Long-Term Dynamics of the Kidney Disease Epidemic Among HIV-Infected Individuals

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Long-Term Dynamics of the Kidney Disease Epidemic Among HIV-Infected Individuals

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Abstract
One of many risks facing HIV+ individuals is the development of kidney dysfunction and end stage kidney disease (ESKD). A differential equation-based mathematical model was developed to assess the impact of antiretroviral therapy on the progression to kidney disease and on reducing mortality due to kidney failure. Analytical and numerical predictions of long-term HIV+ ESKD prevalence show that therapy can lead to either extremely low levels of disease prevalence or increased prevalence, depending on drug efficacy levels and mechanisms of action. Maintenance of HIV+ ESKD prevalence below one individual is possible with sufficient efficacy (e.g., 99%) against the progression from AIDS to HIV+ ESKD and against entry to the AIDS population, when the reduction in mortality in the AIDS and HIV+ ESKD populations is modest (e.g., 10%). However, the concomitant decrease in mortality in the AIDS and HIV+ ESKD populations due to therapy is predicted to sustain greater disease prevalence.

Keywords: continuous ODE model, epidemic modeling, HIV infection, kidney disease, antiretroviral therapy

1 Introduction

An infectious pathogen can have devastating effects on human populations. In 2020, the world witnessed the beginning of the COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, resulting in over a million deaths as of October 2020 [10]. In 2018, Acquired Immune Deficiency Syndrome (AIDS), caused by Human Immunodeficiency Virus (HIV), claimed the lives of 470,000 individuals in sub-Saharan Africa alone [22]. AIDS eventually leads to opportunistic infections and death in almost all cases without therapy. Individuals with HIV/AIDS are at risk for the development of kidney diseases, including chronic kidney disease (CKD) and HIV-associated nephropathy (HIVAN) [2, 17]. These conditions frequently progress to end stage kidney disease (ESKD, or also called end stage renal disease (ESRD)), in which individuals require a life-long renal replacement therapy such as dialysis or kidney transplantation [1]. CKD and ESKD are now considerable causes for morbidity and mortality among those with HIV infection [2]. A racial predilection is seen in HIVAN in which a higher proportion are of African descent than any other race; a recent study reported that almost 90% of individuals with ESKD due to HIVAN in the United States are African-American [4, 12, 24].

The recommended treatment for individuals with HIV/AIDS as well as for the HIV-infected who have ESKD (henceforth referred to as HIV+ ESKD) is antiretroviral therapy (ART), which is given as a combination of drugs that interferes with virus replication. ART benefits individuals at risk for the development of HIV-related kidney dysfunction and correlates with a decreased incidence in HIVAN [11]. The therapy decreases mortality in HIV-infected individuals [21, 25]; in fact, life expectancy with HIV on ART has been shown to be on par with that of matched uninfected individuals [7]. Furthermore, ART lowers the development of HIV+ ESKD and also reduces mortality among those with HIV+ ESKD [1, 17]. While this therapy is beneficial for those with HIV and those at risk for or showing renal dysfunction, a concern has arisen recently that the COVID-19 pandemic will result in disruption of antiretroviral treatment for many individuals with HIV/AIDS. In sub-Saharan Africa, bearing the majority of new HIV infections globally [6] and where 67.5% of the nearly 38 million HIV+ individuals live [22], lockdowns from COVID-19 have delayed access to HIV support services, and travel restrictions have prevented health care workers from delivering ART to communities [14, 16, 18]. Indeed, a recent mathematical modeling study predicted that interruption in the supply of ART for the HIV-infected population would lead to a 1.6-fold increase in HIV-related deaths in a year [9].

In 2005, Schwartz et al. [19] published a model of the HIV+ ESKD epidemic that estimated the impact of ART on the development of kidney disease. Even assuming 95% effective therapy, the model projected a rise in HIV+ ESKD prevalence in the future, as a result of the growth in the AIDS population. Given that ART not only blocks entry to both AIDS
and HIV+ ESKD, but it also reduces mortality in both populations, a question that remains is what effect do the various mechanisms of action and levels of ART have on the long-term persistence of HIV+ ESKD? Here, we propose a new model, which expands the previous model [19], to investigate the balance of the opposing effects of ART on the prevalence of HIV+ ESKD. We solve the model and analyze its long-term behavior using stability analysis. We describe characteristics of the steady state, and we also calculate the critical drug efficacy, which we define as the minimum efficacy of ART that would be required to maintain HIV+ ESRD prevalence below one individual. With numerical simulations that demonstrate our results, we show which ART mechanisms and at what levels lead to decreased or increased HIV+ ESKD prevalence, and we describe the trade-offs between the opposing population-level consequences of ART on the epidemic dynamics. We find that due to the rise in lifespans afforded by ART, we “lose” the gains that result from ART’s effect on blocking the development of renal disease, consistent with previous results from the simpler model. We close with a discussion of the implications of these results, including in the context of decreased access to ART during the COVID-19 pandemic.

2 Methods

2.1 Model

In the model of Schwartz et al. [19], the two populations, AIDS (A) and HIV+ ESKD or nephropathy (N), were formulated as a continuous system of ODEs as well as by a discrete system of difference equations of the same two populations; both approaches yielded equivalent results. Here we expand upon the ODE model to include greater complexity in the population dynamics and actions of ART (Figure 1).

Specifically, we use the continuous ODE model and introduce separate entry and exit terms in the A population. We capture new individuals entering the A population at a constant rate, b, and those dying exponentially due to AIDS at rate ρ, or due to non-AIDS causes, at rate ρA. We also include mortality in the N population due to non-HIV+ ESKD causes, ρN. As in [19], mortality in N due to HIV+ ESKD is represented by δ. The inclusion of separate mortality rates representing deaths due to disease-related or disease-unrelated causes was motivated by the vastly different mortality rates reported in the literature (see Table 1). The current model presumes that all patients with HIV+ ESKD arise from the AIDS population at rate s and are thus subtracted from the AIDS population. Parameters representing antiretroviral therapy (ART) are ε, h,η and j, and can take on values between 0 and 1 to represent ART efficacy from 0% to 100%. We model ART that prevents individuals from developing AIDS (either for HIV-infected individuals who do not have AIDS or HIV-uninfected individuals taking ART as pre-exposure prophylaxis) with ε. ART that blocks progression from AIDS to HIV+ ESKD is modeled by h. The effect of ART on reducing mortality among those with AIDS is modeled by η and among those with HIV+ ESKD by j. The resulting model is as follows:

\[
\begin{align*}
\frac{dA}{dt} &= (1 - \epsilon)b - (1 - h)sA - (1 - \eta)\rho A - \mu_A A \\
\frac{dN}{dt} &= (1 - h)sA - (1 - j)\delta N - \mu_N N
\end{align*}
\]

with A(0) = A0 and N(0) = N0.

2.2 Model Analysis

Theorem 2.1. Each solution of \((A(t), N(t))\) of the model with non-negative initial conditions is non-negative for all \(t > 0\).

Proof. Let \(X = (A, N)^T\) and \(f(X) = (f_1(X), f_2(X))\). We can write our model as \(\frac{dX}{dt} = f(X)\) where

\[
\begin{align*}
f(X) &= \begin{bmatrix} f_1(X) \\ f_2(X) \end{bmatrix} \\
&= \begin{bmatrix} (1 - \epsilon)b - (1 - h)sA - (1 - \eta)\rho A - \mu_A A \\ (1 - h)sA - (1 - j)\delta N - \mu_N N \end{bmatrix}.
\end{align*}
\]
First, we have

\[ A'(t)\big|_{t=0} = (1 - \epsilon)b \geq 0. \]

Since all non-ART parameters are positive, \( 0 \leq \epsilon, h, \eta, j \leq 1 \), and \( A'(t) \geq 0 \) on the boundary, it follows that \( A(t) \geq 0 \) for all \( t \). Next, we have

\[ N'(t)\big|_{t=0} = (1 - h)sA \geq 0. \]

By similar reasoning, it follows that \( N(t) \geq 0 \) for all \( t \). Hence our model is biological meaningful and \( \mathcal{R}_2^\circ \) is positively invariant. Therefore our model is mathematically well-posed.

### 2.2.1 Analytical Solution

The solution of the model system is

\[ A(t) = \left( 1 - \epsilon \right) b/k + \left( A_0 - \left( 1 - \epsilon \right) b/k \right) e^{-kt}, \]

\[ N(t) = N_0 e^{-\delta t} + \left( 1 - \epsilon \right) b(1 - h)s \left( 1 - e^{-kt} \right)/kk' + \left( 1 - h \right)s \left( e^{-kt} - e^{-\delta t} \right) \left( A_0 - \left( 1 - \epsilon \right) b/k \right), \]

where \( k = (1 - h)s + (1 - \eta)\rho + \mu_A \) and \( k' = (1 - j)\delta + \mu_N \).

### 2.2.2 Stability Analysis

The model has one equilibrium point \((A^*, N^*)\),

\[ A^* = \frac{(1 - \epsilon)b}{[(1 - h)s + (1 - \eta)\rho + \mu_A] \left( 1 - j \right) \delta + \mu_N}. \]

\[ N^* = \frac{(1 - \epsilon)b}{[(1 - h)s + (1 - \eta)\rho + \mu_A] \left( 1 - j \right) \delta + \mu_N - (1 - j)\delta + \mu_N}. \]

The Jacobian matrix of the system is

\[ J = \begin{bmatrix} -(1 - h)s - (1 - \eta)\rho - \mu_A & 0 \\ (1 - h)s & -(1 - j)\delta - \mu_N \end{bmatrix}. \]

The eigenvalues of the Jacobian matrix are

\[ \lambda_1 = -(1 - h)s + (1 - \eta)\rho + \mu_A \]

\[ \lambda_2 = -(1 - j)\delta + \mu_N. \]

Negative eigenvalues imply \((A^*, N^*)\) is a stable equilibrium. Furthermore, using the analytical solution, for any initial conditions, the solution approaches the equilibrium

\[ \lim_{t \to \infty} A(t) = A^* \]

\[ \lim_{t \to \infty} N(t) = N^*. \]

Hence \((A^*, N^*)\) is a globally asymptotically stable equilibrium point. There is no ESKD-free equilibrium.
2.2.3 Characteristics of the Equilibrium

We point out characteristics of the equations derived for the steady state $(A^*, N^*)$ that provide useful biological insights. The ART parameter $\epsilon$ appears only in the numerator of each steady state, and ART parameters $\eta$ and $j$ appear only in denominators (specifically, $\eta$ in each denominator, and $j$ in the $N^*$ denominator). Thus, when ART inhibits entry to the AIDS population $(0 < \epsilon \leq 1)$, $A^*$ will be reduced, and when ART reduces mortality $(0 < \eta \leq 1$ or $0 < j \leq 1$), $A^*$ or $N^*$ will increase. ART parameter $h$ is more interesting in that it appears in the denominator of $A^*$, and in both the numerator and denominator of $N^*$, and hence $h$ is a key parameter of interest in this study.

2.2.4 Calculation of Critical Drug Efficacy, $h_c$

Focusing our interest on HIV+ ESKD, we can determine the condition required to reduce the steady state level below one individual, or $N^* < 1$. Setting $N^* < 1$ and choosing our main ART parameter of interest, $h$ (the effect of ART on $s$, the rate of progression from AIDS to HIV+ ESKD), we solve for $h$ to derive $h_c$.

Setting $N^* < 1$, we have

$$
(1 - h)s(1 - \epsilon)b \leq [(1 - j)\delta + \mu_N][(1 - h)s + (1 - \eta)\rho + \mu_A].
$$

Solving for $h$ gives

$$
h_c > 1 - \frac{[(1 - \eta)\rho + \mu_A][(1 - j)\delta + \mu_N]}{s(1 - \epsilon)b - s[(1 - j)\delta + \mu_N]}. \tag{2.6}
$$

We call this expression the critical drug efficacy $h_c$ needed to block progression from AIDS to HIV+ ESKD such that the HIV+ ESKD steady state is less than one individual. Recall that $h$ (like $\epsilon$, $\eta$, and $j$) ranges from 0 to 1. When the second term on the right hand side of (2.6) is much smaller than one, then the critical efficacy will be difficult to achieve, as compared to when the term is closer to one. In the latter case, there are fewer constraints on the other parameter values required to satisfy $h_c > 1$. Thus, equation (2.6) provides the requirement in terms of the other model parameters explicitly.

2.2.5 Model Parameterization

Values for parameters and initial conditions (Table 1) are taken from the literature on Black individuals (in order to represent the vast majority of those with HIV+ ESKD in the United States (US) or fitted as described below. We focus on the US because data on AIDS and HIV+ ESKD were available from two registries in the US, the Centers for Disease Control and Prevention (CDC) [3] and the United States Renal Data System (USRDS) [23], respectively. The data used were for all Black individuals living with AIDS (from all sex and age groups) from 1991–1995 (i.e., the time period before ART was rolled out) [3] or calculated from new cases and deaths due to AIDS Nephropathy annually [23] (as in [19]). The value for $b$ was determined by the best fit of the CDC data to the model equation for $A$, using other model parameter values in Table 1 under the condition of no therapy (i.e., $\epsilon = h = \eta = 0$, as was the case in 1991–1995 when ART was not yet available).

3 Results

In this section, we illustrate our model results by showing simulations of the epidemic dynamics under conditions with and without ART. Values for parameters and initial conditions (shown in Table 1) are taken from the literature or fitted, as described. First we provide the epidemic trajectories without ART. In the absence of ART, both populations, AIDS $(A)$ and HIV+ ESKD $(N)$, grow rapidly to steady state (Figure 2). We are mainly interested in understanding how ART, which in practice acts on $h$, $s$, $\rho$, and $\delta$ simultaneously, affects HIV+ ESKD prevalence. In this case, $h$, $\epsilon$, $\eta$, and $j > 0$. It is informative, however, to consider simple cases where ART is blocking a single rate individually. Figure 3 shows the steady state values reached for AIDS $(A^*$, left) and for HIV+ ESKD $(N^*$, right) as each ART parameter $(h, \epsilon, \eta, j)$ varies from $0$ to $1$ (i.e., representing $0$ to $100\%$ effective inhibition).

When ART completely inhibits the progression from AIDS to HIV+ ESKD, $h = 1$. In this case (solid line), the AIDS $(A)$ population is very mildly increased, while the HIV+ ESKD $(N)$ population decreases to $0$. Similarly, if ART completely prevents individuals from developing AIDS, $\epsilon = 1$. In this case (dashed line), both populations, AIDS $(A)$ and HIV+ ESKD $(N)$, decrease to $0$.

ART also benefits infected individuals by decreasing mortality, thereby lengthening lives. If ART fully prevents mortality due to HIV+ ESKD $(\delta)$, then $j = 1$. Under this condition (dashed-dotted line), the steady state AIDS population $(A)$ is unchanged, but the HIV+ ESKD $(N)$ population increases to a steady state more than $4$-fold higher than its previous level. In fact, we can calculate the magnitude of the increase in $N^*$ as $j$ takes on values from $0$ to $1$ from the $N^*$ equation:

$$
\frac{N^*_j}{N^*_j} = \frac{\delta + \mu_N}{(1 - j)\delta + \mu_N}.
$$

Thus, using the values in Table 1 and illustrated by comparing the values of $N^*$ as $j$ varies from $0$ to $1$ (Figure 3 right), we have

$$
\frac{N^*_j}{N^*_j} = \frac{\delta + \mu_N}{\mu_N} = 4.35.
$$

Alternatively, when ART completely blocks AIDS mortality $\rho$, then $\eta = 1$. In this case (dotted line), both populations increase, with HIV+ ESKD $(N)$ increasing to an almost $7$-fold higher steady state level. We can likewise calculate the mag-
nitude of the increase in \( N^* \) as \( \eta \) takes on values from 0 to 1:

\[
\frac{N^*_0}{N^*_\eta=0} = \frac{(1-h)s + \mu_A + \rho}{(1-h)s + \mu_A + (1-\eta)\rho}
\]

and thus using the values in Table 1 and illustrated by comparing the values of \( N^* \) as \( \eta \) varies from 0 to 1 (Figure 3 right), we have

\[
\frac{N^*_0(h=1)}{N^*_\eta=0} = \frac{(1-h)s + \mu_A + \rho}{(1-h)s + \mu_A} = 6.91.
\]

Figure 2 also demonstrates how \( A^* \) and \( N^* \) change as a function of each ART parameter alone: ART inhibition of HIV+ ESKD development (by \( h \)) or mortality (by \( j \)) has no or little effect on AIDS (unsurprisingly); ART inhibition of entry to AIDS (by \( e \)) appears linear in its decrease in \( A^* \) as \( e \) increases, while inhibition of AIDS mortality (by \( \eta \)) appears exponential in its growth of \( A^* \) as \( \eta \) increases. Meanwhile, the effect of increasing \( h \) or \( e \) on \( N^* \) appears as a linear decrease (as these parameters reduce entry into the HIV+ ESKD or AIDS populations, respectively); increasing \( j \) or \( \eta \), which reduce mortality, appear to exponentially increase \( N^* \). Thus the percent effectiveness of ART against different mechanisms of inhibition does not scale equally.

Realistically, treatment with ART acts along these mechanisms simultaneously: it blocks the progression from AIDS to HIV+ ESKD \((h)\), it blocks the entry to AIDS \((e)\), it lowers AIDS mortality \((\eta)\), and it lowers HIV+ ESKD mortality \((j)\). Using our model, we demonstrate the predicted effect of pairs of ART parameters on reducing \( N^* \) below 1, 50, 100, or 200 individuals. Figure 4(top) shows the values of \( h \) and \( e \) that reduce \( N^* \) below these thresholds. Higher values of \( h \) and \( e \) give lower thresholds for \( N^* \). When we consider ART that blocks progression from AIDS to HIV+ ESKD \((h > 0)\) with a simultaneous reduction in AIDS mortality \((\eta > 0)\), however, we find a different result. As \( \eta \) increases, a higher \( h \) is needed to maintain a low \( N^* \) (Figure 4 middle). Equivalent results are seen with ART that simultaneously blocks entry to AIDS \((e > 0)\) and HIV+ ESKD mortality \((j > 0)\) (not shown). Thus, we find that we “lose” the gains that result from ART’s effect on blocking progression \((h)\) or entry \((e)\). This can be explained in that when ART decreases the mortality rate, longer lifespans are achieved, maintaining prevalence of \( N \). Finally, when ART acts on all four mechanisms simultaneously (i.e., \( h, e, \eta, j > 0 \)), lower \( N^* \) thresholds can be reached (Figure 4 bottom). Here we set \( h = \epsilon = \eta = j = 0.01 \). This simulation demonstrates an example in which equation (2.6) is satisfied. The population trajectories indicate that HIV+ ESKD prevalence declines to \( N^* < 1 \); in fact our model gives \( N^* = 0.16 \). In this scenario, ART works concurrently against the four different mechanisms (i.e., the progression from AIDS to HIV+ ESKD, entry to AIDS, AIDS mortality, and HIV+ ESKD mortality) without requiring any one mechanism to be 100% effective. Here, HIV+ ESKD prevalence is reduced below one with very high efficacy of ART across entry modes \((h \) and \( e)\) and modest efficacy to reduce deaths \((\eta \) and \( j)\).

Using our model, we sought a single value across all four ART parameters (i.e., \( h, e, \eta, j \)) that gives \( N^* < 1 \). We found, however, that even 0.99 was insufficient, giving \( N^*_0 = 5.33 \) (Figure 5 bottom). In fact, for \( N^* < 1 \), we would need 0.999 (giving \( N^*_0 = 0.06 \)); even 0.995 gives 1 < \( N^* < 2 \). Thus, extremely high levels of ART efficacy across all mechanisms (i.e., \( \geq 99.9\%) \) would be required to maintain \( N^* < 1 \) with a uniform ART efficacy.

### 4 Discussion and Conclusions

The mathematical model presented in this work provides a framework for examining the dynamics of the epidemiology of HIV+ ESKD and the role played by antiretroviral therapy.
(ART) for HIV infection. The study demonstrates the power of simple modeling and straightforward mathematical analysis with numerical simulation to clarify the effects of therapy on population dynamics, to illustrate the dominant trends, and to elucidate the mechanisms behind these trends. This model expands upon a previous model by taking into account additional dynamics in both populations, in order to study the effects of therapy across different mechanisms. We analyzed the model by finding the analytical solution, conducting steady state and stability analyses yielding the single equilibrium point, and calculating the critical drug efficacy required to maintain HIV+ ESKD prevalence below one individual. Our numerical simulations showed epidemic trajectories of long-term dynamics with no therapy, therapy that acts on different mechanisms alone or in combination, and the therapeutic levels required to drop the long-term kidney disease prevalence below one individual.

Ultimately, the HIV+ ESKD burden (i.e., the steady state level $N^*$) will depend on the combination of the efficacies of ART across each of the four mechanisms: blocking progression from AIDS to HIV+ ESKD, reducing entry to AIDS, decreasing the mortality of AIDS, and decreasing the mortality of HIV+ ESKD. While extremely low prevalence is possible with ART, the effect of therapy on reducing mortality, thereby extending the lifespans of those with AIDS and HIV+ ESKD, is predicted to maintain persistence of kidney disease.

This result is consistent with the conclusions of a simpler model [19]. However, the expanded model examined here has several advantages over the previous work. In particular, Schwartz et al. modelled the entry and exit of AIDS ($A$) with a single parameter, $g$, representing the overall growth of the population. The overall growth rate can be affected by ART, represented by the parameter $m$. The parameters $g$ and $m$ were estimated using least squares data fitting of this equation to the CDC data. While the confidence in the parameter estimation using this approach was high (due to small root mean square errors), the model suffered from solutions that were unbounded, which is biologically unrealistic. In the current model, we resolve this issue by introducing separate entry and exit terms in the $A$ population. We use a constant entry term, $b$, and an exponential decay term, $\rho$, motivated by the ease of fitting to the available data. This approach also allows us to model the effects of ART on each of these processes separately: we represent ART that prevents individuals from developing AIDS with $\epsilon$, and ART that decreases the death rate due to AIDS with $\eta$. Furthermore, we include a death rate of
Figure 4: Level curves showing $N^*$ thresholds as ART parameters vary. $h$, effect of ART on progression from AIDS to HIV+ ESKD; $\epsilon$, effect of ART on entry to AIDS; $\eta$, effect of ART on AIDS mortality; $j$, effect of ART on HIV+ ESKD mortality. Top: $N^*$ as $h$ and $\epsilon$ vary between 0 and 1. $\eta = j = 0$. For each value of $N^*$, in order to maintain prevalence below that threshold, the values of $h$ and $\epsilon$ must be above and to the right of the curve, respectively. Middle: $N^*$ as $h$ and $\eta$ vary between 0 and 1. $\epsilon = j = 0$. For each value of $N^*$, in order to maintain prevalence below that threshold, the values of $h$ and $\eta$ must be above and to the left of the curve, respectively. Bottom: $N^*$ as $h$, $\epsilon$, $j$, and $\eta$ vary between 0 and 1. $\epsilon = h$ and $j = \eta$. For each value of $N^*$, in order to maintain prevalence below that threshold, the values of $h = \epsilon$ and $\eta = j$ must be above and to the left of the curve, respectively.

Figure 5: Epidemic trajectories in the presence of ART acting across all mechanisms simultaneously. AIDS (A) population (number of individuals), black. HIV+ ESKD (N) population (number of individuals), red. Parameter values and initial conditions are given in Table I unless otherwise indicated. Top: Model simulation with $h = 0.99$, $\epsilon = 0.99$, $\eta = 0.1$, $j = 0.1$. Bottom: Model simulation with $h = 0.99$, $\epsilon = 0.99$, $\eta = 0.99$, $j = 0.99$. $h$, effect of ART on progression from AIDS to HIV+ ESKD; $\epsilon$, effect of ART on entry to AIDS; $\eta$, effect of ART on AIDS mortality; $j$, effect of ART on HIV+ ESKD mortality.
treated individuals with AIDS who die from non-AIDS causes by \( \mu_s \). The Schwartz et al. model also neglected to include mortality in the \( N \) population due to non-HIV + ESKD causes, \( \mu_N \), unlike the current model. A final advantage of the current model is one of mutual exclusivity. Specifically, while both models presume that all patients with HIV + ESKD arose from the AIDS population at rate \( s \), the current model thus subtracts these cases from the AIDS population, which ensures that each of the populations \( A \) and \( N \) is mutually exclusive.

Given that the current study considers more demographics in the AIDS population and more mechanisms of ART than previous work, it allows us to investigate in greater detail the role of AIDS demographics and the trade-off between the opposing effects of ART on kidney disease prevalence. Our results show that it is important to reduce entry to the AIDS population (i.e., the rate of new AIDS cases). We also show how higher efficacy of ART against entry to AIDS and progression from AIDS to HIV + ESKD give a lower prevalence, but greater efficacy of ART on reducing mortality gives a higher prevalence, so in a sense, we “lose” the gains achieved by blocking entry rates. In other words, while the effects of ART along all its mechanisms of action benefit the individual patient, the reductions in mortality worsen the epidemic on the population level, because the extension of lifespans increases the risk pool of the epidemic. The implication of this finding is that efforts that focus on prevention (to HIV/AIDS and to HIV + ESKD) should be promoted at the highest levels possible, for the sake of the individual as well as for the population.

Finally, we note that the overall effectiveness of ART will be due to many factors in addition to the activity of the drugs. Interruptions in access or delivery of ART stemming from the COVID-19 pandemic will reduce the net effect of therapy, and the degree of these interruptions will vary among countries worldwide, with those affected most by HIV/AIDS possibly suffering the greatest interruptions. The lack of adherence to drug regimens by individual patients and the evolution of drug resistance are factors that will lower the overall ART effectiveness as well.

In future work, the model can be extended to include time-varying parameters and calibrated with new epidemiological data on HIV/AIDS and HIV + ESKD. Further studies can also determine how much treatment levels and the development of renal disease have changed over time, include stochastic or hybrid modeling to examine small population dynamics resulting from effective therapy, estimate the efficacy that ART has had in slowing the progression from AIDS to kidney disease, and use optimal control techniques to determine treatments that would best stem the growth of this epidemic.

**Author Contributions**

HG contributed methodology, validation, formal analysis, investigation, data curation, writing, and visualization. HAO contributed methodology, validation, formal analysis, investigation, data curation, and writing. EJS contributed conceptualization, methodology, formal analysis, investigation, writing, visualization, supervision, project administration, and funding acquisition.

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