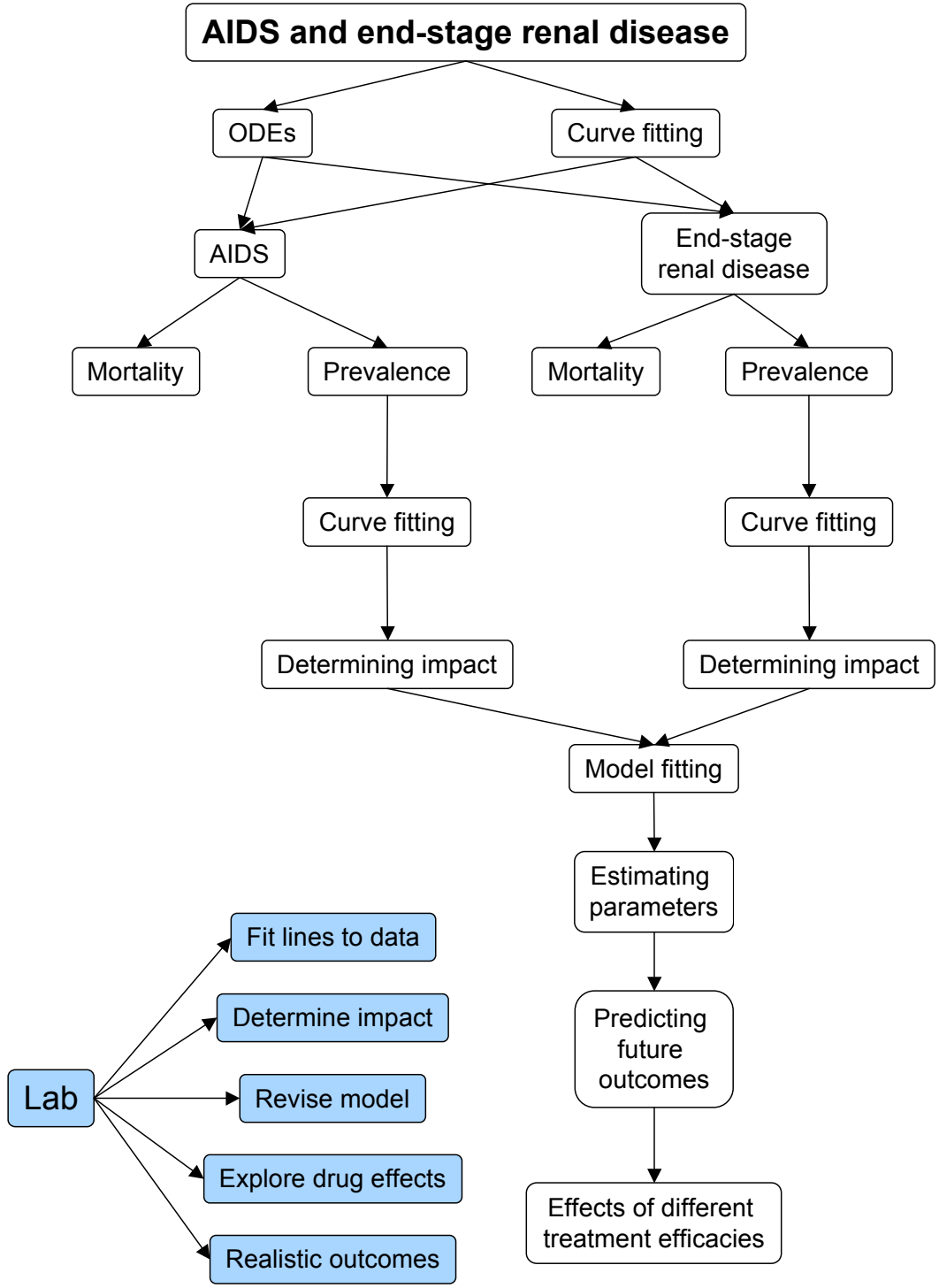
Case study: AIDS and end-stage renal disease

Robert Smith?

Department of Mathematics and Faculty of Medicine
The University of Ottawa


AIDS and end-stage renal disease
ODEs
Curve fitting
AIDS
End-stage renal disease
Mortality
Prevalence
Mortality
Prevalence
Curve fitting
Curve fitting
Determining impact
Determining impact
Model fitting
Estimating parameters
Predicting future outcomes
Effects of different treatment efficacies
Lab
Fit lines to data
Determine impact
Revise model
Explore drug effects
Realistic outcomes

End-stage renal disease

- Many patients with AIDS develop end-stage renal disease
- One of the opportunistic infections that kills you
- Basically, kidney failure
- In the US, this is particularly prevalent in African Americans
- Thus, we'll focus on this subset of the population.

Antiretroviral drugs

- HAART has drastically changed the face of HIV
- Reduced the number of AIDS deaths
- Made HIV a disease it's possible to live with
- Not clear what effect HAART has had on the prevalence of AIDS or end-stage renal disease...
- ...so we'll investigate it ourselves.

Our questions

1. Has HAART had an impact on the prevalence of AIDS?
2. Has HAART had an impact on the prevalence of end-stage renal disease?
3. If aggressive treatment is initiated now, with different effects, what will the long-term outcome be?

Our approach

We'll need to

- formulate a model
- fit parameters to data
- draw conclusions
- predict the future

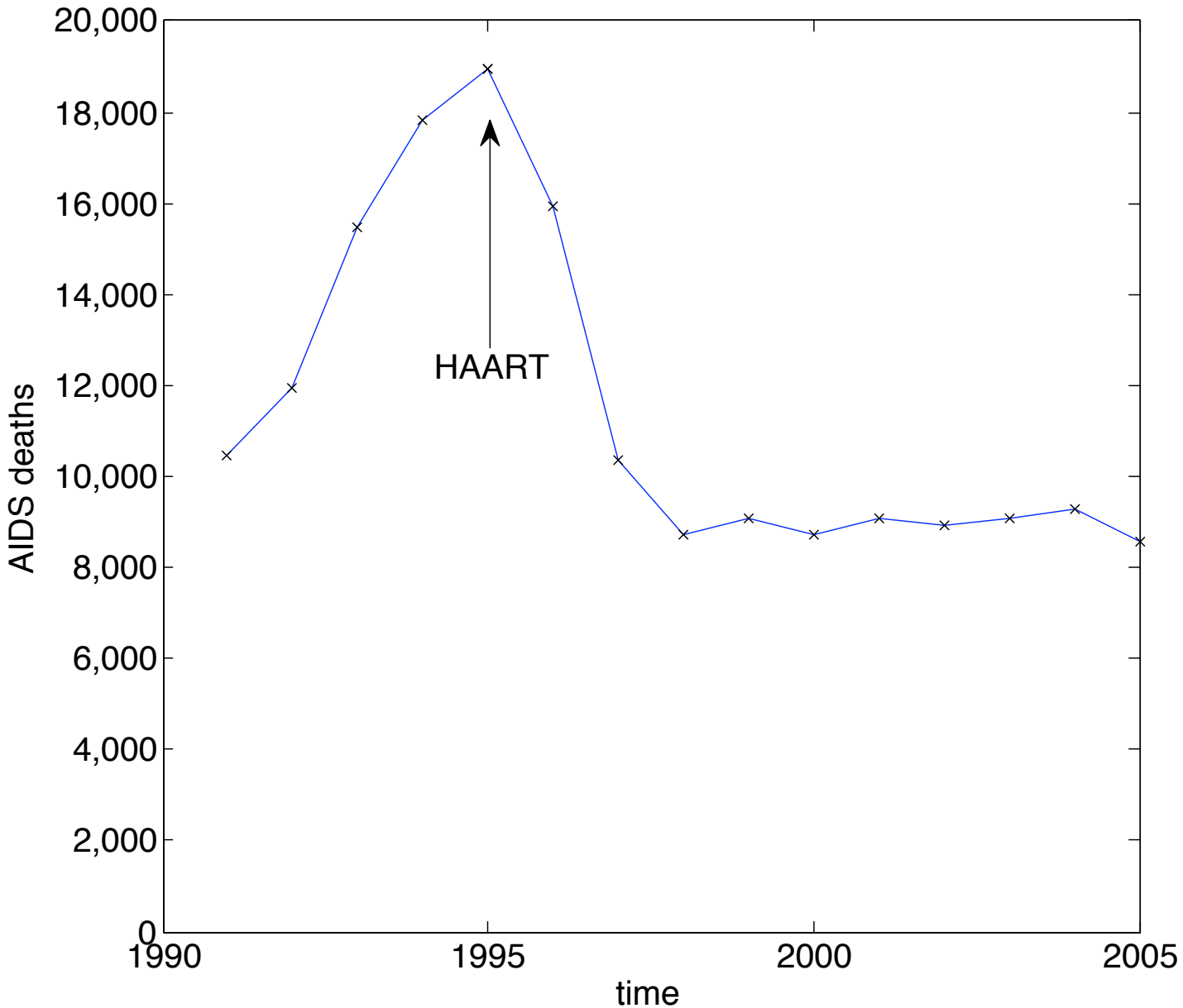
This combines various strands of modelling while incorporating real-world data.

Impact of HAART on AIDS mortality?

- Mortality data from the CDC:
- These are the number of deaths due to AIDS for African Americans in the US
- To see it a bit more clearly, let's plot it.

1991	10475
1992	11946
1993	15460
1994	17844
1995	18971
1996	15909
1997	10333
1998	8744
1999	9097
2000	8723
2001	9085
2002	8927
2003	9077
2004	9302
2005	8562

HAART has clearly had an effect

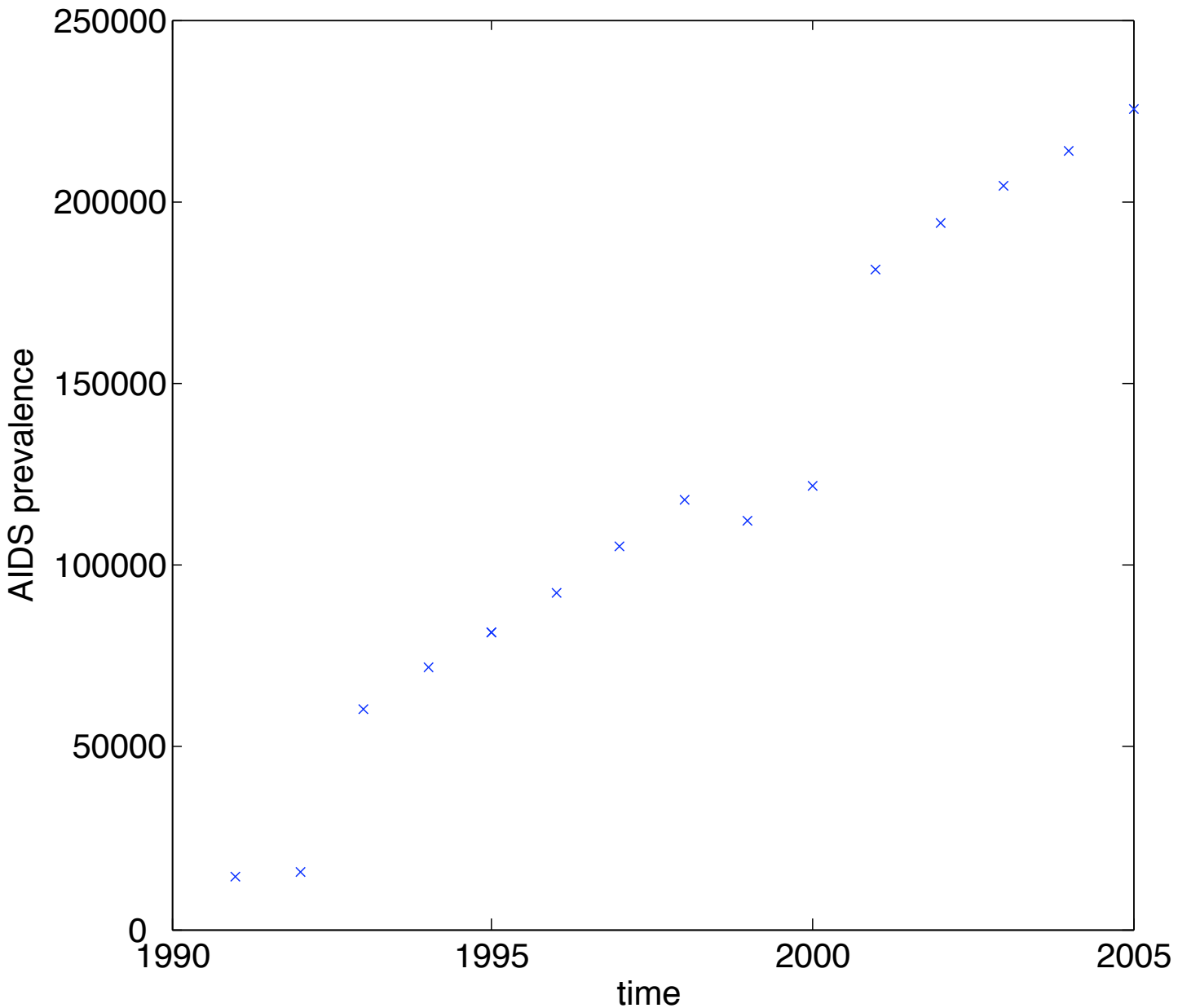


What about prevalence?

- We expect prevalence to increase
  - not as many people are dying
  - other people are progressing from HIV to AIDS
- But perhaps not as sharply as it did before HAART
- Prevalence data from the CDC:
- Again, we'll plot this.

1991	14561
1992	15897
1993	60649
1994	71847
1995	81317
1996	92319
1997	105464
1998	117890
1999	112483
2000	121903
2001	181475
2002	193814
2003	204466
2004	214017
2005	225270

Prevalence of AIDS



Formulating a null hypothesis

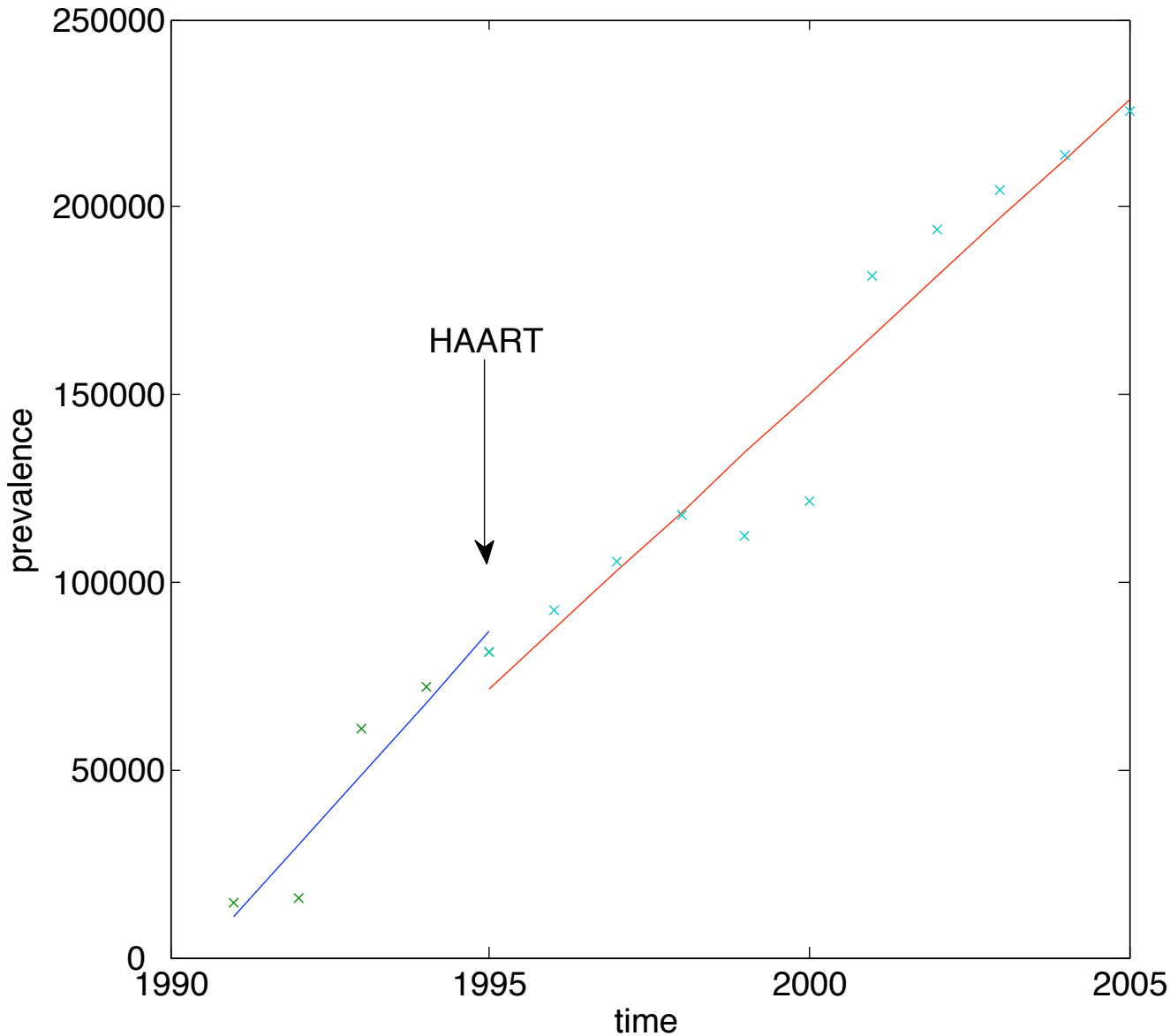
- Q. How can we tell if HAART has made a difference?
- A. Construct a null hypthesis and test against it:
- N_0: HAART has had no significant impact on the prevalence of AIDS

  (note that we are not assuming the prevalence goes up or down).

Testing the null hypothesis

- Q. How can we test the impact?
- A. Fit curves to pre- and post-HAART data
- Compare with entire data set
- The data is approximately linear, so this will make life easier.

Prevalence pre- and post-HAART

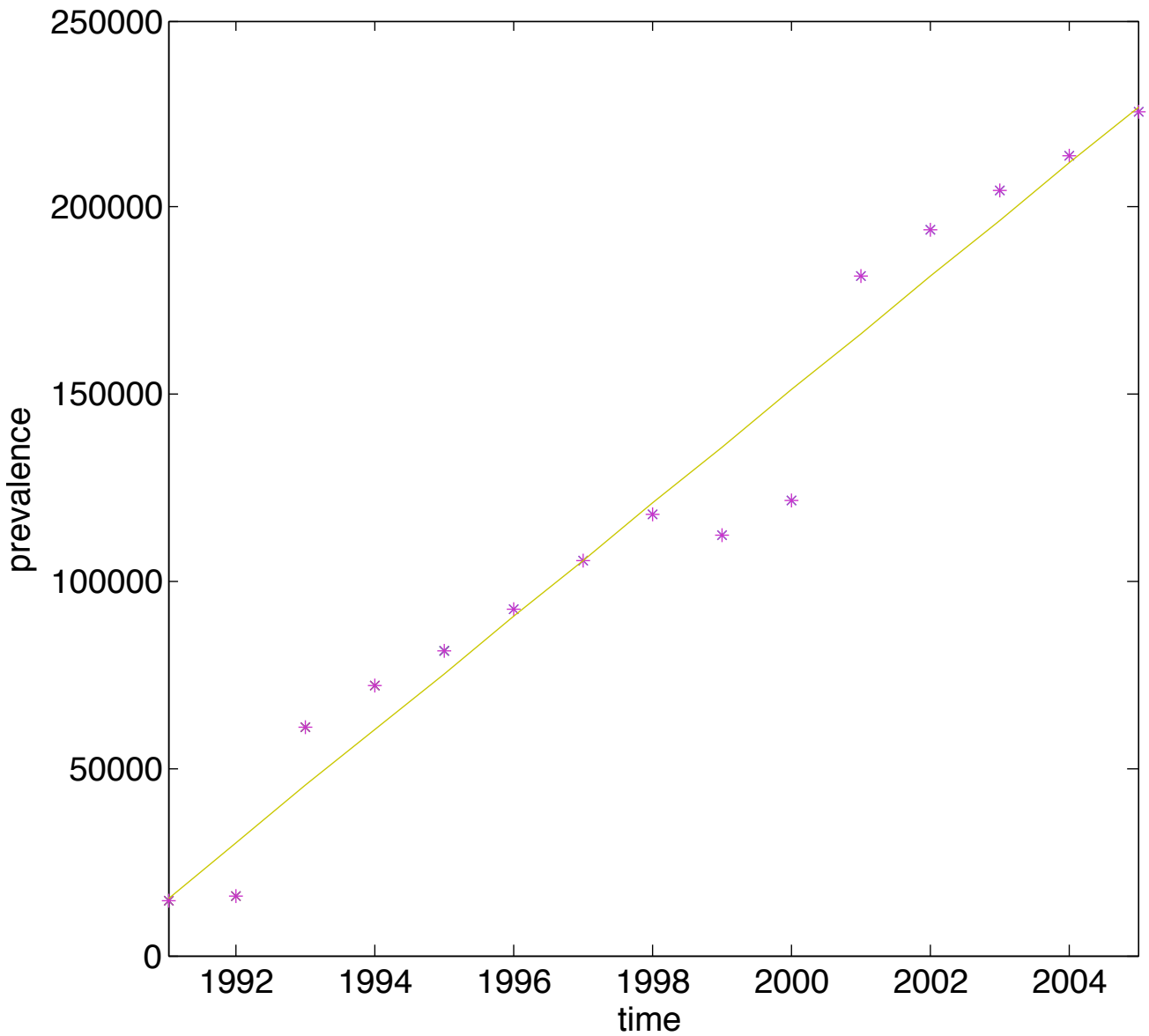


Initial thoughts

- The slope of the first line is steeper than the second
- Both lines are good fits: $r = 0.949$ and $r = 0.967$, respectively
- So it looks like HAART may have reduced the rate of increase of the prevalence

  (as we'd hope)
- However, this is only half the story
- We still need to compare to the fit overall.

Prevalence overall



Impact of HAART on AIDS prevalence

- Is this a better or worse fit?
- The eye can't tell, so we need to rely on the regressional coefficient
- In this case $r = 0.981$
- ...higher than either *r* from before!
- Thus, we can't reject the null hypothesis
- It follows that HAART has had no significant impact on prevalence of AIDS among African Americans in the US

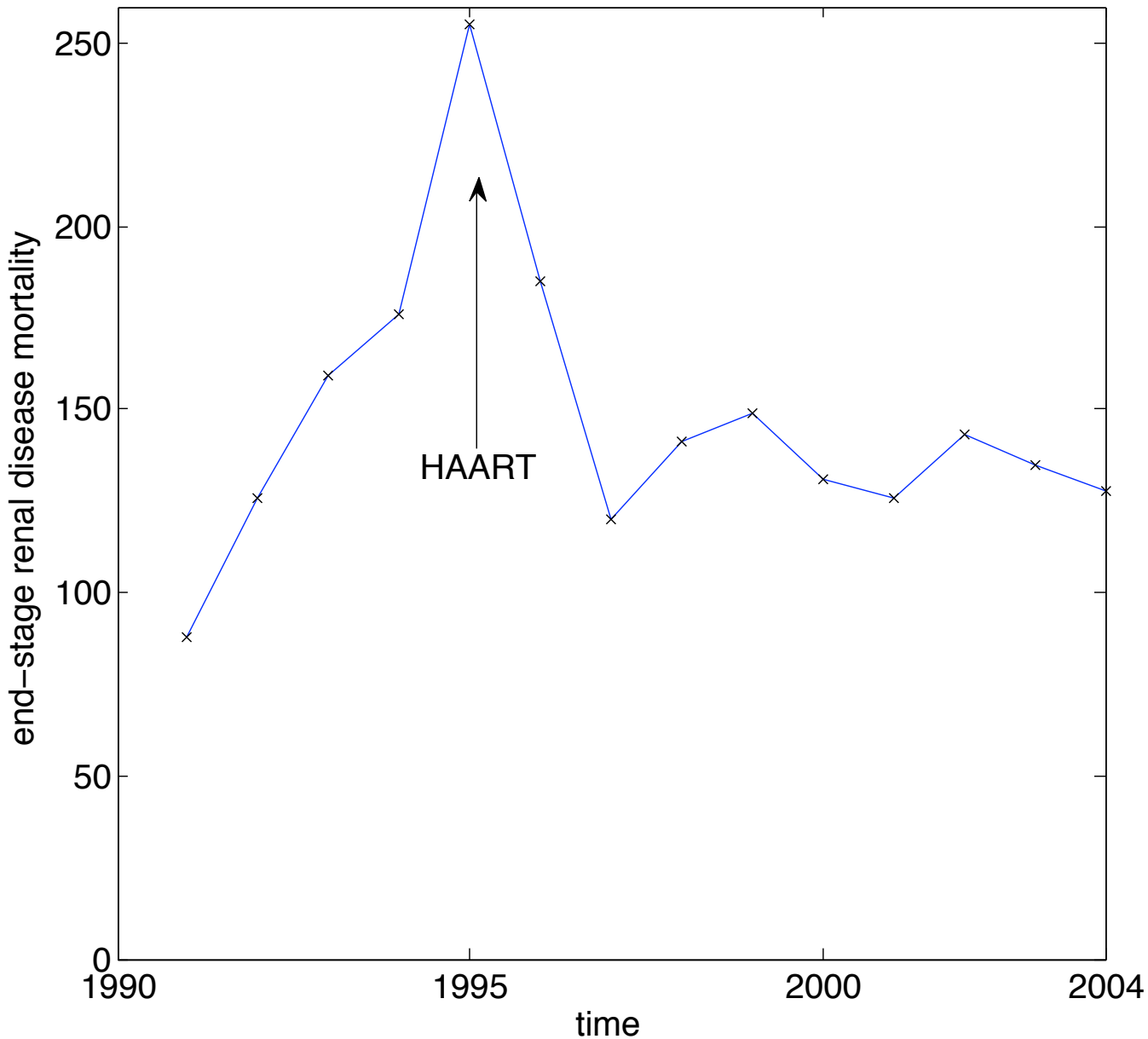
  (It has drastically reduced mortality, though).

Impact on mortality?

- Mortality data from the US Renal Data System:
- These are the number of deaths due to end-stage renal disease for African Americans in the US
- Again, let's plot it.

1991	88
1992	126
1993	159
1994	176
1995	255
1996	185
1997	120
1998	141
1999	149
2000	131
2001	126
2002	143
2003	135
2004	128

HAART has clearly had an effect

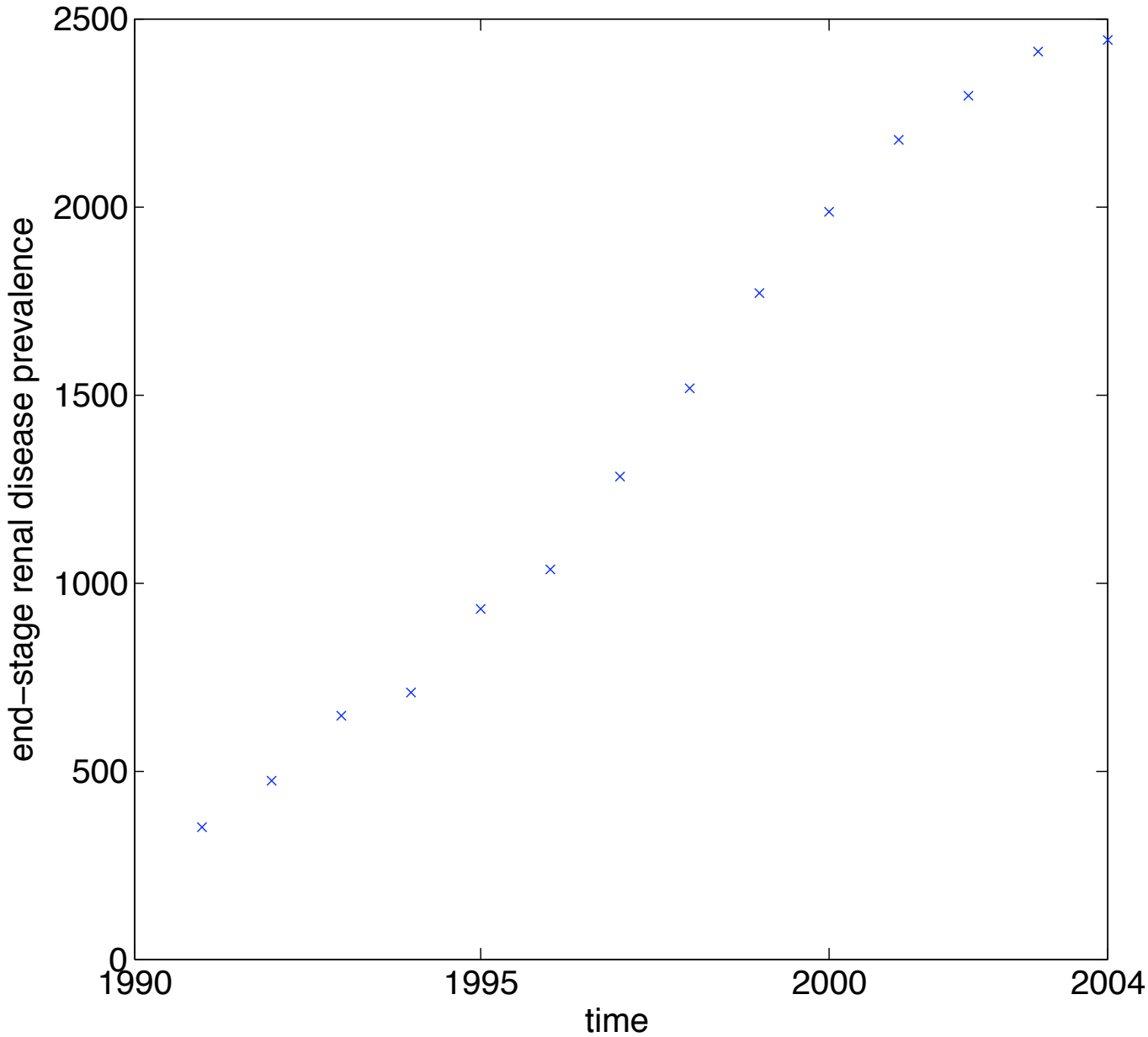


What about prevalence?

- We again expect prevalence to increase
- Prevalence data from the US Renal Data System:
- Again, we'll plot this.

1991	14561
1992	15897
1993	60649
1994	71847
1995	81317
1996	92319
1997	105464
1998	117890
1999	112483
2000	121903
2001	181475
2002	193814
2003	204466
2004	214017
2005	225270

Prevalence of AIDS

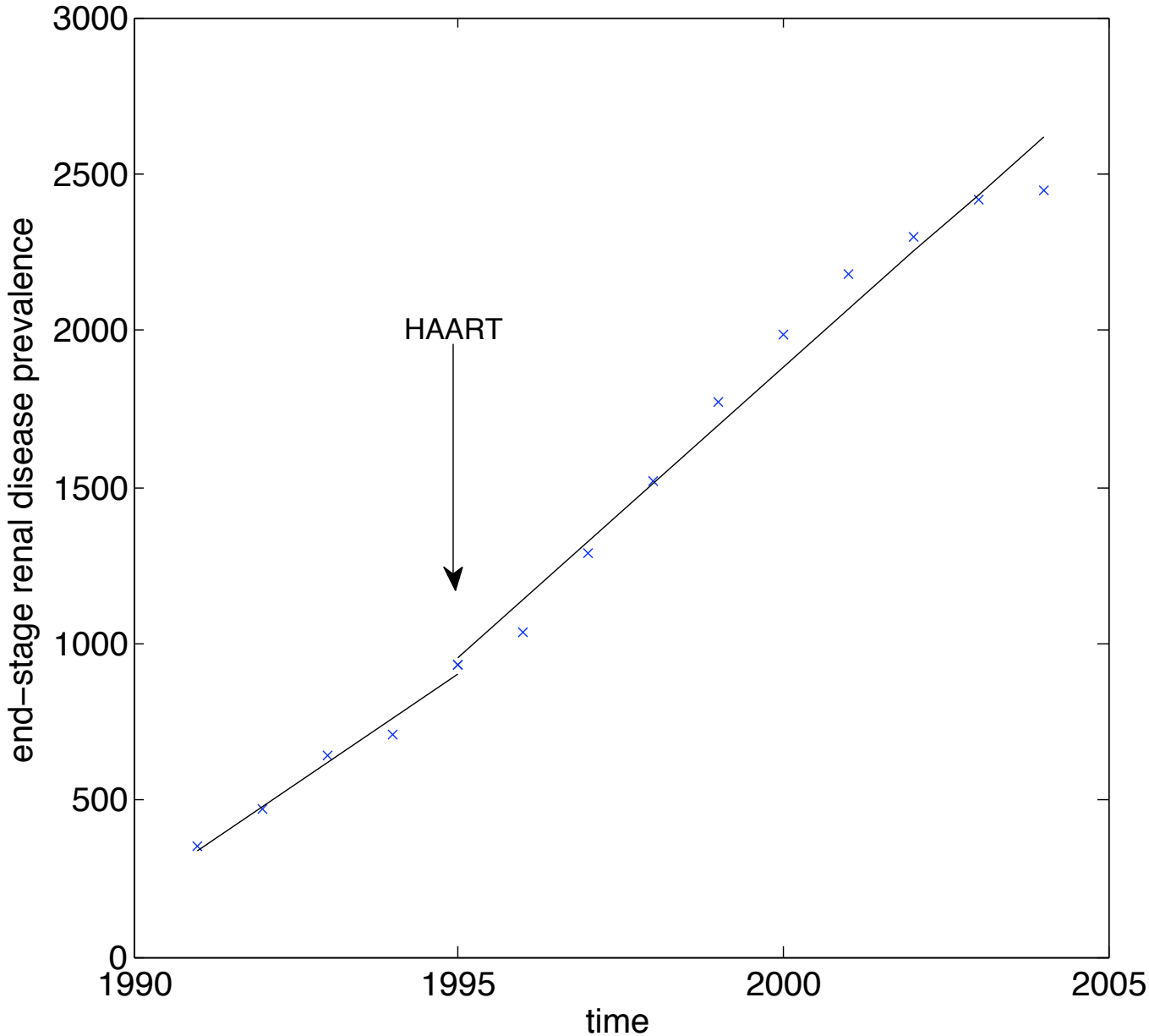


Formulating another null hypothesis

- N_0: HAART has had no significant impact on the prevalence of end-stage renal disease
- Again, we'll fit linear curves to pre- and post-HAART, as well as the entire data set

  (it helps that the data is approximately linear, of course).

Prevalence pre- and post-HAART

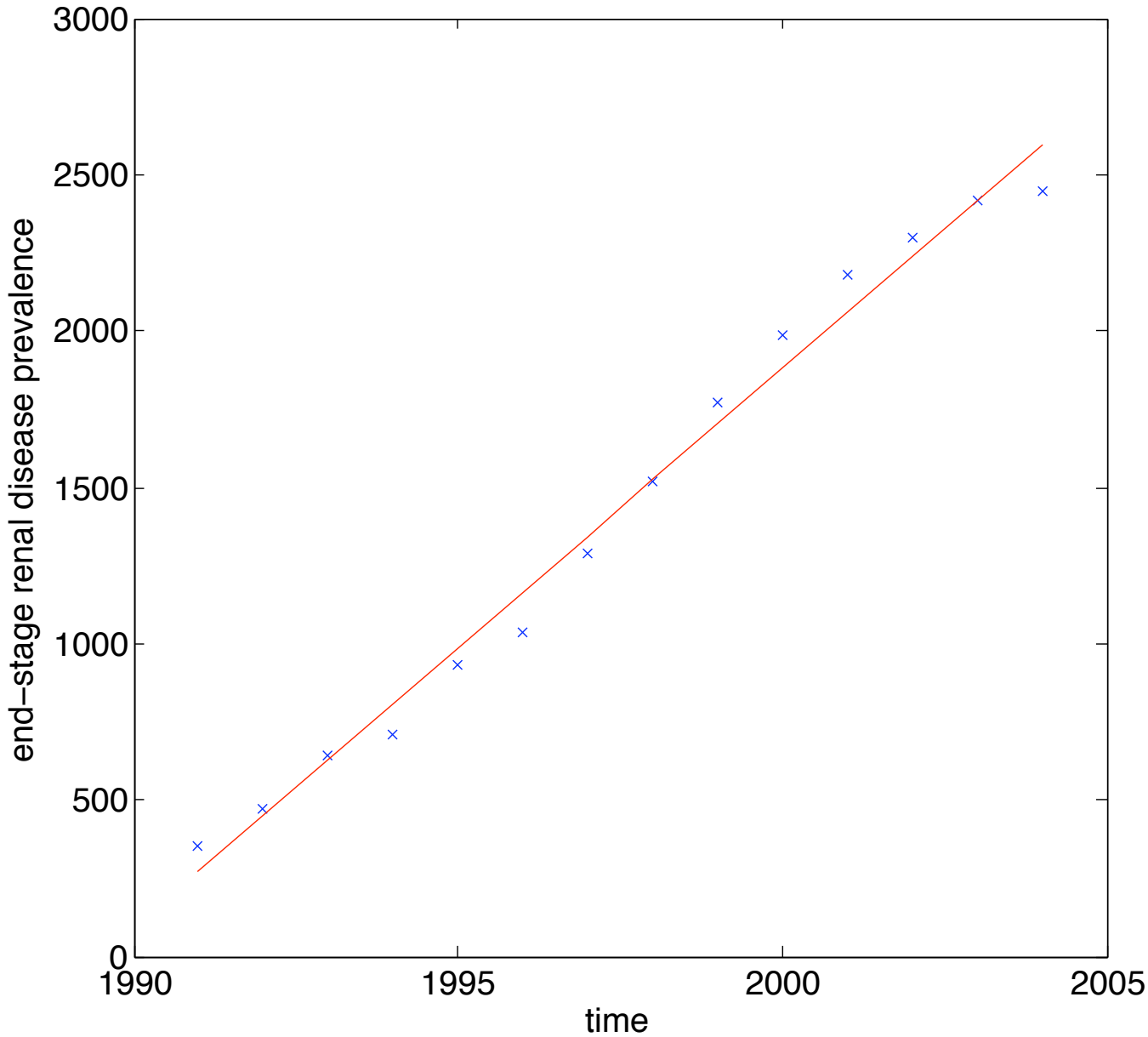


Initial thoughts

- The slope of the second line is steeper than the first
- Both lines are even better fits: $r = 0.98887$ and $r = 0.98683$, respectively
- So it looks like HAART may have increased the prevalence of end-stage renal disease

  (not out of the question, as many more people are alive because of HAART).

Prevalence overall



Impact on prevalence

- Once again, the eye can't tell, so we need to rely on the regressional coefficient
- In this case $r = 0.99352$
- ...higher than either r from before!
- Thus, we can't reject the null hypothesis
- It follows that HAART has had no significant impact on prevalence of either AIDS or end-stage renal disease among African Americans in the US

  (It has drastically reduced mortality, though).

Model fitting

- What we've done in each case is fit models to data
- True, they were simple, linear models, but we still made choices
- We can now use these linear fits to estimate parameters and construct a more complex differential equation model.

How to construct such a model?

- We have two variables of interest: AIDS prevalence and end-stage renal disease prevalence
- Since end-stage renal disease doesn't cause AIDS, we can consider AIDS in isolation
- This makes our first equation much easier.

The equation for AIDS prevalence

- We now have faith that it's a linear fit, so let's construct a linear differential equation
- Prevalence is increasing, so the derivative will be positive
- Thus, we could write

$$\frac{dA}{dt} = g$$

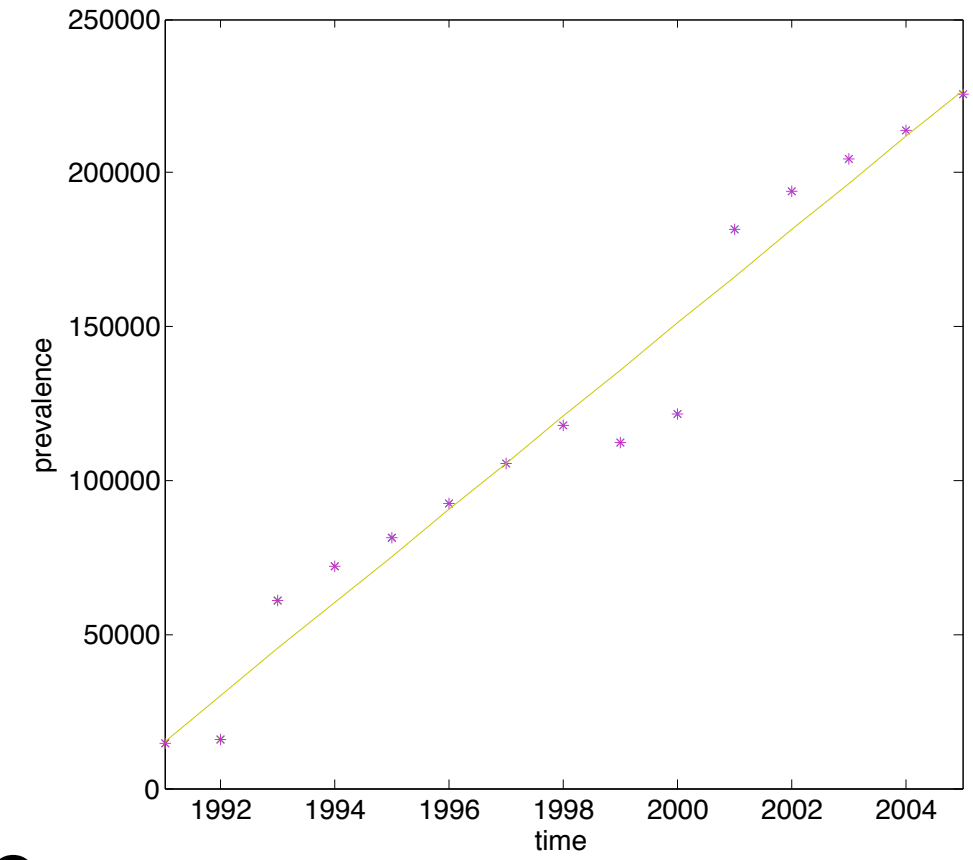
- This is simple and we could solve it if we wanted to, but we won't
- We need estimates for *g* and *A(0)*.

Estimating *g* and *A(0)*

- Using our linear fit, we can estimate
- $g = 15133$

  (the slope)
- $A(0) = 14959$

  (the intercept)
- Technical note: Time really starts at 1991, so we need to transpose the x-axis by 1991.



Equation for end-stage renal disease

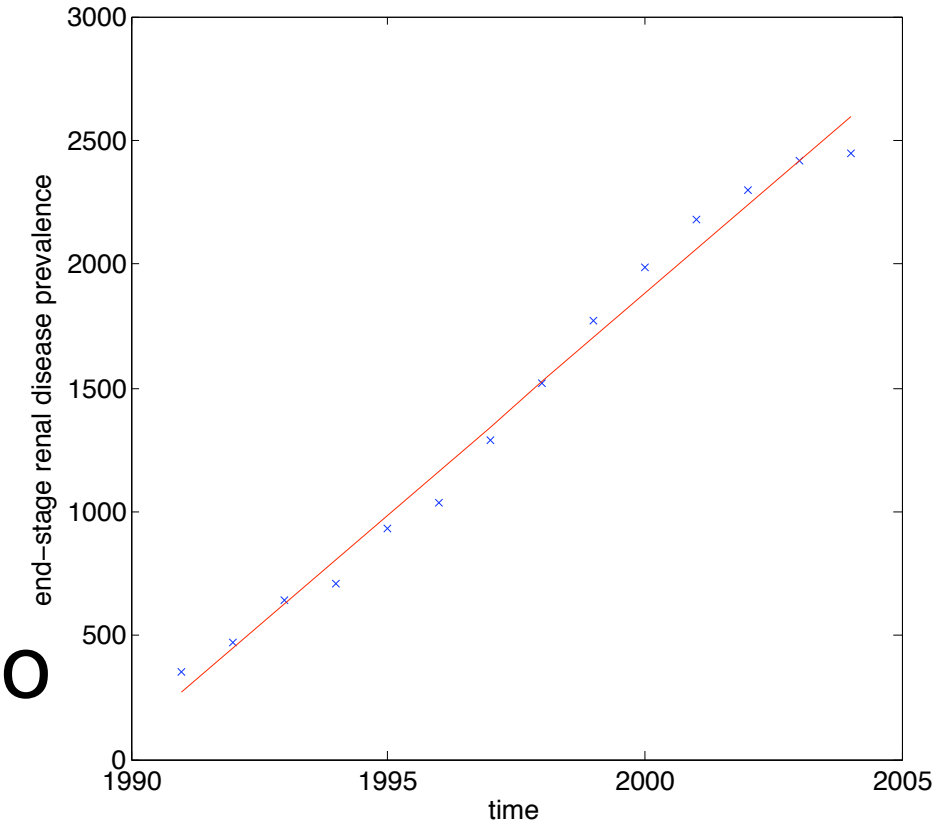
- This is a bit trickier
- A proportion *s* of people with AIDS develop end-stage renal disease
- People with end-stage renal disease die at rate δ, proportional to the prevalence of end-stage renal disease

$$\frac{dN}{dt} = sA - \delta N$$

- Solving this is harder (and depends on *A(t)*)
- We need estimates for s, δ and N(0).

Estimating *N(0)*

- Using our linear fit, we can estimate
- *N(0)* = 268 (intercept)
- slope = 179
- Slope is the derivative, so we can use this to estimate s and δ.



Estimating s and δ

- Picking two points that are close to the linear fit, we have

$$\begin{aligned}
\frac{dN}{dt} &= sA - \delta N &= 179 \\
s(20564) - \delta(1287) &= & 179 \\
s(117890) - \delta(1521) &= & 179
\end{aligned}$$

$$\begin{aligned}
\begin{bmatrix} s \\ \delta \end{bmatrix} &= \begin{bmatrix} 20564 & -1287 \\ 117890 & -1521 \end{bmatrix}^{-1} \begin{bmatrix} 179 \\ 179 \end{bmatrix} \\
&= \begin{bmatrix} 0.0048 \\ 0.2563 \end{bmatrix}.
\end{aligned}$$

Summarising parameter estimates

We thus have

- $A(0)$ = 14959
- $N(0)$ = 268
- g = 15133
- s = 0.0048
- δ = 0.2563

Note that we didn't solve either equation, even though one was easy and the other was doable.

Predicting future outcome

- Now that we have our model, we can use it to predict the future
- Unfortunately, by definition, we don't have actual evidence about the future

  (and if we wait for the evidence to arrive, it won't be the future any more)
- To compensate for this, we'll make a range of predictions.

Initiating aggressive HAART now

- Currently, treatment hasn't done much to slow the epidemic of end-stage renal disease
- However, treatment also hasn't been applied as aggressively as it could
- Especially in disadvantaged groups like African Americans
- Can HAART eliminated end-stage renal disease?

Effects of treatment

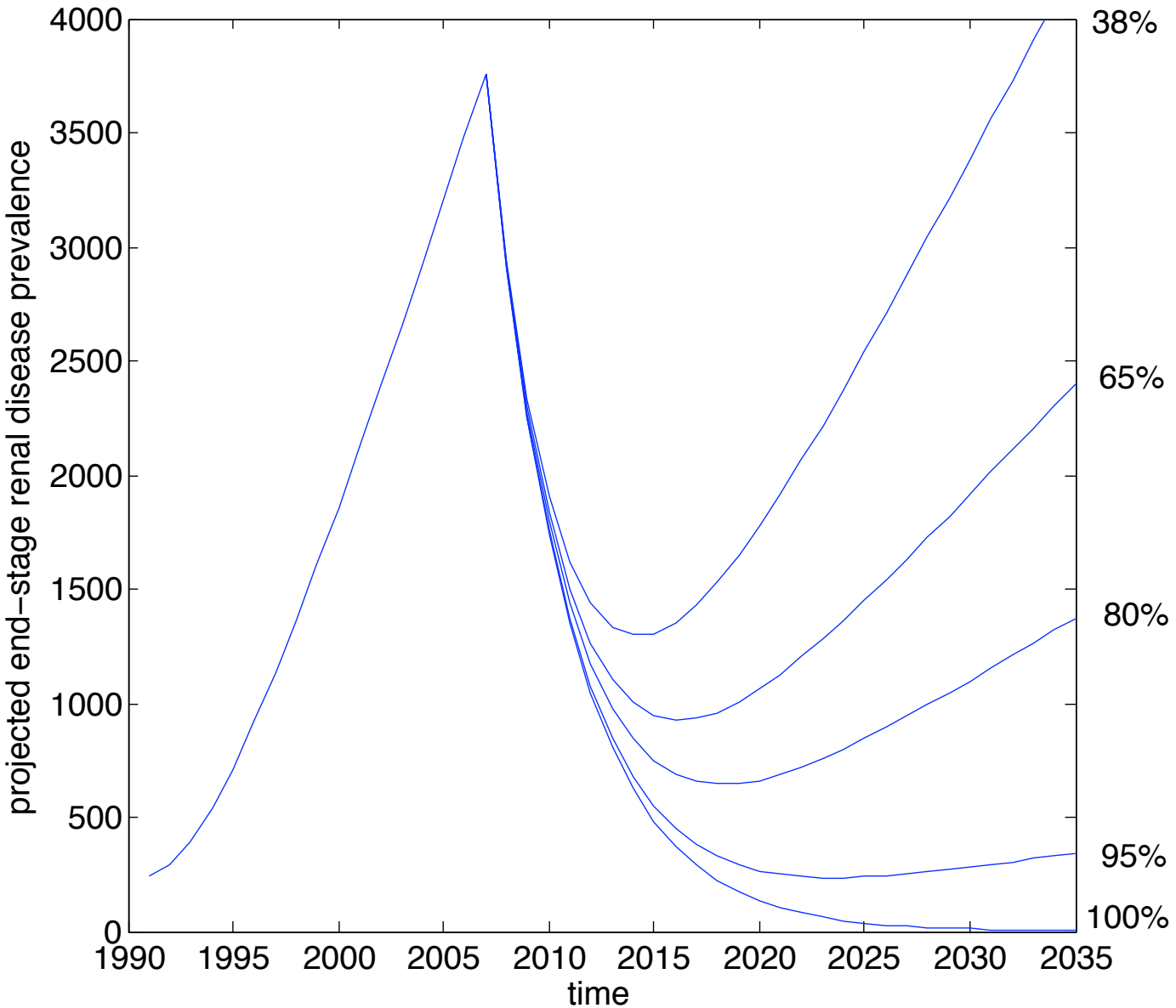
- We can represent treatment by a factor (1-*h*)
- If *h*=0, then treatment has no effect on progression to end-stage renal disease
- If *h*=1, treatment completely suppresses progression to end-stage renal disease
- Our equation thus becomes

$$\frac{dN}{dt} = s(1-h)A - \delta N$$

A range of blocking effects

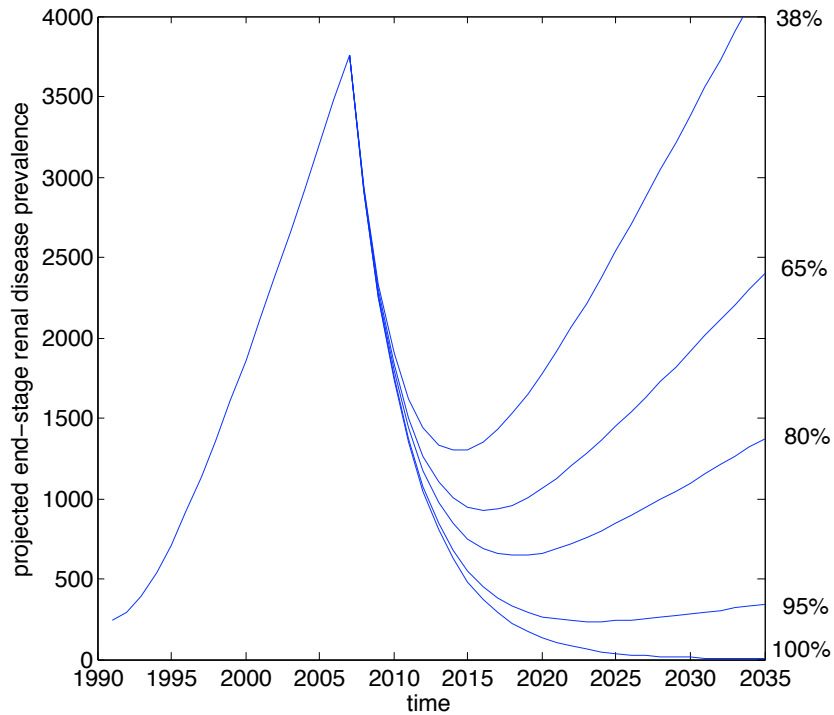
- Let's consider a number of values of *h*:
- *h* = 0.38, 0.65, 0.80, 0.95, 1
- We'll run the original equation from 1991 til 2007, then each of the new equations from 2007 until 2035
- We'll plot each of them on the same graph, so we can compare the effects.

Effects of aggressive HAART



What does this tell us?

- The only way to eliminate end-stage renal disease is if HAART is 100% effective at blocking progression (unlikely)
- All other therapies have an initial dip and then rise again
- Even 95% effective therapy will eventually lead to an increase in prevalence.



So what was the point?

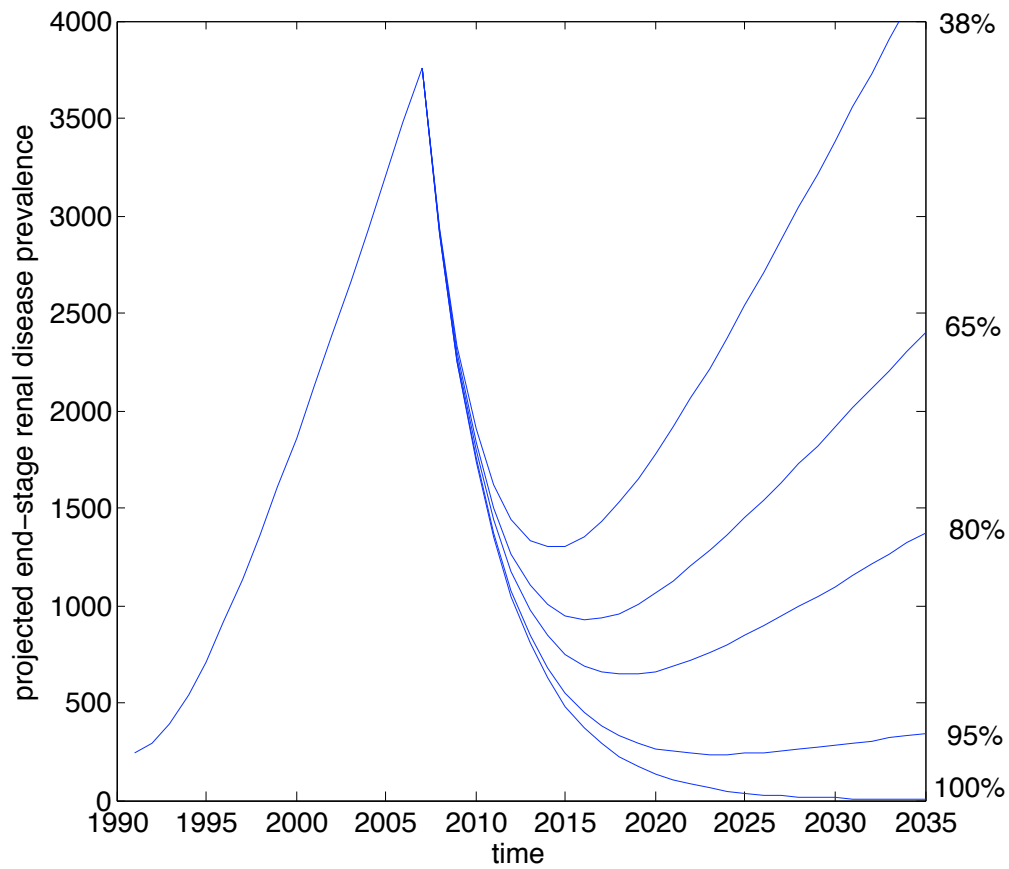
- This doesn’t mean our model doesn’t tell us anything useful
- Even therapy that was only 38% effective would not result in an increase in prevalence for about 25 years
- If we’re looking for eradication, then we’d be disappointed
- But these delays give us time to come up with new strategies and hold back the disease.

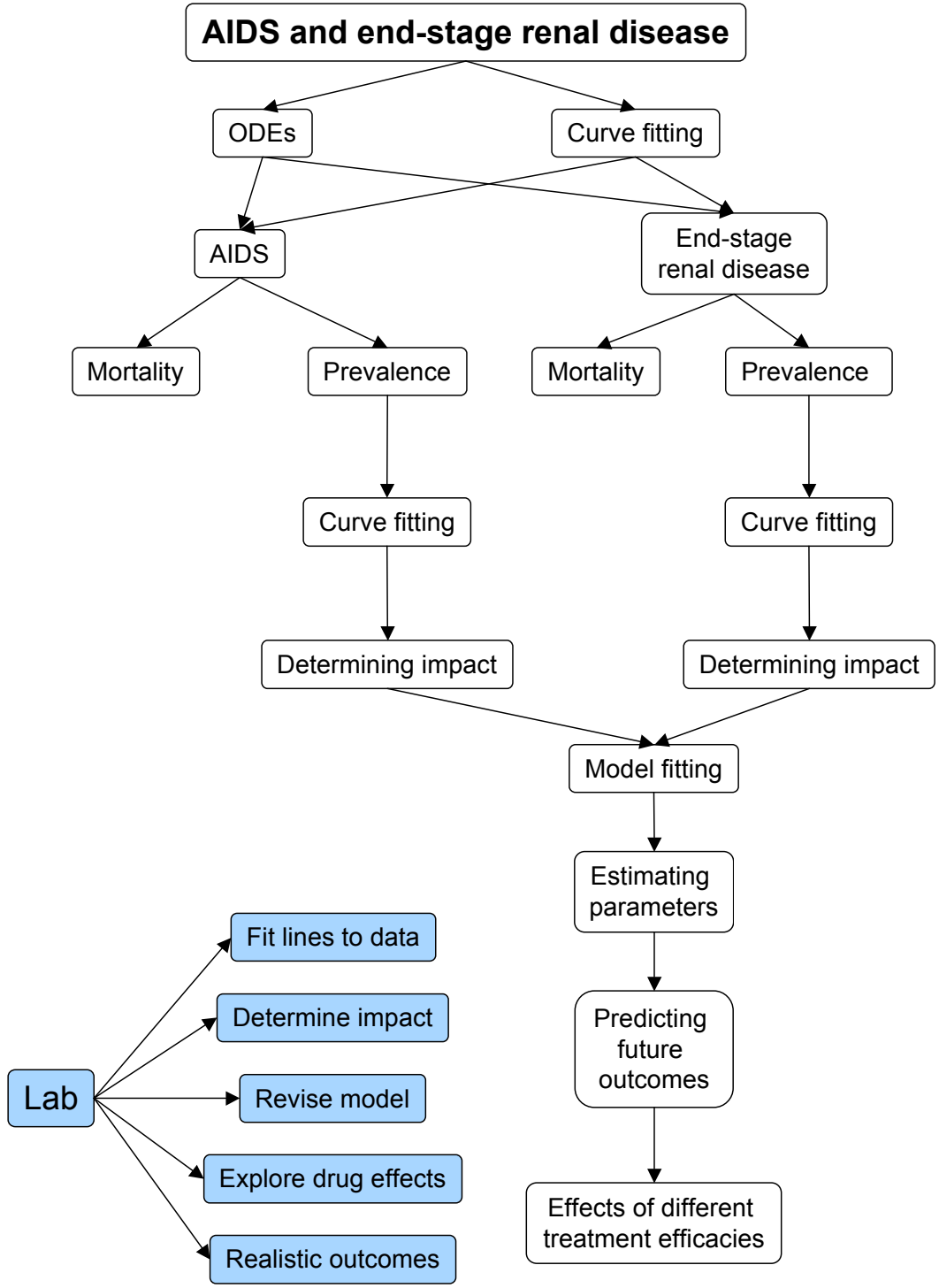
What's the take-home message?

- Our model tells us that putting all our energy into perfecting treatment might not be the best use of our time
- Unless we can have 100% effective treatment, we're not going to eradicate the disease
- However, even fairly ineffective therapy can do a lot of good in the meantime.

Why model?

- In this way, modelling gives us useful information about whether to proceed or not, knowing likely outcomes
- And we did this with nothing more sophisticated than linear regression and simple ordinary differential equations.




AIDS and end-stage renal disease
ODEs
Curve fitting
AIDS
End-stage renal disease
Mortality
Prevalence
Mortality
Prevalence
Curve fitting
Curve fitting
Determining impact
Determining impact
Model fitting
Estimating parameters
Predicting future outcomes
Effects of different treatment efficacies
Lab
Fit lines to data
Determine impact
Revise model
Explore drug effects
Realistic outcomes

Lab work

- Use the mortality data on AIDS and end-stage renal disease to fit lines to pre-HAART and post-HAART data
- Compare this to a linear fit to the entire data
- Adjust the model to include the effect of HAART reducing the prevalence of AIDS
- Explore different effects: 20%, 50%, 80%
- Use the model to interpret biological outcomes as treatment approaches (or exceeds) 100%.