

Highly Active Antiretroviral Therapy and the Epidemic of HIV+ End-Stage Renal Disease

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The rise in the number of patients with HIV-associated nephropathy and HIV-infection with end-stage renal disease (HIV+ ESRD) continues to be a substantial concern for the ESRD program. In order to assess the impact of highly active antiretroviral therapy (HAART) on the progression of patients with AIDS to the development of ESRD and to project the prevalence of HIV+ ESRD through 2020, a mathematical model of the dynamics of HIV+ infection in the ESRD population was developed. Epidemiologic data on AIDS and HIV+ ESRD among black individuals in the United States were obtained since 1991 from the Centers for Disease Control and Prevention and US Renal Data System, respectively. The model was constructed to predict the prevalence of HIV+ ESRD incorporating the current rate of growth in AIDS prevalence. Two possible trends were considered: linear AIDS growth and exponential AIDS growth. The likely effectiveness of HAART in slowing progression to HIV+ ESRD was estimated from the best fit of the model to the data after 1995, when HAART was introduced. The model was then used to evaluate recent data and to project the prevalence of HIV+ ESRD through 2020. The model suggested that HAART has reduced the rate of progression from AIDS to HIV+ ESRD by 38%. The model projected an increase in HIV+ ESRD prevalence in the future as a result of the increase in the AIDS population among black individuals. This increase was predicted even assuming a 95% reduction in the progression from AIDS to HIV+ ESRD. Despite the potential benefit of HAART, the prevalence of HIV+ ESRD in the United States is expected to rise in the future as a result of the expansion of the AIDS population among black individuals. It is concluded that prevention of progression to ESRD should focus on early antiretroviral treatment of HIV-infected patients who have evidence of HIV-associated nephropathy.

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Patients with HIV infection are at risk for the development of chronic renal disease. HIV-related renal diseases, most notably HIV-associated nephropathy (HIVAN), occur typically in black individuals (1–3) and have become the third leading cause of end-stage renal disease (ESRD) among black individuals aged 20 to 64 in the United States (4). HIV-infected individuals who develop ESRD often present with AIDS and experience a rapid disease course. Currently, there is no evidence-based standard of therapy.

Although optimal therapeutic strategies for HIVAN have been debated over the past decade, the introduction of effective antiviral therapy has dramatically changed the AIDS epidemic in the United States. As a result, the traditional approach of a randomized, double-blind study to explore whether HIVAN is

best treated by antiretroviral strategies has been rendered unfeasible by the current accepted therapeutic practices for HIV infection. However, substantial data that allow us to analyze retrospectively the impact of introducing highly active antiretroviral therapy (HAART) into the risk population for HIVAN, almost exclusively by nonnephrologists, already exist.

Nephrologists have proposed several therapeutic strategies for the subgroup of HIV-infected patients with renal disease that reach them. Treatment options include steroids, angiotensin-converting enzyme (ACE) inhibitors, and antiretroviral therapy. Although steroids and ACE inhibitors have shown modest success (5,6), antiretroviral therapy, in particular HAART, has demonstrated a beneficial effect on HIV-related renal diseases, including HIVAN (7–14). This benefit suggests that HAART could potentially slow the progression of HIVAN and other HIV-related renal diseases. A recent article by Eggers and Kimmel (15) suggested that HAART, to a large extent, has stabilized the problem of HIVAN in this country, without recognizing the dynamics of the epidemic or the issue of access to therapy.

This analysis was undertaken to assess the effect of HAART on HIVAN and to project future prevalence using epidemiologic data with the intent of better evaluating the needs of both the renal and AIDS communities. Although data on patients with HIVAN are unavailable, epidemiologic data on patients

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with AIDS as well as AIDS nephropathy (HIV+ ESRD) in the United States are available from the Centers for Disease Control and Prevention (CDC) and the US Renal Data System (USRDS). To explore the potential association between HAART and the progression to ESRD, we built a mathematical model of the dynamics of HIV+ ESRD using the epidemiologic data on patients with AIDS and HIV+ ESRD. Data from the years 1999 through 2002 were used to assess the accuracy of the model, and the model then was used to project the prevalence of HIV+ ESRD over the next 20 years.

Materials and Methods

Epidemiologic Data

The prevalence of black individuals who are living with AIDS in the United States and the number of deaths among black individuals as a result of AIDS in the United States each year from 1991 to 2002 were obtained from the CDC (16–19). The annual incidence and mortality of HIV+ ESRD (N) from 1991 to 2002 was obtained from the USRDS (20). The annual mortality rate of HIV+ ESRD was calculated according to D_t/N_{t-1} , where D_t is the number of deaths caused by HIV+ ESRD in year t , $N_t = N_{t-1} + C_t - D_t$, and C_t is the number of new cases of HIV+ ESRD in year t . The initial prevalence of HIV+ ESRD (N_0) was determined from the total incidence and total mortality of HIV+ ESRD before 1991. Epidemiologic data collection was limited to the black population because the vast majority of patients with HIV+ ESRD in the United States are black (1,21,22). The most recent data then were used to assess the accuracy of the model.

Mathematical Model of HIV+ ESRD Epidemic

A mathematical model of the dynamics of the HIV+ ESRD epidemic was constructed using the epidemiologic data on patients with AIDS and HIV+ ESRD. The model then was used to project HIV+ ESRD prevalence through 2020. To capture the main characteristics of HIV+ ESRD dynamics, we assumed that all patients with HIV+ ESRD were previously included in the AIDS pool, that the changes observed in 1995 were due to the therapy that was introduced at the time (*i.e.*, HAART), and that all histologic lesions of patients with HIV+ ESRD are similarly affected by HAART.

The model is described by two equations representing populations with AIDS and HIV+ ESRD; the flow diagram is shown in Figure 1. The population with AIDS (A) increases linearly over time at rate g . A proportion (s) of those with AIDS progresses to HIV+ ESRD (N). Individuals with HIV+ ESRD die at mortality rate δ .

To account for the changes observed after 1995, most likely attributable to therapy such as HAART, model parameters g , s , and δ are scaled by treatment efficacy parameters m , h , and j . The effect of HAART on the AIDS growth rate is represented by parameter m such that when $m = 1$, HAART has no effect on g ; when $m < 1$, HAART decreases AIDS growth; and AIDS growth increases when $m > 1$. Thus $A(t) = A_0 + mgt$. The effect of therapy on the rate of progression to HIV+ ESRD is represented by the term $(1 - h)$, where $h = 0$ indicates no effect of therapy and $h = 1$ represents therapy that completely blocks the development of HIV+ ESRD. Likewise, the effect of therapy on HIV+ ESRD mortality is represented by the term $(1 - j)$, where $j = 0$ specifies no effect on mortality and $j = 1$ specifies therapy that completely prevents deaths caused by HIV+ ESRD. Thus, the population of HIV+ ESRD each year is calculated according to $N(t + 1) = N(t) + (1 - h)sA(t) - (1 - j)\delta N(t)$. Parameter m can assume any value, and parameters h and j can range between 0 and 1.

As an alternative to linear growth of the population with AIDS, we

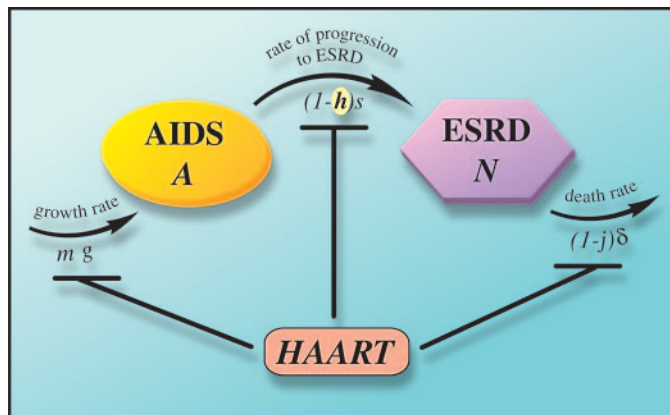


Figure 1. Flow diagram of HIV+ ESRD population dynamics (with linear AIDS growth). The AIDS population (A) increases linearly over time at rate g . A proportion (s) of patients with AIDS develop HIV+ ESRD, or AIDS nephropathy (N). Mortality of HIV+ ESRD is given by δ . Parameters m , h , and j represent the effect of HAART. Illustration by Josh Gramling, Gramling Medical Illustration.

also made projections assuming a “worst-case scenario” in which the population with AIDS increases exponentially, as may be the case. In this instance, we used the model equations $dA/dt = mgA(t)$ and $dN/dt = (1 - h)sA(t) - (1 - j)\delta N(t)$, with solutions $A(t) = A_0 e^{mgt}$ and $N(t) = (1 - h)sA_0 [e^{mgt} - e^{-(1 - j)\delta t}] / [mg + (1 - j)\delta] + N_0 e^{-(1 - j)\delta t}$.

Parameter Estimation

The AIDS growth rate g was determined by linear regression using the AIDS prevalence data from 1991 to 1995. The parameters s and δ were determined by fitting the model equations to pre-HAART prevalence data. The treatment efficacy parameters m , h , and j were optimized by least squares data fitting to post-HAART prevalence data.

Results

Data Trends before and after Introduction of HAART

Among the population of black individuals who are living with AIDS, the number of deaths dropped sharply after 1995, the year that HAART was introduced (Figure 2A). Similarly, the incidence of HIV+ ESRD initially fell and then stabilized somewhat after 1995 (Figure 2B). Furthermore, the mortality rate of HIV+ ESRD dropped drastically after 1995, from 69% in 1991 to 24% in 2002 (Figure 2C). This suggests that HAART may have reduced the number of AIDS deaths as well as the incidence and mortality of HIV+ ESRD.

Estimated Effect of HAART

The prevalence of black individuals who are living with AIDS and of black individuals who are living with HIV+ ESRD in the United States is shown in Figure 3 with the model values. The model was fit to the AIDS and HIV+ ESRD prevalence data from 1991 to 1995, before HAART was introduced. After 1995, we fit the model to the data to determine the most likely effect of HAART on the HIV+ ESRD epidemic. We investigated whether HAART showed no association, was associated with the increase in AIDS but had no association with HIV+ ESRD prevalence, or was associated with both the increase in AIDS

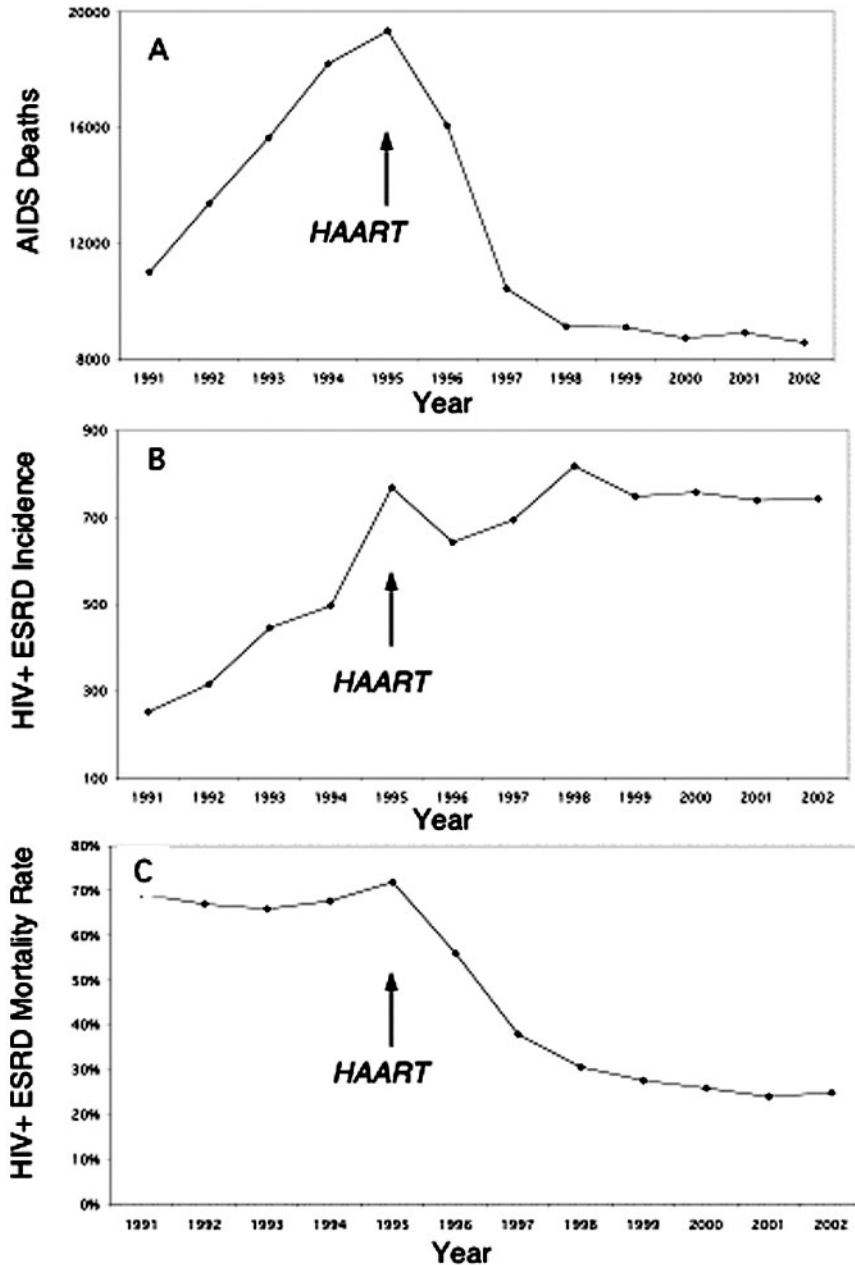


Figure 2. AIDS deaths, HIV+ ESRD incidence, and HIV+ ESRD mortality among black individuals in the United States. Data on AIDS deaths (A), HIV+ ESRD incidence (B), and HIV+ ESRD mortality (C) all show an inflection point in 1995, the year that highly active antiretroviral therapy (HAART) was introduced.

and HIV+ ESRD prevalence. The model fit best for both the AIDS and the HIV+ ESRD data using conditions such that HAART was associated with not only AIDS but also HIV+ ESRD dynamics (Figure 3). The HAART parameters that gave the best fit were $m = 0.90$, $j = 0.67$, and $h = 0.38$. These optimized parameter values gave the lowest root mean squared error for both AIDS and HIV+ ESRD (Table 1). Thus, the model showed that HAART most likely reduced the AIDS growth rate as well as both the progression to HIV+ ESRD and the mortality rate of HIV+ ESRD patients. Furthermore, this suggests that HAART slowed the development of HIV+ ESRD by 38%, or, alternatively, the efficacy of HAART in slowing progression to ESRD was 38%.

Future Projections on HIV+ ESRD Prevalence

We then used our model to project HIV+ ESRD prevalence through the year 2020, taking into account the potential effect of HAART as well as the growth of the at-risk population, black individuals with AIDS. Because of the increasing population of black individuals who are living with AIDS, an increase in HIV+ ESRD prevalence was predicted. Figure 4A shows the predicted prevalence of HIV+ ESRD using conditions such that HAART continues to affect the linear growth of AIDS and HIV+ ESRD mortality, and it blocks progression to HIV+ ESRD by 38% ($h = 0.38$) as before. A 65, 80, or even 95% block of progression to ESRD would result in a temporary decline in HIV+ ESRD prevalence followed by an eventual increase. Only

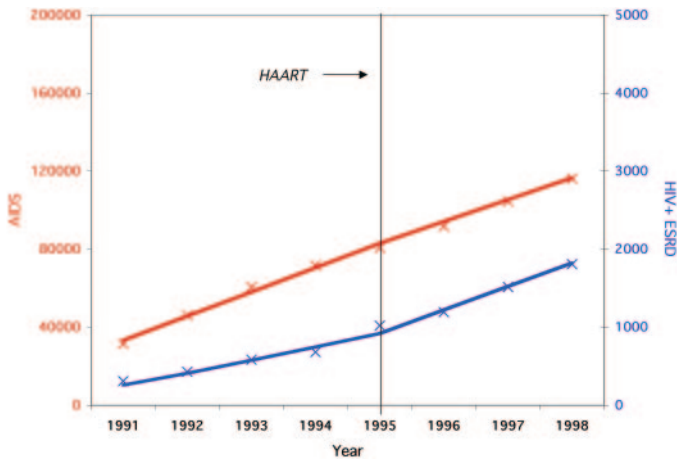


Figure 3. Prevalence data and model values. AIDS prevalence data (red ×) and HIV+ ESRD prevalence data (blue ×) with model values for AIDS prevalence (red lines) and HIV+ ESRD prevalence (blue lines) from 1991 to 1998. Initial values and parameters of model are $A_0 = 20807$, $N_0 = 166$, $g = 12428/\text{yr}$, $s = 0.0103/\text{yr}$, $\delta = 0.74/\text{yr}$, $m = 1$, $h = 0$, and $j = 0$. Model values after 1995 depict conditions representing an effect of HAART on the AIDS growth rate ($m = 0.90$), the progression to HIV+ ESRD ($h = 0.38$), and HIV+ ESRD mortality ($j = 0.67$). The vertical line indicates 1995, when HAART was introduced. The AIDS population was modeled representing a linear increase over time.

Table 1. Least squares data fitting between data and model values under different conditions of HAART^a

Condition	RMS Error	
	AIDS	HIV+ ESRD
No effect of HAART	2645	168
HAART affects AIDS	1678	178
HAART affects AIDS and HIV+ ESRD	1678	48

^aHAART, highly active antiretroviral therapy; RMS, root mean squared.

a 100% block would continually reduce HIV+ ESRD prevalence (Figure 4A). Hence, the model predicted an increase in HIV+ ESRD prevalence even with a continued effect of therapy such as HAART.

The mortality rate of HIV+ ESRD fell by 67% ($j = 0.67$) after 1995, from roughly 72 to 24%. If the mortality rate of HIV+ ESRD continued to decline in the future to 15% or even 10%, then consequently the number of patients who would be living with HIV+ ESRD would be predicted to increase further (Figure 4B).

We also made projections in the case that the population of black individuals who are living with AIDS is growing exponentially. This represents a worst-case scenario. The predicted prevalence of HIV+ ESRD given exponential growth in the at-risk population is shown in Figure 4C. A continual 38% block in progression to ESRD by HAART, as well 65, 80, or 95% blocks,

would result in an exponential increase in HIV+ ESRD. Likewise, the HIV+ ESRD prevalence is expected to grow exponentially if AIDS grows exponentially, if HAART affects AIDS and development of HIV+ ESRD, and if the mortality rate of HIV+ ESRD is 24% (current rate), 15%, or 10% (Figure 4D).

In Figure 4, we also show that our model projections for HIV+ ESRD prevalence (considering a 24% mortality rate for HIV+ ESRD and a 38% block to development of HIV+ ESRD as a result of HAART) are reasonably close to data available for 1999 through 2002. These data validate the model and furthermore suggest that if mortality has remained consistent at 24%, then the reduction in HIV+ ESRD development as a result of HAART (h) has become even greater than 38% during this period (Figure 4, A and C). This is a critical point because it emphasizes the need for constant attention to increasing efficacy just to maintain a constant incidence.

Our model predicted furthermore that HIV+ ESRD prevalence would plateau if the population at risk for HIV+ ESRD (black individuals with AIDS) stopped growing (*i.e.*, if new AIDS cases equaled AIDS deaths). Similarly, the model predicted that HIV+ ESRD prevalence would decrease continually if the AIDS population in black individuals decreased, which would occur if there were fewer new AIDS cases than AIDS deaths. Thus, an upward trend in HIV+ ESRD prevalence is predicted, as a 100% block by therapy or a negative rate of growth of the AIDS epidemic among black individuals would be needed to reverse it; a 0% rate of growth of the AIDS epidemic among black individuals would result in a plateau. HIV+ ESRD prevalence is shown for these conditions given linear AIDS growth (Figure 5) or exponential AIDS growth (Figure 6).

Increase in Effectiveness of Therapy Each Year after Introduction of HAART

In Figure 7, we show the effect of therapy on reducing the development of HIV+ ESRD (h) from 1996 to 2000. The h value has increased consistently since the introduction of HAART, from 5% in 1996 to 38% in 2000, and quantifies the reduction in new cases of HIV+ ESRD as compared with the pre-HAART years; h has been adjusted for the concomitant decrease in HIV+ ESRD mortality.

Discussion

This study examines the prevalence of HIV+ ESRD before and after the introduction of HAART. Using data from the USRDS and the CDC, our analysis suggests that HAART has slowed the development of HIV+ ESRD by 38%. Using this estimate of the effect of HAART on the progression to ESRD and given the current rise in patients who are living with AIDS, this study predicts that a similar rise in the prevalence of HIV+ ESRD will be observed. This result is predicted whether the growth in the AIDS population is linear (conservative predictions) or exponential (worst-case predictions). Our model reasonably predicted the data for 1999 through 2002 and suggests that the efficacy of HAART in slowing the development of HIV+ ESRD has become even greater than 38% during this period.

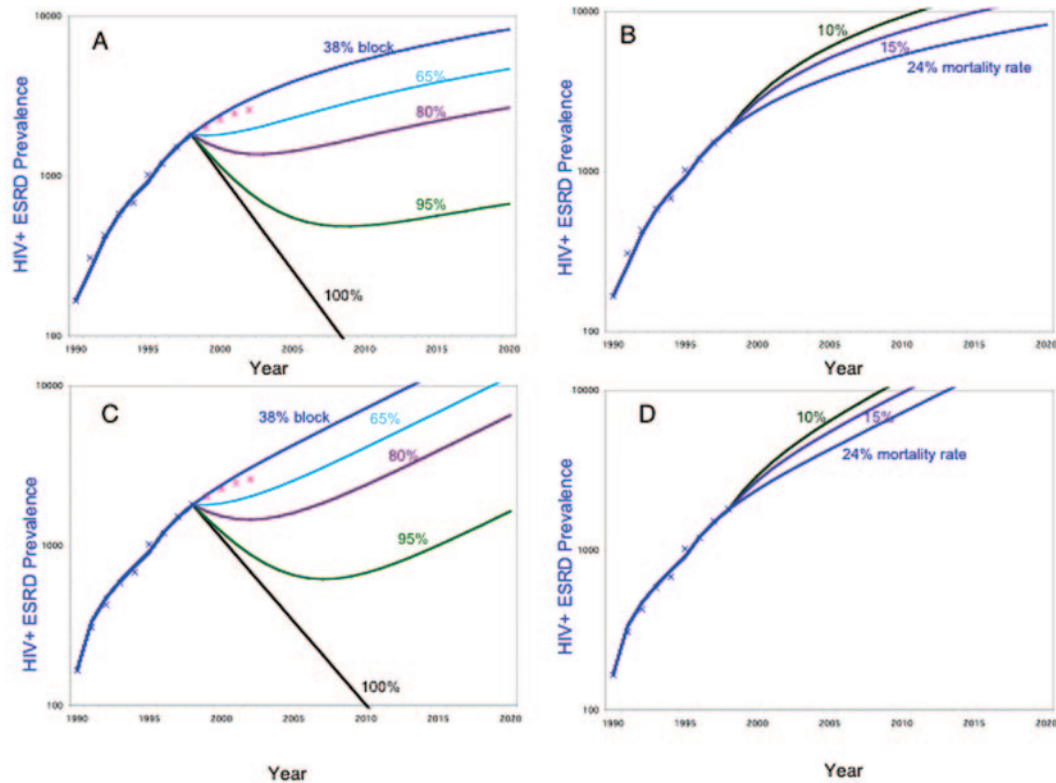


Figure 4. Model projections on HIV+ ESRD prevalence through 2020, with current data for 1999 and 2002. (A) Future HIV+ ESRD prevalence with a 38% block of progression to HIV+ ESRD (current estimate of model) or with increased effectiveness (65, 80, 95, and 100%), given linear AIDS growth. Model parameters are $g = 12428/\text{yr}$; $s = 0.0103/\text{yr}$; $\delta = 0.74/\text{yr}$; $m = 0.90$; $j = 0.67$; and $h = 0.38, 0.65, 0.80, 0.95, \text{ and } 1$. Blue \times indicates prevalence data, 1991 to 1998; pink * indicates prevalence data, 1999 to 2002; solid lines indicate model projections. (B) Future HIV+ ESRD prevalence with 24% HIV+ ESRD mortality (current estimate of model) or with reduced mortality (15 and 10%), given linear AIDS growth. Model parameters are as in A except that $h = 0.38$ and $j = 0.67, 0.80, \text{ and } 0.86$. (C) Future HIV+ ESRD prevalence with a 38% block of progression to HIV+ ESRD (current estimate of model) or with increased effectiveness (65, 80, 95, and 100%), given exponential AIDS growth. Model parameters are $g = 0.19/\text{yr}$; $s = 0.0103/\text{yr}$; $\delta = 0.74/\text{yr}$; $m = 0.53$; $j = 0.67$; and $h = 0.38, 0.65, 0.80, 0.95, \text{ and } 1$. (D) Future HIV+ ESRD prevalence with 24% HIV+ ESRD mortality (current estimate of model) or with reduced mortality (15 and 10%), given exponential AIDS growth. Model parameters are as in C except that $h = 0.38$ and $j = 0.67, 0.80, \text{ and } 0.86$.

These results are consistent with previous studies that suggested a beneficial effect of antiretroviral therapy on HIV-related renal diseases (7–14,23). As emerging data in both humans and a murine transgenic model of HIVAN suggest that HIVAN is a direct result of viral gene expression (24–30), it follows that antiretroviral therapy, through a decrease in viral replication in both blood and kidney, can slow HIVAN progression. Although antiretroviral therapy may not have a direct effect on viral gene expression in already-infected renal epithelial cells, it may affect both the generation of newly infected epithelial cells and infected interstitial inflammatory cells. Because data report that black individuals show slightly less HAART usage (31) and current therapies are confounded by drug efficacy as well as compliance issues, these results suggest that the burden of renal disease in the HIV-infected population will continue to be a significant concern. Antiretroviral therapy such as HAART, however, is likely to be effective for preventing progression to ESRD and for reducing mortality in patients with HIV+ ESRD. This leads to the conclusion that strong evidence for HIVAN on kidney biopsy merits HAART, an

approach that is currently not the standard practice, especially in the absence of other criteria indicating therapy.

We used USRDS incidence data on HIV+ ESRD to approximate the patients who have or are likely to develop HIVAN, on the basis of the observations that a large percentage of HIV-infected patients who have renal disease and undergo renal biopsy have HIVAN (22,32). Because the vast majority of patients with HIV+ ESRD are black, the epidemic of HIV+ ESRD is following the HIV epidemic in the black population, and for that reason, we restricted our search for data to this population. In addition, the model was built with patients with HIV+ ESRD arising from the AIDS pool because most patients with HIV+ ESRD have an AIDS-defining condition, such as an opportunistic infection or a CD4 count <200 cells/ml (33,34). Because HIV+ ESRD may also develop in HIV-infected individuals without AIDS (35) and not all HIV-related renal diseases may be as responsive to HAART as HIVAN (22), the future projections of HIV+ ESRD prevalence presented here should be regarded as *minimal* estimates. Furthermore, available data do not allow us to assess the impact of corticosteroids

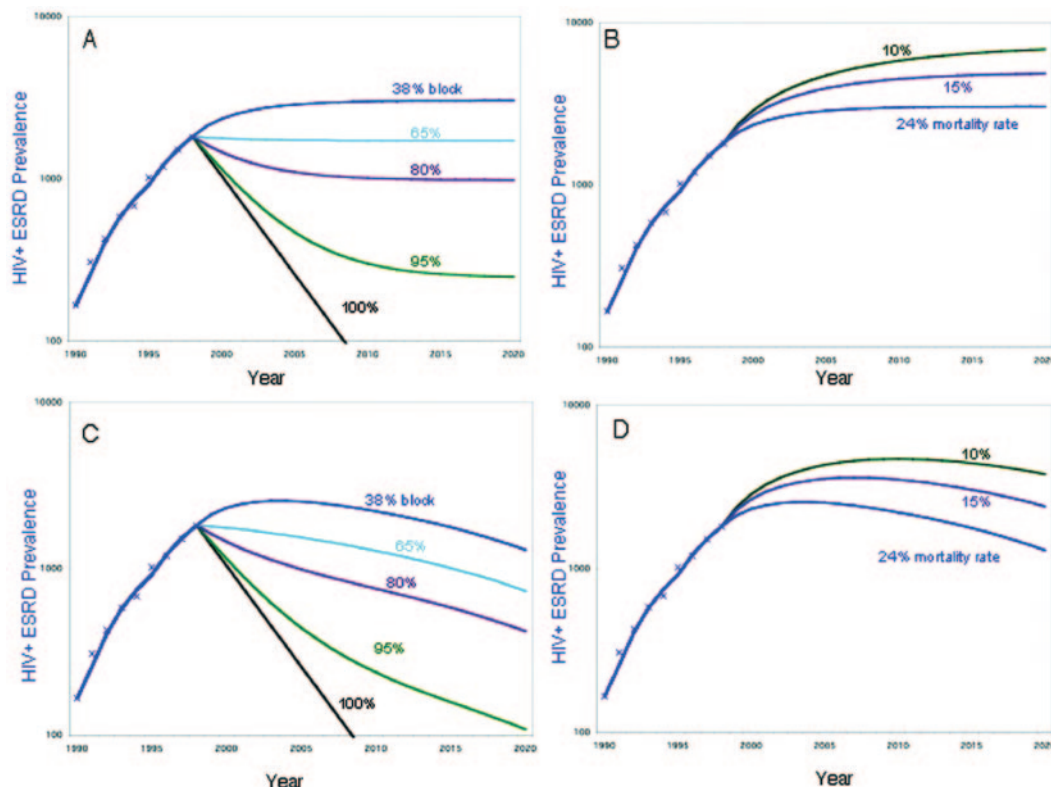


Figure 5. HIV+ ESRD prevalence does not increase as long as AIDS prevalence remains constant or decreases (linear model). (A) Future HIV+ ESRD prevalence with a 0% rate of growth of the AIDS epidemic among black individuals. Model parameters are as in Figure 4A except that $m = 0$. (B) Future HIV+ ESRD prevalence with a 0% rate of growth of the AIDS epidemic among black individuals. Model parameters are as in Figure 4B except that $m = 0$. (C) Future HIV+ ESRD prevalence with a negative rate of growth of the AIDS epidemic among black individuals. Model parameters are as in Figure 4A except that $m = -0.3$. (D) Future HIV+ ESRD prevalence with a negative rate of growth of the AIDS epidemic among black individuals. Model parameters are as in Figure 4B except that $m = -0.3$.

or ACE inhibitors on either patient or renal survival. Reports suggest a beneficial effect on the progression of renal disease among patients with HIVAN with these medications (5,6,8,36), although they have not been tested in prospective, randomized trials. If the benefit of these therapies to renal survival is confirmed, then an increased impact on the incidence of patients who reach ESRD may be observed with their more widespread use. The data used in the current analysis that demonstrate benefit of HAART, however, come largely from nonnephrologists, who would be less likely to use these other forms of therapy.

These results led us to conclusions that agree with some but not all of those reached in a recent report (15). We support efforts to implement more prevalent use of HAART and better preventive measures. In this study, we have shown the trends in HIV+ ESRD that are expected with increased HAART usage. More important, however, these data demonstrate that the growth of the population with HIV infection and ESRD will be most affected over the next few decades by measures that are focused on reducing the growth of the population of black individuals who are living with AIDS. Our results also indicate, however, that the

HIV+ ESRD epidemic should not be considered stable. Stating that the epidemic is under control is at best misleading. Unless HAART efficacy improves dramatically, we are fooling ourselves into believing that we are not in a “honeymoon” period that will end as the HIV-seropositive population at risk for developing ESRD grows. Furthermore, the beneficial effect of HAART may not be sustained long term if therapy is discontinued or if the patient develops HIV-1 strains that are resistant to antiretroviral treatment.

Our success in managing the HIVAN epidemic is shown best in the analysis of the efficacy of therapy. The effectiveness of therapy (h value) presented in this work indicates the reduction in the development of HIV+ ESRD after the introduction of HAART as compared with before its introduction, in 1995. The graph of h over time (Figure 7), which shows that h has continued to increase each year, gives us a sense of how we have done as a society at increasing access to care or improving care by therapy. The observed improvement could be from new drugs or from improved access to drugs in the at-risk population or particularly from increased awareness of renal disease in the general AIDS-treating community and increased penetrance of HAART to black pa-

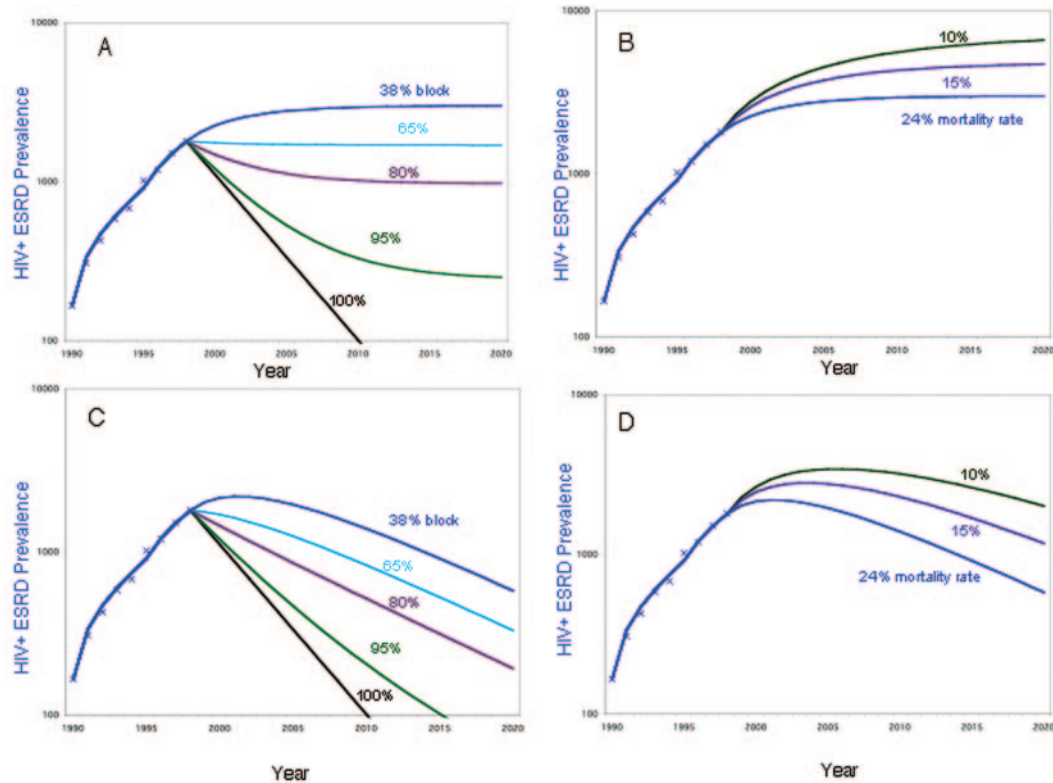


Figure 6. HIV+ ESRD prevalence does not increase as long as AIDS prevalence remains constant or decreases (exponential model). (A) Future HIV+ ESRD prevalence with a 0% rate of growth of the AIDS epidemic among black individuals. Model parameters are as in Figure 4C except that $m = 0$. (B) Future HIV+ ESRD prevalence with a 0% rate of growth of the AIDS epidemic among black individuals. Model parameters are as in Figure 4D except that $m = 0$. (C) Future HIV+ ESRD prevalence with a negative rate of growth of the AIDS epidemic among black individuals. Model parameters are as in Figure 4C except that $m = -0.5$. (D) Future HIV+ ESRD prevalence with a negative rate of growth of the AIDS epidemic among black individuals. Model parameters are as in Figure 4D except that $m = -0.5$.

tients in general. We must aim to achieve 100% reduction in development of ESRD with HAART and find a way to reduce the growth of the population with AIDS, or these patients will be a concern for the ESRD program over the long term. Our focus must remain on h rather than taking solace in a steady incidence, as was suggested (15). Furthermore, while improving h , we must also be aware of the potential for tremendous growth in the number of patients with chronic kidney disease. Because data on this population will not be as easily available as data on patients with ESRD from the USRDS, this may represent a new epidemic that will not be as easily recognized. Arguably, given the increased risk for hospitalization and mortality in this population (37–39), clinical and research efforts need to focus on the mechanisms behind these increased risks as well as treatment strategies to minimize them.

This analysis demonstrates a beneficial effect of HAART on the rate at which HIV-infected patients with AIDS progress to ESRD; yet the absolute number of patients who reach ESRD is projected to increase in the future. Although the increasing utilization of HAART has resulted in a reduced mortality rate, the prevalence of patients with AIDS and subsequently the

population at risk for ESRD will continue to increase. These results suggest that HIVAN and other causes of renal disease among HIV-infected patients will pose a substantial public health and resource problem in the near future. This projected epidemic indicates that we should enhance our current efforts to understand the pathobiology of HIV-related renal diseases and to develop more effective strategies for their prevention and treatment.

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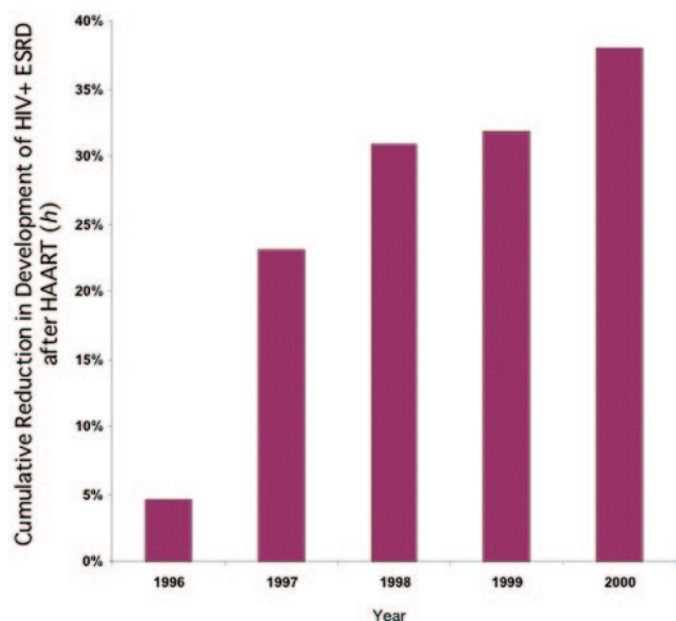


Figure 7. Increase in h each year since introduction of HAART. Reduction in development of HIV+ ESRD (h), 1996 to 2000. The value h has been adjusted for the concomitant decrease in HIV+ ESRD mortality.

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