,419,623[78]
N_{IN}	Total population, Indonesia	253,609,643[87]
HA_{SZ}	HIV/AIDS prevalence, Swaziland	26.5%[78]
HA_{IN}	HIV/AIDS prevalence, Indonesia	0.4%[87]
LE_{SZ}	Current population life expectancy at birth, Swaziland	32 y[195]
LE_{IN}	Current population life expectancy at birth, Indonesia	72.2 y[87]
LE_{SZ80}	Pre-AIDS life expectancy, Swaziland	61.5 y[193]
LE_{IN80}	Pre-AIDS life expectancy, Indonesia	52.5y [196]
LE_{HESZ}	Current HIV-excluded life expectancy, Swaziland	61.5 y[193]
LE_{HEIN}	Current HIV-excluded life expectancy, Indonesia	74.3y
$\omega_{A'}$	Adjusted AIDS attributable death rate (d), Swaziland	$(1/ ST_{ASZ'})/365$
P_{HIV}	Proportion of HIV/AIDS+ hosts with HIV only	0.93[92]
P_{AIDS}	Proportion of HIV/AIDS+ hosts with active AIDS	0.07[92]
A_{POPSZ}	People living with active AIDS, Swaziland	N_{SZ}* HA_{SZ} * P_{AIDS}
IC_{POPSZ}	People who are fully immunocompetent or HAART treated, Swaziland	N_{SZ} - A_{POP}
IC_{PSZ}	Percent of population that is fully immunocompetent or HAART treated, Swaziland	IC_{POPSZ}/NSZ
A_{PSZ}	Percent of population with	A_{POPSZ}/NSZ

	active AIDS, Swaziland	
A_{POPIN}	People living with active AIDS, Indonesia	$N_{IN}*HA_{IN}*P_{AIDS}$
IC_{POPIN}	People who are fully immunocompetent or HAART treated, Indonesia	$N_{IN} - A_{POPIN}$
IC_{PIN}	Percent of population that is fully immunocompetent or HAART-treated, Indonesia	IC_{POPIN}/N_{IN}
A_{PIN}	Percent of population with active AIDS, Indonesia	A_{POPIN}/N_{IN}

Appendix 2: Chapter 2 Model Description, Equations and Parameters Used

Model Description and Equations

We duplicate the descriptive system used in Chapter 1 in this model. As such, we use a ^{superscript} to dually describe HIV and HAART status; and we use a $_{subscript}$ to describe both bacterial infection status and adherence to antibiotics. We also introduce the subscript combination "+-" to describe infection-negative, prophylaxis-positive, susceptibles, thereby distinguishing them from hosts using antibiotics to treat active infection.

The entire system is described by a set of ordinary differential equations where the symbol Î is used to represent the sum of all infectives that can that infect susceptibles at a rate of β, where β depends on immune status, ζ, which represents the immune status-dependent rate of transition from exposed to actively infective, ω_I represents rate of death due to bacterial infection (as informed by TB data), ω_A represents AIDS-attributable rate of death, ω all other cause-related rate of death, α represents per capita birthrate, ρ represents the immune status-dependent rate of loss of immunity, γ represents

the HIV/AIDS and antibiotic category dependent rate of recovery from bacterial infection, θ represents the rate of transition between the partially antibiotic adherent and untreated states; and ψ represents the HAART-dependent increase in infection-attributable death for patients with active AIDS.

$$\frac{dS_{-+}^{+-}}{dt} = -\beta^{+-}S_{-+}^{+-}\hat{I} - S_{-+}^{+-}(\omega + \omega_A) + \alpha S_{-+}^{+-}$$

$$\frac{dE_{-+}^{+-}}{dt} = \beta^{+-}S_{-+}^{+-}\hat{I} - E_{-+}^{+-}(\omega + \omega_A) - \zeta E_{-+}^{+-}$$

$$\frac{d\,S_{-+}^{++}}{dt} = -\beta^{++}S_{-+}^{++}\hat{I} - \omega S_{-+}^{++} + \alpha S_{-+}^{++}$$

$$\frac{dE_{-+}^{++}}{dt} = \beta^{++}S_{-+}^{++}\hat{I} - E_{-+}^{++}(\omega + \omega_A) - \zeta E_{-+}^{++}$$

$$\frac{dS_{--}^{--}}{dt} = -\beta^{--}S_{--}^{--}\hat{I} - \omega S_{--}^{--} + \alpha(S_{--}^{--} + S_{--}^{++} + E_{--}^{--} + E_{--}^{++} + I_{++}^{--} + I_{++}^{++} + R_{--}^{--} + R_{--}^{++}) + \rho^{--}R_{--}^{--}$$

$$\frac{dE_{--}^{--}}{dt} = \beta^{--}S_{--}^{--}\hat{I} - \omega E_{--}^{--} - \zeta^{--}E_{--}^{--}$$

$$\frac{d\,I_{++}^{--}}{dt} = \zeta^{--}E_{--}^{--}C_1 - \gamma_{++}^{--}I_{++}^{--} - \omega I_{++}^{--}$$

$$\frac{dI_{+/}^{--}}{dt} = \zeta^{--}E_{--}^{--}C_2 - \gamma_{+/}^{--}I_{+/}^{--} - I_{+/}^{--}(\omega + \omega_I) + \alpha I_{+/}^{--} + \theta_{+/}I_{+-}^{--} - \theta_{+-}I_{+/}^{--}$$

$$\frac{dI_{+-}^{--}}{dt} = \zeta^{--}E_{--}^{--}C_3 - \gamma_{+-}^{--}I_{+-}^{--} - I_{+-}^{--}(\omega + \omega_I) + \alpha I_{+-}^{--} - \theta_{+/}I_{+-}^{--} + \theta_{+-}I_{+/}^{--}$$

$$\frac{dR_{--}^{--}}{dt} = \gamma_{++}^{--}I_{++}^{--} + \gamma_{+/}^{--}I_{+/}^{--} + \gamma_{+-}^{--}I_{+-}^{--} - \rho^{--}R_{--}^{--}$$

$$\frac{dS_{--}^{+-}}{dt} = -\beta^{+-}S_{--}^{+-}\hat{I} - S_{--}^{+-}(\omega + \omega_A) + \alpha(S_{--}^{+-} + E_{--}^{+-} + I_{++}^{+-} + R_{--}^{+-}) + \rho^{+-}R_{--}^{+-}$$

$$\frac{dE_{--}^{+-}}{dt} = \beta^{+-}S_{--}^{+-}\hat{I} - E_{--}^{+-}(\omega_A + \omega_I) - \zeta^{+-}E_{--}^{+-}$$

$$\frac{d\,I_{++}^{+-}}{dt} = \zeta^{+-}E_{--}^{+-}C_1 + \zeta E_{-+}^{+-} - \gamma_{++}^{+-}I_{++}^{+-} - I_{++}^{+-}(\omega + \psi^{+-}\omega_I + \omega_A)$$

$$\frac{dI_{+/}^{+-}}{dt} = \zeta^{+-}E_{--}^{+-}C_2 - \gamma_{+/}^{+-}I_{+/}^{+-} - I_{+/}^{+-}(\omega + \psi^{+-}\omega_I + \omega_A) + \alpha I_{+/}^{+-} - \theta_{+-}I_{+/}^{+-} + \theta_{+/}I_{+-}^{+-}$$

$$\frac{dI_{+-}^{+-}}{dt} = \zeta^{+-}E_{--}^{+-}C_3 - \gamma_{+-}^{+-}I_{+-}^{+-} - I_{+-}^{+-}(\omega + \psi^{+-}\omega_I + \omega_A) + \alpha I_{+-}^{+-} - \theta_{+/}I_{+-}^{+-} + \theta_{+-}I_{+/}^{+-}$$

$$\frac{d\,R_{--}^{+-}}{dt} = \gamma_{++}^{+-}I_{++}^{+-} + \gamma_{+/}^{+-}I_{+/}^{+-} + \gamma_{+-}^{+-}I_{+-}^{+-} - R_{--}^{+-}(\omega + \omega_A) - \rho^{+-}R_{--}^{+-}$$

$$\frac{d\,S_{--}^{++}}{dt} = -\beta^{++}S_{--}^{++}\hat{I} - \omega S_{--}^{++} + \rho^{++}R_{--}^{++}$$

$$\frac{d\,E_{--}^{++}}{dt} = -\beta^{++}S_{--}^{++}\hat{I} - \omega E_{--}^{++} - \zeta^{++}E_{--}^{++}$$

$$\frac{dI_{++}^{++}}{dt} = \zeta^{++}E_{--}^{++}C_1 + \zeta E_{-+}^{++} - \gamma_{++}^{++}I_{++}^{++} - \omega I_{++}^{++}$$

$$\frac{dI_{+/}^{++}}{dt} = \zeta^{++}E_{--}^{++}C_2 - \gamma_{+/}^{++}I_{+/}^{++} - I_{+/}^{++}(\omega + \psi^{++}\omega_I) + \alpha I_{+/}^{++} - \theta_{+-}I_{+/}^{++} + \theta_{+/}I_{+-}^{++}$$

$$\frac{dI_{+-}^{++}}{dt} = \zeta^{++}E_{--}^{++}C_3 - \gamma_{+-}^{++}I_{+-}^{++} - I_{+-}^{++}(\omega + \psi^{++}\omega_I) + \alpha I_{+-}^{++} + \theta_{+-}I_{+/}^{++} - \theta_{+/}I_{+-}^{++}$$

$$\frac{dR_{--}^{++}}{dt} = \gamma_{++}^{++}I_{++}^{++} + \gamma_{+/}^{++}I_{+/}^{++} + \gamma_{+-}^{++}I_{+-}^{++} - \omega R_{--}^{++} - \rho^{++}R_{--}^{++}$$

We add the following equations, where "Q" is used to differentiate drug-resistant infectives from those with drug-sensitive strains, to capture emerging resistance for each immune category:

$$\frac{dQ^{--}}{dt} = \phi^{--}I_{++}^{--} + \phi^{--}I_{+-}^{--} + \phi^{--}I_{--}^{--}$$

$$\frac{dQ^{+-}}{dt} = \phi^{+-}I_{++}^{+-} + \phi^{+-}I_{+-}^{+-} + \phi^{+-}I_{--}^{+-}$$

$$\frac{dQ^{++}}{dt} = \phi^{++}I_{++}^{++} + \phi^{++}I_{+-}^{++} + \phi^{++}I_{--}^{++}$$

Relative Emergence Estimates

Determining the relative emergence attributable to each host category (represented by the symbol "ϕ" in the model) required estimates of the per cell, per bacterial generation mutation rate; the total number of infected cells per host; the expected number of bacterial generations per infection duration; the per category infection duration; and the relative success of the mutant strain. Whereas, in Chapter 1, these calculations were done during post-processing analysis for each antibiotic category, relative emergence is now computed within the ODE model, though the emergence remains record-keeping, since the emergent strain does not circulate independently.

Table S6. Relative Probability of Emergence

As described in Appendix 1, each value for ϕ was computed using the per cell, per bacterial generation mutation rate; the total number of infected cells per host; the expected number of bacterial generations per infection duration; the per category infection duration; and the relative success of the mutant strain.

Symbol	Definition	Population	Value/Source
ϕ_{++}^{--}	Relative probability of emergence in antibiotic-adherent, HIV/AIDS-host	Both	$1.12x10^{-2}$[58, 89, 91]
$\phi_{+/}^{--}$	Relative probability of emergence in	Both	

	partially adherent, HIV/AIDS-host		2.42 x10^{-2}; assumed.
ϕ_{+-}^{--}	Relative probability of emergence in untreated, HIV/AIDS-host	Both	2.23 x10^{-3}; assumed.
ϕ_{++}^{+-}	Relative probability of emergence in antibiotic-adherent, HIV/AIDS+, HAART-, host	Both	2.40 x10^{-2}; assumed.
$\phi_{+/}^{+-}$	Relative probability of emergence in partially adherent, HIV/AIDS+, HAART-,host	Both	4.24x10^{-2}; assumed.
ϕ_{+-}^{+-}	Relative probability of emergence in untreated, HIV/AIDS+, HAART-host	Both	1.03x10^{-2}; assumed.
ϕ_{++}^{++}	Relative probability of emergence in antibiotic-adherent, HIV/AIDS+, HAART+, hosts	Both	1.12x10^{-2}; assumed.
$\phi_{+/}^{++}$	Relative probability of emergence in partially adherent, HIV/AIDS+, HAART+, hosts	Both	2.42 x10^{-2}; assumed.
ϕ_{+-}^{++}	Relative probability of emergence in untreated, HIV/AIDS+, HAART+, hosts	Both	2.23 x10^{-3}; assumed.

Appendix 3: Chapter 3 Model Description, Equations and Parameters Used

SEIR Model Description and Equations

In this chapter, we modify our classification system slightly to account for pathogen co-circulation within the host pool. The immune and antibiotic treatment statuses of those individuals corresponding to the "susceptible" compartment are described using the same convention (*e.g.*, HIV/AIDS- susceptibles are represented asS_{--}^{--}) as in Chapters 1 and 2. However, exposed, infective and recovered members of the population are now categorized by pathogen strain type. Borrowing descriptors from the Hardy-Weinberg model [156], we use "p" in the subscript to describe wild-type (drug-sensitive) strains, and "q" to describe mutant (drug-resistant) strains. The second portion of the subscript remains identical to the system used previously. For example, an HIV/AIDS+, HAART-, individual who contracts a drug-resistant infection, and is fully antibiotic adherent is represented as I_{q+}^{+-}. (We note that, among those in the exposed category, only the first part of the subscript descriptor is used, since antibiotic adherence status only applies to those who are actively infective.

The model, composed of the system of ordinary differential equations below, follows the progression of TB infection through a population stratified by immune and antibiotic status. Parameter values and sources described above (Appendices 1 and 2); however, note that we now include ζ values corresponding to the transition rate from to the actively infective state, once exposed to an antibiotic-resistant infection. We assume that ζ values corresponding to the mutant strain are equivalent to those corresponding to the wild-type strain (previously discussed); and all values are immune status-dependent.

$$
\begin{aligned}
S_{--}^{--\prime}(t) &= -\beta_p^{--} S_{--}^{--}(t) i_{all,p}(t) - \beta_q^{--} S_{--}^{--}(t) i_{all,q}(t) \\
&\quad +\rho^{--} R_{--}^{--} \\
&\quad +\alpha\big(S_{--}^{--} + E_p^{--} + E_q^{--} + I_{p+}^{--} + R_{--}^{--} + S_{--}^{++} + E_p^{++} + E_q^{++} + I_{p+}^{++} + R_{--}^{++} + S_{-+}^{++} + E_{q2}^{++} + R_{-+}^{++}\big) \\
&\quad -\omega S_{--}^{--}
\end{aligned}
$$

$$
\begin{aligned}
S_{--}^{+-\prime}(t) &= -\beta_p^{+-} S_{--}^{+-}(t) i_{all,p}(t) - \beta_q^{+-} S_{--}^{+-}(t) i_{all,q}(t) \\
&\quad +\rho^{+-} R_{--}^{+-} \\
&\quad +\alpha\big(S_{--}^{+-} + E_p^{+-} + E_q^{+-} + I_{p+}^{+-} + R_{--}^{+-} + S_{-+}^{+-} + E_{q2}^{+-} + R_{-+}^{+-}\big) \\
&\quad -(\omega+\omega_v) S_{--}^{+-}
\end{aligned}
$$

$$
\begin{aligned}
S_{-+}^{+-\prime}(t) &= -\beta_q^{+-} S_{-+}^{+-}(t) i_{all,q}(t) \\
&\quad +\rho^{+-} R_{-+}^{+-} \\
&\quad +\alpha\big(S_{-+}^{+-} + E_{q2}^{+-} + I_{q2}^{+-} + R_{-+}^{+-}\big) \\
&\quad -(\omega+\omega_v) S_{-+}^{+-}
\end{aligned}
$$

$$
\begin{aligned}
S_{--}^{++\prime}(t) &= -\beta_p^{++} S_{--}^{++}(t) i_{all,p}(t) - \beta_q^{++} S_{--}^{++}(t) i_{all,q}(t) \\
&\quad +\rho^{++} R_{--}^{++} \\
&\quad -\omega S_{--}^{++}
\end{aligned}
$$

$$
S_{-+}^{++\prime}(t) = -\beta_q^{++} S_{-+}^{++}(t) i_{all,q}(t) + \rho^{++} R_{-+}^{++}(t) - \omega S_{-+}^{++}(t)
$$

$$
\begin{aligned}
E_p^{--\prime}(t) &= \beta_p^{--} S_{--}^{--}(t) i_{all,p}(t) - \zeta_p^{--} E_p^{--}(t) - \omega E_p^{--\prime} \\
E_q^{--\prime}(t) &= \beta_q^{--} S_{--}^{--}(t) i_{all,q}(t) - \zeta_q^{--} E_q^{--}(t) - \omega E_q^{--\prime} \\
E_p^{+-\prime}(t) &= \beta_p^{+-} S_{--}^{+-}(t) i_{all,p}(t) - \zeta_p^{+-} E_p^{+-}(t) - (\omega+\omega_v) E_p^{+-\prime} \\
E_q^{+-\prime}(t) &= \beta_q^{+-} S_{--}^{+-}(t) i_{all,q}(t) - \zeta_q^{+-} E_q^{+-}(t) - (\omega+\omega_v) E_q^{+-\prime} \\
E_p^{++\prime}(t) &= \beta_p^{++} S_{--}^{++}(t) i_{all,p}(t) - \zeta_p^{++} E_p^{++}(t) - \omega E_p^{++\prime} \\
E_q^{++\prime}(t) &= \beta_q^{++} S_{--}^{++}(t) i_{all,q}(t) - \zeta_q^{++} E_q^{++}(t) - \omega E_q^{++\prime} \\
E_{q2}^{+-\prime}(t) &= \beta_q^{+-} S_{-+}^{+-}(t) i_{all,q}(t) - \zeta_q^{+-} E_{q2}^{+-}(t) - (\omega+\omega_v) E_{q2}^{+-\prime} \\
E_{q2}^{++\prime}(t) &= \beta_q^{++} S_{-+}^{++}(t) i_{all,q}(t) - \zeta_q^{++} E_{q2}^{++}(t) - \omega E_{q2}^{++\prime}
\end{aligned}
$$

$$
\begin{aligned}
I_{p+}^{--\prime}(t) &= C_+\zeta_p^{--} E_p^{--}(t) - \phi_+^{--} I_{p+}^{--}(t) - \gamma_+^{--} I_{p+}^{--}(t) - \omega I_{p+}^{--}(t) \\
I_{q+}^{--\prime}(t) &= C_+\zeta_q^{--} E_q^{--}(t) + \phi_+^{--} I_{p+}^{--}(t) - \gamma_+^{--} I_{q+}^{--}(t) - \omega I_{q+}^{--}(t) \\
I_{p/}^{--\prime}(t) &= C_/\zeta_p^{--} E_p^{--}(t) - \phi_+^{--} I_{p/}^{--}(t) - \theta_{/-} I_{p/}^{--}(t) + \theta_{-/} I_{p-}^{--}(t) - \gamma_+^{--} I_{p/}^{--}(t) + \alpha\big(I_{p/}^{--}(t) + I_{p/}^{++}(t)\big) - (\omega+\omega_b) I_{p/}^{--}(t) \\
I_{q/}^{--\prime}(t) &= C_/\zeta_q^{--} E_q^{--}(t) + \phi_+^{--} I_{p/}^{--}(t) - \theta_{/-} I_{q/}^{--}(t) + \theta_{-/} I_{q-}^{--}(t) - \gamma_+^{--} I_{q/}^{--}(t) + \alpha\big(I_{q/}^{--}(t) + I_{q/}^{++}(t)\big) - (\omega+\omega_b) I_{q/}^{--}(t) \\
I_{p-}^{--\prime}(t) &= C_-\zeta_p^{--} E_p^{--}(t) - \phi_+^{--} I_{p-}^{--}(t) + \theta_{/-} I_{p/}^{--}(t) - \theta_{-/} I_{p-}^{--}(t) - \gamma_+^{--} I_{p-}^{--}(t) + \alpha\big(I_{p-}^{--}(t) + I_{p-}^{++}(t)\big) - (\omega+\omega_b) I_{p-}^{--}(t) \\
I_{q-}^{--\prime}(t) &= C_-\zeta_q^{--} E_q^{--}(t) + \phi_+^{--} I_{p-}^{--}(t) + \theta_{/-} I_{q/}^{--}(t) - \theta_{-/} I_{q-}^{--}(t) - \gamma_+^{--} I_{q-}^{--}(t) + \alpha\big(I_{q-}^{--}(t) + I_{q-}^{++}(t) + I_{q+}^{++} + I_{q+}^{--} + I_{q2}^{++}\big) - (\omega+\omega_b) I_{q-}^{--}(t)
\end{aligned}
$$

$$
\begin{aligned}
I_{p+}^{+-\prime}(t) &= C_+\zeta_p^{+-} E_p^{+-}(t) - \phi_+^{+-} I_{p+}^{+-}(t) - \gamma_+^{+-} I_{p+}^{+-}(t) - (\omega+\omega_v) I_{p+}^{+-}(t) \\
I_{q+}^{+-\prime}(t) &= C_+\zeta_q^{+-} E_q^{+-}(t) + \phi_+^{+-} I_{p+}^{+-}(t) - \gamma_+^{+-} I_{q+}^{+-}(t) + \alpha I_{q+}^{+-} - (\omega+\omega_v) I_{q+}^{+-}(t) \\
I_{p/}^{+-\prime}(t) &= C_/\zeta_p^{+-} E_p^{+-}(t) - \phi_+^{+-} I_{p/}^{+-}(t) - \theta_{/-} I_{p/}^{+-}(t) + \theta_{-/} I_{p-}^{+-}(t) - \gamma_+^{+-} I_{p/}^{+-}(t) + \alpha I_{p/}^{+-}(t) - (\omega+\psi\omega_b+\omega_v) I_{p/}^{+-}(t) \\
I_{q/}^{+-\prime}(t) &= C_/\zeta_q^{+-} E_q^{+-}(t) + \phi_+^{+-} I_{p/}^{+-}(t) - \theta_{/-} I_{q/}^{+-}(t) + \theta_{-/} I_{q-}^{+-}(t) - \gamma_+^{+-} I_{q/}^{+-}(t) + \alpha I_{q/}^{+-}(t) - (\omega+\psi\omega_b+\omega_v) I_{q/}^{+-}(t) \\
I_{p-}^{+-\prime}(t) &= C_-\zeta_p^{+-} E_p^{+-}(t) - \phi_+^{+-} I_{p-}^{+-}(t) + \theta_{/-} I_{p/}^{+-}(t) - \theta_{-/} I_{p-}^{+-}(t) - \gamma_+^{+-} I_{p-}^{+-}(t) + \alpha I_{p-}^{+-}(t) - (\omega+\psi\omega_b+\omega_v) I_{p-}^{+-}(t) \\
I_{q-}^{+-\prime}(t) &= C_-\zeta_q^{+-} E_q^{+-}(t) + \phi_+^{+-} I_{p-}^{+-}(t) + \theta_{/-} I_{q/}^{+-}(t) - \theta_{-/} I_{q-}^{+-}(t) - \gamma_+^{+-} I_{q-}^{+-}(t) + \alpha I_{q-}^{+-}(t) - (\omega+\psi\omega_b+\omega_v) I_{q-}^{+-}(t)
\end{aligned}
$$

$$
\begin{aligned}
I_{p+}^{++\prime}(t) &= C_{+}\zeta_{p}^{++}E_{p}^{++}(t) - \phi_{+}^{++}I_{p+}^{++}(t) - \gamma_{+}^{++}I_{p+}^{++}(t) - \omega I_{p+}^{++}(t) \\
I_{q+}^{++\prime}(t) &= C_{+}\zeta_{q}^{++}E_{q}^{++}(t) + \phi_{+}^{++}I_{p+}^{++}(t) - \gamma_{+}^{++}I_{q+}^{++}(t) - \omega I_{q+}^{++}(t) \\
I_{p/}^{++\prime}(t) &= C_{/}\zeta_{p}^{++}E_{p}^{++}(t) - \phi_{+}^{++}I_{p/}^{++}(t) - \theta_{/-}I_{p/}^{++}(t) + \theta_{-/}I_{p-}^{++}(t) - \gamma_{+}^{++}I_{p/}^{++}(t) - (\omega+\omega_{b})I_{p/}^{++}(t) \\
I_{q/}^{++\prime}(t) &= C_{/}\zeta_{q}^{++}E_{q}^{++}(t) + \phi_{+}^{++}I_{p/}^{++}(t) - \theta_{/-}I_{q/}^{++}(t) + \theta_{-/}I_{q-}^{++}(t) - \gamma_{+}^{++}I_{q/}^{++}(t) - (\omega+\omega_{b})I_{q/}^{++}(t) \\
I_{p-}^{++\prime}(t) &= C_{-}\zeta_{p}^{++}E_{p}^{++}(t) - \phi_{+}^{++}I_{p-}^{++}(t) + \theta_{/-}I_{p/}^{++}(t) - \theta_{-/}I_{p-}^{++}(t) - \gamma_{+}^{++}I_{p-}^{++}(t) - (\omega+\omega_{b})I_{p-}^{++}(t) \\
I_{q-}^{++\prime}(t) &= C_{-}\zeta_{q}^{++}E_{q}^{++}(t) + \phi_{+}^{++}I_{p-}^{++}(t) + \theta_{/-}I_{q/}^{++}(t) - \theta_{-/}I_{q-}^{++}(t) - \gamma_{+}^{++}I_{q-}^{++}(t) - (\omega+\omega_{b})I_{q-}^{++}(t)
\end{aligned}
$$

$$
\begin{aligned}
I_{q2}^{+-\prime}(t) &= \zeta_{q}^{+-}E_{q2}^{+-}(t) - \gamma^{+-}I_{q2}^{+-}(t) + \alpha I_{q2}^{+-} - (\omega+\omega_{v})I_{q2}^{+-}(t) \\
I_{q2}^{++\prime}(t) &= \zeta_{q}^{++}E_{q2}^{++}(t) - \gamma^{+-}I_{q2}^{++}(t) - \omega I_{q2}^{++}(t)
\end{aligned}
$$

$$
\begin{aligned}
I_{all,p} &= I_{p+}^{--}(t) + I_{p/}^{--}(t) + I_{p-}^{--}(t) + I_{p+}^{+-}(t) + I_{p/}^{+-}(t) + I_{p-}^{+-}(t) + I_{p+}^{++}(t) + I_{p/}^{++}(t) + I_{p-}^{++}(t) \\
I_{all,q} &= I_{q+}^{--}(t) + I_{q/}^{--}(t) + I_{q-}^{--}(t) + I_{q+}^{+-}(t) + I_{q/}^{+-}(t) + I_{q-}^{+-}(t) + I_{q+}^{++}(t) + I_{q/}^{++}(t) + I_{q-}^{++}(t) + I_{q2}^{+-}(t) + I_{q2}^{++}(t)
\end{aligned}
$$

$$
\begin{aligned}
R_{--}^{--\prime}(t) &= \gamma_{p+}^{--}I_{p+}^{--}(t) + \gamma_{p/}^{--}I_{p/}^{--}(t) + \gamma_{p-}^{--}I_{p-}^{--}(t) + \gamma_{q+}^{--}I_{q+}^{--}(t) + \gamma_{q/}^{--}I_{q/}^{--}(t) + \gamma_{q-}^{--}I_{q-}^{--}(t) - \rho^{--}R_{--}^{--}(t) - \omega R_{--}^{--}(t) \\
R_{--}^{+-\prime}(t) &= \gamma_{p+}^{+-}I_{p+}^{+-}(t) + \gamma_{p/}^{+-}I_{p/}^{+-}(t) + \gamma_{p-}^{+-}I_{p-}^{+-}(t) + \gamma_{q+}^{+-}I_{q+}^{+-}(t) + \gamma_{q/}^{+-}I_{q/}^{+-}(t) + \gamma_{q-}^{+-}I_{q-}^{+-}(t) - \rho^{+-}R_{--}^{+-}(t) - (\omega+\omega_{v})R_{--}^{+-}(t) \\
R_{--}^{++\prime}(t) &= \gamma_{p+}^{++}I_{p+}^{++}(t) + \gamma_{p/}^{++}I_{p/}^{++}(t) + \gamma_{p-}^{++}I_{p-}^{++}(t) + \gamma_{q+}^{++}I_{q+}^{++}(t) + \gamma_{q/}^{++}I_{q/}^{++}(t) + \gamma_{q-}^{++}I_{q-}^{++}(t) - \rho^{++}R_{--}^{++}(t) - \omega R_{--}^{++}(t) \\
R_{-+}^{+-\prime}(t) &= \gamma_{q2}^{+-}I_{q2}^{+-}(t) - \rho^{+-}R_{-+}^{+-}(t) - (\omega+\omega_{v})R_{-+}^{+-}(t) \\
R_{-+}^{++\prime}(t) &= \gamma_{q2}^{++}I_{q2}^{++}(t) - \rho^{++}R_{-+}^{++}(t) - \omega R_{-+}^{++}(t)
\end{aligned}
$$

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