From Promise to Programmes: Treatment as Prevention
Kaiser Family Foundation
July 26, 2012

[1] The Kaiser Family Foundation makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

[START RECORDING]

GEOFF GARNETT: On treatment and its influence on prevention. I'm Geoff Garnett. I'm an infectious disease epidemiologist from the Bill and Melinda Gates Foundation and we're going to start off this session chaired by James Hakim who's a renowned clinical researcher from Zimbabwe. James.

JAMES HAKIM: Good afternoon. I'll introduce our first presenter, Dr. Alison Brown, who is a principal scientist for HIV Surveillance at the Health Protection Agency in the United Kingdom. Alison.

ALISON BROWN: Thank you very much for inviting me to speak today. My name is Alison Brown and I'm a HIV scientist at the Health Protection Agency in the United Kingdom.

Today we want to use national comprehensive surveillance data from the United Kingdom to make three points. Firstly, that is the UK, the National Health Service means that we have open access to HIV testing which is free, free HIV care and free access to treatment. As a result, practically everybody who's been diagnosed with HIV in the United Kingdom is already incorporated into our HIV care.

Secondly, of the people who receiving, of the people who have a diagnosis of an HIV infection, a high proportion are treated and of these, only a minority have a detectable viral load.

Finally, despite high access to care and a quite high ART coverage, we think particularly in gay men, that HIV transmission is still continuing. We think these data show that on its own, treatment as prevention may not be sufficient to reduce HIV transmission at the population level. While it's important, primary prevention needs to remain a focus as well.

Viral load has been established a key predictor for HIV transmission at the individual level and we know that when individuals are treated and adhere to treatment to receive an undetectable viral load, that the risk of transmission at the individual is negligible.

This has caused increasing speculation, particularly from the States that if the treatment cascade whereby people newly diagnosed with HIV somehow don't become established in care and retained in care, if this treatment cascade was eliminated, then HIV transmission would actually be reduced in the population. We're going to show real data from the UK in MSM to show situation where we already have a high ART coverage amongst the population.

First of all, a bit of information about MSM in the UK. Men who have sex with men have an HIV prevalence of 5-percent in the UK and 10-percent in London have sustained a high number of HIV diagnosis is around 3,000 a year. HIV care is provided free of charge and as a consequence, practically all newly

diagnosed MSM are retained in HIV care, and over 80-percent of MSM in care receive treatment.

So today, we want to show these real data from the United Kingdom to show that impact of high antiretroviral coverage in HIV transmission amongst MSM through assessing community viral load, the number of proportion of the population who are affected, which we define as a viral load over 1,500 copies and finally, to looking at markers of HIV incidence including back calculation methods to measure incidence as well as looking at new HIV diagnoses and median CD4 count, median age and diagnosis.

This is observational study and we used comprehensive completely national data in the United Kingdom among HIV infected men between 2006 and 2010. The data we have related to diagnosis MSM was not estimated. It's based on real data of MSM attending HIV services and for these men, whether they're on treatment and their viral load and their CD4 count. To estimate proportion of men who are undiagnosed, we used the multi-perimeter evidence synthesis method to combine surveillance data with behavioral surveys to produce robust estimates or the proportion of people who are living with HIV and unaware of their infection.

In addition to these surveillance data, we'll look at antiretroviral coverage and assess for each of the diagnosed and undiagnosed population estimate the proportion who are

infected and then finally look at HIV instance indicators and the number of MSM.

So this graph shows the number of HIV positive MSM including the undiagnosed population between 2006 and 2010 and you can see between this time, the number of gay men living with HIV is increased from 30,000 in 2006 to 40,000 in 2006. Consistently across this time period, 25-percent of gay men are estimated to be undiagnosed.

Looking at the middle section of the bars towards the end of the bars, this shows the proportion in numbers who are receiving HIV care and you can see the proportion receiving treatment has accrued from 71-percent in 2006 to over 80-percent in 2010, so you can see in the UK, we know that as a minimum estimate, 95-percent of gay men who have been diagnosed and are included into care and we can see that have an extremely high antiretroviral care coverage.

Moving on now, we look at four different groups of MSM, an estimate proportion of men who are infected in each of these categories. Taking the section on the left, we can see that we have about 10,000 men who we estimate to be undiagnosed and of those, we estimate 85-percent of them have been infected.

We do this, we are assuming that they're undiagnosed MSM have the same distribution of viral load of the untreated MSM in their first year of diagnosis. This is likely to be an underestimate and that's because the undiagnosed population

have an elevated proportion of men who have recently acquired their infection and will have a higher infectivity.

Secondly, the men who are diagnosed late would rapidly go on to receive antiretroviral therapy and were removed from this population, lowering the actual viremia.

The middle section shows gay men who are diagnosed but who are not receiving treatment. We have a very small minority of gay men who have a CD4 count under 350 who should be receiving treatment and who aren't receiving treatment. The majority go onto receiving treatment within six months of their diagnosis.

In contrast to the undiagnosed population where 85-percent are infectious, the right-hand proportion are infectious amongst the diagnosed and treated population where only 5-percent have a viral load which is indicative of being infectious.

Those are the four groups of the population and if we add these together, we get an overall picture of the proportion of gay men living with HIV in the UK who are infectious. We estimate this to be 35-percent. We then broke down the proportion who are infectious to see who was and you can see from the pie charts on the right that nearly two thirds of the estimate infectious population were assumed to be those undiagnosed.

Among those who are diagnosed in the other portions of the pie chart, you can see only 5-percent were treated. These were people who very recently started treatment who have not yet managed to obtain an undetectable viral load. You can see the vast majority of those who untreated, there's just a small portion of people who are eligible and have not yet taken up treatment.

We have a situation where we have a relatively small proportion of all gay men who are infected and yet our surveillance data show that HIV transmission is continuing. We're very lucky to have CD4 count diagnosis of over 90-percent of HIV diagnoses, so using these methods, in collaboration with Paul Burrell, we used this information to calculate and use a back calculation technology to estimate the number of infections each year through estimating the length of time between HIV infection and diagnosis. You can see these results show that around 2,000 to 3,000 people are have new HIV infections, between 2001 and 2010, between 2,000 gay men and 3,000 are newly infected each year.

We have corroborating evidence as well using our own surveillance data which show between 2006 and 2010, a time when HIV treatment was very, very high, the number of HIV diagnoses actually increased in gay men. We know that this in part dependant on testing patterns, so we also had a look at the median age and the median CD4 count at the time of diagnosis

and throughout this period, that's been stable, which is also indicative about the fact that new HIV diagnoses are likely to infect a number of new HIV infections.

Finally through the new implementation of the recent infection testing algorithm program, we also know that around 25-percent of MSM are newly diagnosed or recently infected. That also is indicative of continuing transmission.

In a situation where we have over 95-percent of gay men in care and 82-percent of those treated have undetectable viral loads, why is HIV transmission continuing?

Firstly, if we go back to the slide that shows the number of gay men living with HIV in the UK, you can see why the numbers of gay men and while the numbers of gay men has increased, the proportion who are receiving treatment has increased, the black line shows the number of gay men we estimate to be infectious and that's remained absolutely steady, so the absolute number of men who have remained infectious, despite the improvements of antiretroviral coverage has remained the same.

Also, looking at the pie chart we showed earlier, we think the majority of new infections are coming from the undiagnosed population, so the treatment is presented a message. It may not be in-cutting on HIV transmission because it's not targeting the right population. We also know that in the UK, we need to make improvements on the HIV testing

coverage. While the STI clinics have a higher uptake of HIV testing, we know from behavioral surveys that only 15 to 25-percent of gay men have an HIV test every year.

In conclusion, UK access to HIV testing and treatment is excellent due to the NHS. Despite very high antiretroviral coverage, HIV transmission has not decreased with MSM. We're not saying that treatment hasn't had an impact. HIV instance would much likely have been much higher without this extensive ART coverage, but we think the undiagnosed is the probable source of new infections and this means that as well as prevention, we need to focus on primary prevention including giving higher rates of HIV testing to produce later rates of HIV diagnosis. The primary prevention remains key, both in same sex campaigns and behavioral interventions.

I'd like to end to by thanking my colleagues at the HIV STI Department and in particular, Paul Burrell. Thank you. [Applause].

JAMES HAKIM: Thank you, Dr. Brown. So this paper is now open for discussion.

ROBERT REMUS: Robert Remus from Toronto. Thank you very much, very interesting and important information. You said that in your calculations, the majority of transmissions were from people who were undiagnosed, which goes along with everything that you said; do you have any idea what actual rate of what is the rate of secondary transmission from undiagnosed

versus the diagnosed, if you remember, there was a meta-analysis a few years ago that suggested it was around 5 to 6. Did you find something similar or have you not looked at it?

ALISON BROWN: We haven't actually looked at this directly, so that's a great question, but what we have shown is we looked at the distribution of people who have an undetectable viral load. Because we think amongst the diagnosed population, which is a vastly majority of HIV infections in the UK, have a negligible viral load, we think, why is transmission continuing? Why is it considering it must be mainly due to the undiagnosed infection, but we've not actually specifically looked to model it through this technique.

MORITZ: Moritz [inaudible] from Germany. I may have missed it, but how do you estimate the size of the undiagnosed population?

ALISON BROWN: Okay. We combined surveillance data with modeling techniques through a technique called the multi-perimeter evidence synthesis, which combines uplinks anonymous testing and serves key populations to look at undiagnosed and then that uses behavioral surveys to make adjustments to account for the size of those populations to create robust measures of the number who are living with undiagnosed infection and also the proportion of the population.

NICK PARTRIDGE: Nick Partridge from Terrence Higgins Trust in the United Kingdom. Thank you very much for the great presentation. On the basis of this, do you think it is achievable for there to be an AIDS free generation of gay men in the not too distant future and if not, what else should we be doing to substantially reduce continuing HIV transmission amongst gay men in the UK?

ALISON BROWN: I think it's a bit too soon to comment either way about there being an HIV free generation amongst MSM and I do think the results are very positive and that is does show that treatment does work. We have the vast majority of the populations of gay men who are living in the UK have managed to achieve living in a state where they no longer have infection, that's fantastic news. I think to continue reducing transmission or to reduce transmission, we absolutely have to improve HIV testing among gay men to reduce the pool of undiagnosed infections and I think that's the key.

JAMES HAKIM: Go and take the last two.

MALE SPEAKER 1: You mentioned that the age at diagnosis of new cases has remained stable, do you have any information about how long the newly diagnosed cases might have been infectious before they were diagnosed? Because e obviously if this window were closed, it might have a greater impact because there'd be less opportunity for transmission.

ALISON BROWN: We know that the median age of HIV diagnosis amongst gay men is 37 years. Through the back population technique we showed to look at the number of new infections per year; that was also estimated. Obviously there's a big variation. We know that about 30-percent of gay men are diagnosed at a stage when they have a CD4 count under 350. I'm afraid I don't know off the top of my head what it is, but I think it's something in the region of three and four years, but I'm not entirely sure.

JAMES HAKIM: We'll take the last question here.

MALE SPEAKER 2: [Inaudible] from Abt Associates in the United States and I had one comment and one question. First comment is you mentioned a lot of things that you have through NHS, many of which are enviable, but then you left out one for room full of researchers and of course, that is data and that's just envy speaking. Have you actually gone through to estimate the difference that would have occurred had the increases the treatment had not occurred? I heard you allude to the fact that you think it would be likely be greater, but you estimated the size of what you think the impact was.

ALISON BROWN: What the impact of treatment was?

MALE SPEAKER 2: Increased rates of treatment relative to those who are contracting HIV, yes.

ALISON BROWN: Through this study no, but we've been collaborating with the UCL, which has had a look to determine

what the impact of treatment has been on HIV transmission and it's found that it has had a sizable impact moderating HIV transmission in the UK, but it's not been a sufficient a level to reduce it.

What we have also done with this study that we didn't present is we presented a number of scenarios where we looked at, if we increase the proportion of men who are currently untreated and actually treated them, what impact that would have on the proportion that was infectious and we found that even if we had 100-perfcent of gay men who were diagnosed who were receiving treatment, it only reduced the portion who were infected by 35-percent to about 30-percent, but the biggest impact was made through having the undiagnosed reducing the proportion of all gay men who were infectious to around 21-percent.

JAMES HAKIM: Thank you, Dr. Brown.

ALISON BROWN: Thanks. [Applause].

JAMES HAKIM: I would like to introduce your second presenter, Dr. Crane, Dr. Heidi Crane, who is an associate professor of medicine at the University of Washington and her main focus is clinical HIV research including chronic and metabolic complications of HIV. Heidi.

HEIDI CRANE: Thank you. I appreciate this opportunity to present this study on behalf of my colleagues and the CNICS Cohort. I don't need to tell this audience about the

importance of sexual risk behavior as a key transmission mode for HIV both in the US as well as globally.

We're fortunate in that US prevention policies are currently removing more and more to test and treat, getting patients diagnosed and into care as early as possible, despite earlier initiation of antiretroviral therapy however, many patients are still at risk for transmitting HIV even after diagnosis and initiation of care. We therefore connected this study to develop a better understanding of HIV transmission risk behavior among patients in clinical care in the United States in the current treatment era.

We conducted this study in CNICS which is a cohort collaboration of eight clinical sites across the United States. For the data I'm presenting today, we're presenting that from five of these sites on HIV infected adults 18 years and older, who completed a clinical assessment as part of routine clinical care.

The CNICS data captures longitudinal comprehensive clinical data including demographic, clinical, medication and laboratory data such as viral loads as well as the data from the clinical assessment, which gives us a marker of their sexual risk behavior. The primary outcome for this study was being at risk for potentially transmitting HIV and we define that as having current sexual risk behavior including incomplete or no condom use in the prior six months and

specifically focusing on those patients who at the same time had a detectable viral load.

We used generalized estimating equations, adjusting for demographic in key clinical factors to look at substance use as well as to depression and other factors that predict that risk behavior.

This is the CNICS clinical assessment. A number of these domains are crucial for the study, specifically medication adherence, depression and anxiety; and substance use, the nice thing about the way CNICS measures substance use is it's not just about injection drug use or not or have you ever been a substance user or not, but it allows you the opportunity to take a much more refined nuanced look at the individual substance as well as past and current drug use.

The CNICS assessment of HIV risk behavior that includes both sex with men and women, anal and vaginal sex, likelihood of condom use by both of these modes as well as serostatus of partners as well as the use of injection drug equipment, sharing equipment and sex after drugs and alcohol.

The data I'm presenting today is from approximately 5,000 patients who completed 13,000 assessments. They complete an assessment very 4 to 6 months. This is approximately two years of data from these sites and these are all patients who had a viral load result during the same period for each of these assessments. The mean age of these patients is 44.

Their CD4 nadir is 284 and over a fifth of them reported unsafe sex over a particular period time based on our earlier definition of incomplete condom use and of these, 7-percent of them had also had a detectable viral simultaneously.

What you can see on this table is there are three columns of patients listed. The first column are those who are not at risk by a measure of sexual risk behavior. The second column are patients who are currently reporting on sexual risk behavior based on incomplete condom use, but have an undetectable viral load and the third column are those patients with sexual risk behavior with detectable viral load. This I just gives you some description of the demographic and clinical characteristics of these patients and you can see here is that female patients and patients over the age of 50 are much less likely to be having potentially at risk behaviors as well as patients who did not currently have depression symptoms.

This gives us a little bit of addition details, specifically about the substance abuse characteristics of these patients and looking through these various substances, I think you can see is that both patients for the most part with past substance use as well as current substance use are more at risk and in particular I'd like highlight the prevalence of amphetamine or crystal use as well as at risk alcohol at the bottom of the chart.

This table gives us a little bit of additional information about their actual sexual risk behavior of these various groups and it's probably not surprising how different the number of partners among those who are at risk versus those who are not. You will note that the end buries the condom use for the anal and vaginal sex as not all patients reported each of these behaviors and some patients can report both.

Finally, I just point out what the increased impact of having sex after alcohol and drug use has on this categorization in terms of being at risk for potential HIV transmission in the setting of a detectable viral load; much more common in those after having sex after drugs and alcohol.

What you can see here on the left figure, the outcome is again potential HIV transmission, inadequate condom in the setting of detectable viral load and these are individual adjusted models looking at these various risk factors and alcohol, amphetamine, cocaine, opiates, injection drugs, marijuana and the final column is actually inadequate medication adherence and you can see all of these factors are significantly associated with the outcome of interest here, in particular may be highlighting the impact of methamphetamine or crystal use in the second column and injection drug use in the fifth column.

We then dug a little bit deeper and the second figure, the outcome of interest is inadequate medication adherence and

then we repeated the analysis with the first six predictors in the first figure and I think what you can see if a very similar pattern. If you look at the first six columns t each of the two figures, you can see very similar associations just sort of highlighting for us the importance of when we intervene successfully for some of these behaviors for some of these behaviors we sometimes have benefits in others.

What you can see here is this is an adjusted model looking at the odds ratios for individual substance use among potentially at risk based on the condom use and having a detectable viral load and as you probably are aware, many of these substance uses, substances are not used in isolation, so this is the association for an you these individual substances, adjusting for all of the others, as well as adjusting for depression and a number of clinical and demographic factors.

I want to highlight a couple of them. One of them is amphetamine, current use of crystal. The odds ratio is 3.5. The other one I want to highlight is at the bottom of this screen is alcohol use and although the odds ratio is much lower than it was for amphetamine, the odds ratio here is 1.4 if you recall from earlier, that is an incredibly prevalent behavior among HIV infected patients in the United States. This is a very important factor to look at as well, based on the prevalence how common it is to have patients in clinical care.

I think the strengths of what we're looking at here is this is an incredibly large, diverse cohort across multiple sites across the United States. That includes an assessment with an incredibly thorough sexual risk behavior instrument that allows us to look at various factors in these behaviors and it allows us the ability to examine not just substance use as a yes/no or past/current variable or injection, but really to further refine and look at individual substances.

I think the limitations of this, as in so many of these studies is that sexual risk behavior is by definition by self-report and therefore an underestimate. One of the strengths of CNICS is that they do it not in an interviewer-base, but integrated in clinical care using tablets with the normalizing statement, etcetera. It's really done as a state of the art, assessment collection technique, but with any sexual risk behavior, we always have to assume that what is reported is an underestimate.

The similarity of the associations between being at risk for potential HIV transmission and inadequate medication adherence highlights for us the importance of when we are infected and intervening for example medication adherence, there are other potential benefits that may be achieved.

This data demonstrates that patients in care are still engaging in risky sexual behavior and even doing so in the setting of a detectable viremia and substance use in

particular, amphetamines, may be one of the important factors that we can focus on.

What we've seen her in conclusion is that a quarter of the patients in multiple sites across the United States are still currently engaging in active risk behaviors with incomplete condom use and these patients have a detectable viral load while they're doing it.

This again highlights heeds or these findings suggest the need for ongoing emphasis on the positive prevention programs, potentially particularly those that focus on younger patients, patients that are MSM and especially those that are substance use issues and as important and as crucial and fabulous as these test treatment policies are, this just highlights that they don't eliminate the need to focus on the prevention of HIV transmission risk among diagnosed patients in clinical care and that getting patients to a non-infectious state is complex and a difficult task for many of these patients and we need to not forget about behavioral interventions in conjunction with the test and treat approach.

I'd like to thank the patients, staff and providers and in particular, I'd like to thank the tremendous group of collaborators and colleagues at the participating CNICS sites as well as all of the work CNICS, the Clinical Assessment, etcetera are all NIH funded projects. [Applause].

JAMES HAKIM: Thank you, Dr. Crane. This paper is now open for discussion.

JIM SHELTON: Yes, Jim Shelton, USAID. It does look like a strong argument for combination prevention and doing several things at the same time. I don't think I heard you mention this, but it also strikes me that it is kind of a bit of a nightmare scenario with respect to drug resistance that the very people who are less adherent to drugs are actually much more likely to undertake risky behaviors of one type or another and sort of increase the chances of that. What would you say to that?

HEIDI CRANE: I'm not quite sure that that's a question, but I guess the key point there is that we need to, as again, not lose our focus on once patients are in care, not test and treat, let us divert focus from some of these behavioral interventions, particularly focused on medication adherence, once we've got patients on antiretrovirals, making sure that they're able to take them and support them in their ability to take them in the most productive way possible.

JIM SHELTON: That's part of it, but I do think this sort of drug resistance issue comes into focus more based on the data that you're talking about. In other words, there's an association here between risky behavior and poor drug adherence based on viral load. Maybe that's obvious if you though that was the case, this is pretty good evidence for it.

TED HAMMETT: Ted Hammet, Abt Associates, Cambridge. Great presentation, thanks. Just a couple questions in terms of what data you have. You didn't mention this, I wonder if you have data in your data set on history of incarceration? Also, whether you have data on the source of support from their treatment, what types of insurance or Medicaid or Ryan White or what are the sources of support from the treatment that these patients are getting. Thanks.

HEIDI CRANE: I don't have data on whether or not they've been incarcerated, I believe, for most of these sites. I do have data for everyone on their insurance status.

SNICKTOVAL MANINI: Hi, Snicktoval Manini [misspelled?] from the University of California, San Francisco. I am wondering if you are able to take into account serostatus, the partner, since seroadaptive behavior is something that's been reported widely in the literature and HIV positive men are much more likely to have unprotected anal sex with other HIV positive men and that wouldn't really result in a new transmission.

HEIDI CRANE: Yes, the main model I presented today did not divide it by serostatus, but we have all of that data and we've done another of those sensitivity analyses and actually the associations for amphetamine get even strong when you start subdividing it in that way.

JAMES HAKIM: Thank you, thank you very much. Geoff?

GEOFF GARNETT: Thank you, so this session is really divided by the all too real data and then we now have some presentations on the future and the theoretical models describing the impact of test and treat.

Our next presenter is a renowned mathematical modeler who has experience modeling all sorts of different infections including HIV and sexually transmitted diseases.

Mirjam Kretzschmar is both from the Center for Infectious for Disease Control and the RIVM in the Netherlands and the University Medical Center in Utrecht. She's going to talk about the prospects of elimination of HIV with a test and treat spreadsheet. Mirjam.

MIRJAM KRETZSCHMAR: Thank you for the introduction, Jeff, and also thank you to the organizers for giving me the opportunity to present this work today.

As you all know, the test and treat has been widely discussed in many different contexts in recent years and it was all sparked off by publication by Granich et al. in 2009 where he used a mathematical model to analyze the effect of testing and treating those found positive for HIV immediately on HIV prevalence in the long run and they predicted that if you do that on a certain level, then it would be impossible to eliminate HIV within a time period of about 50 years.

The basis for this is that treating infected individuals will reduce transmission to others and this has

also been confirmed recently by the HPTN study, population 2011, where they found that within the serodiscordant couples, treating the HIV infected partner could reduce transmission by 96-percent.

Now do we really know whether elimination is possible, and if so, under which circumstances? The aim of our study was to look at the model that Granich and All used in more detail and also try to modify and generalize the model and include more knowledge about natural history about HIV and in particular on variable inactivity and to arrive under which conditions elimination would be possible.

The model that we used is based on the Granich paper, but we generalized it in the sense that we included a variable number of compartments to describe infection aggression and also, within these compartments, used variable infectivity to describe in particular the high infectiousness of primary infection.

The basic idea of the analysis is actually that just as an emergence of an infection or the beginning phase of an epidemic which is governed by a threshold phenomenon which is described by the basic production number, also elimination as a threshold phenomenon, that is determined by another threshold quantity, which we denote as elimination threshold. We don't really need to analyze the completely model dynamics, we don't really need to understand within the model the transient

dynamics, but we can do a linear analysis to actually explore this elimination threshold.

The analysis that we did was that we explicitly derived expressions from those two thresholds from the model equations and we used data about disease progression that was provided to us by the Cascade Collaboration for estimated disease progression rates and we used information on distribution of infectivity that was published by Alex, Booth et al. in 2008.

That strategy was to actually estimate exponential growth rates from incidence data or from doubling times of the epidemics in the early phase and use a relationship between the growth rate and the basic production number via the generation in vertical stimulation and that gives us the missing link actually to determine the elimination threshold.

A basic assumption in this is that those populations and behaviors that drive HIV in the beginning phase are also the ones that determine the elimination dynamics during the elimination phase. These are some results for the model based on the three stages of infection on the graph up here you see the survival curves through the different stages of infection.

Red is the primary stage of infection, green is the chronic intermediate phase and blue is the final phase of AIDS. This is based on progression rates from the Cascade study and this picture here you see infectivity, relative infectivity in

different transmission stages based on the Hollingsworth data from 2008.

When we combine these two pieces of information, we can compute the generation time distribution. This tells us when during the infectious period the typical infected individual, secondary transmission takes place. As you see here, most of the transmission actually under these circumstances takes place during the primary transmission. It's almost 40-percent based on these parameters and then it is a continuous low rate of secondary transmission is the later phases.

This generation time distribution here denoted by *g* in this formula gives us a relationship to exponential growth rate of the epidemics and the basic reproduction number.

Using this, we can compute the elimination threshold and we have it then as a functional transmission parameters intervention parameters. Elimination will be possible if this threshold is lower than one. What we can do now is we can look at how this elimination threshold depends on various model parameters, for example, treatment uptake with increasing treatment uptake of course, elimination threshold will decrease and at some point will cross the threshold of one. Reversely if the dropout rate increases, the elimination threshold will also increase.

What we need here to do this is an estimate of basic reproduction number and we can either estimate that from

incidence or alternatively possibly it would be possible to estimate it from genetic data.

This picture here shows how the elimination threshold for different values of the basic reproduction number separates areas of possible elimination and those areas where it's not possible in dependence of coverage of testing and the dropout rate of treatment. So for example, for basic reproduction number of 1.5, everything that's above this line will be a region of parameter combinations for elimination is possible. If you're below this line, it will not be possible. You see that this threshold increases with basic rate of reproduction number.

The red dot here denotes the parameter combination data that Granich et al. used in their 2009 paper. The figure that I showed in one of my first slides and you see that if we assume testing coverage rate of 90-percent and a dropout rate of 1.5-percent, elimination will be possible if the basic reproduction number is lower than around 5.

We didn't attempt ourselves to estimate basic reproduction numbers, but we looked into the literature for published estimates. Of course these vary greatly and they're all based on different types of data and different methods for estimating them, but just to give you an impression of what kind of numbers ours are here; in the middle column we see estimates for the basic reproduction number, for example for

the Granich study, they estimated a number of 7, so that would mean that our model that actually elimination would not be possible in this situation. The difference with their study now lies in the fact that we included variable ineffectivity in our model.

You also see that some of those estimates actually derive from genetic sequence data. This is a year in terms of doubling time, so it might be possible if we have also more recent estimates using sequence data, we could actually get more reliable estimates for the basic reproduction number.

To conclude, I wanted to show you that elimination as a threshold phenomenon and elimination about possible elimination can be obtained by epidemic growth rates and the generation interval distribution. We see that elimination is only feasible for populations that are below basic reproduction numbers or if their reproduction number is lowered significantly as a result of other additional interventions.

Also high infectivity during primary infection significantly increases the elimination threshold. Finally, if we would have reliable estimates for the basic reproduction number, possibly obtained from phylogenetic analysis, then these prospects of elimination could be quantified more reliably.

Then I want to acknowledge my co-authors, Martins Vanderkloof [misspelled?], Daniela de Angelis, Rohl Kontinu

[misspelled?] and also I want to thank the Kranksheit Collaboration by providing disease progression data and Paul Burrell for giving us some statistical advice. Thank you. [Applause].

JAMES HAKIM: Thank you very much. Do we have any questions or comments? Perhaps I can start off. You described the relationship between the basic reproductive number and elimination with an overall coverage. Have you explored the details of who's actually been covered by the treatment and whether that influences ability to eliminate infection?

MIRJAM KRETZSCHMAR: No, we haven't done that because this model up to now is the unstructured model and of course it will be a very good and interesting second step to try to include some structure into the model; for example, different levels of sexual activity or age. Of course that makes it more complex and I don't know how far we can go and still be able to do this explicit analysis because then we get a more complicated model, but I agree with you that that would be a very interesting next step.

JAMES HAKIM: The issue is how we design our programs to fit, so we can actually eliminate infections.

RON HATTIS: Ron Hattis, Beyond AIDS. I want to commend you. This is exactly the type of sophisticated analysis that's needed, but there are other variables that I didn't hear mentioned that I wanted to ask you. When I first

started writing about the concept of treatment as prevention in 1996, I didn't have any of these modeling tools and that may be one of the reasons why it was hard to publish it at that time. Also, we only had data proof with AZT. We were theorizing on ART.

One of the critical things is how early you pick up a case. You mentioned toward the end the very high infectivity, of viral loads of primary infection for example. Catching it then, did you test the model with different assumptions of how quickly you could pick it up? Of course, one way to catch new infections at the very earliest stage is through partner services and outreach, as soon as someone tested positive, to link them into care and try to persuade then to share who their contacts are so they can be tested and treated. Were any different variables relating to those things included in the model to see how they would affect the outcome?

MIRJAM KRETZSCHMAR: Okay, right now in the model, the coverage is basically described by one parameter that determines how fast individuals move from infection into the treated stage. Of course, we can vary that and look at the sensitivity of the results for this parameter, but again, if you want to do more complex analysis by looking at partner notification and treatment, then that would require having a more complex model structure, but basically the same type of analysis could be done possibly would require a more

complicated analysis or we could only do it numerically, but yes, includes some, it's possible. For this model that I present here, it would be very easy to do this kind of sensitivity analysis and yes, we have also done it partly.

NICK PATRIDGE: Nick Partridge, Terrence Higgins Trust. You had a strikingly different figures for the UK than England and Wales in your penultimate slide. Could you explain why you had such different figures and what I should understand by having such strikingly different figures?

MIRJAM KRETZSCHMAR: Pardon me, what difference between which figures?

NICK PARTRIDGE: Can you go back two slides?

MIRJAM KRETZSCHMAR: This? [Interposing] this one?

NICK PARTRIDGE: There we go. You've got UK at 3.67 and then England and Wales at 10.05. What happens when you take out Scotland and Northern Ireland [laughter], there's such a massive difference.

MIRJAM KRETZSCHMAR: These estimates are all just take from different papers from the literature and they're all based on different types of data, different estimation models, so they're not at all comparable. Even the different number they give, let's say, exponential growth rate and doubling time are not exponential rates might not be compatible.

So I can't comment on this. If you really want to and use this approach, we should go back to the original data and

do the estimates ourselves to try to get consistent estimates. This was just to give an impression on what is the, let's say, order of magnitude these estimates are in that we found in the literature.

GEOFF GARNETT: We've really got to work on how we estimate the basic input number. The back?

SAM FRIEDMAN: Yes, Sam Friedman, New York. I've just been funded to use network techniques to find people with recent and acute infection and intervene with them with treatment and other interventions. Of course, these people will be connected through their networks and I'm just wondering how this model might be able to incorporate and help us to evaluate the implications of such interventions, where if I would take essentially a restructuring of the model.

MIRJAM KRETZSCHMAR: Thank you, very good question. This model is not able to include network structures. It's simply a compartmental model, so if you really want to include network structures and connectivity, you need a different type of model and then usually, it's not possible anymore, to explicitly compute the basic reproduction number or any thresholds.

The way thresholds are related to disease progression parameters is going to change. So I think yes, it's the same answer as to previous questions. We need to take this analysis further to more complex models, but I also want to stress here

that in a sense, it's of course a relative analysis because we related the elimination threshold to the basic reproduction number.

So in a sense, we cancel out the model structure that's underlying if we can estimate the basic reproduction number from incidents data, it's not directly related to the underlying model structure and if we say something about the relationship between basic reproduction number and elimination threshold, assuming that the model structure is not going to change a lot in the meantime, then I think this is a valid analysis, even if in reality, the model or the underlying population might be much more complex.

MALE SPEAKER 3: I wonder if the basic reproductive number might be quite different in different subgroups in different people with different behaviors, which makes it really sort of complicated because an overall number might be applied to a population, but among high risk MSM or a subgroup, there might still have a very high reproductive number, so if you're talking about elimination, it's a very complex issue to evaluate using the data that we have, I think.

MIRJAM KRETZSCHMAR: Yes, I agree, but as I also said, that we explicitly make here the assumption underlying, we say that those populations that drive the HIV epidemic in the beginning are the same as those that determine what are eliminations possible, let's say at the elimination phase. So

if these are, for example, MSM populations, they determine the basic reproduction number in the same way as they contribute to the elimination threshold, but of course, you can also do this analysis for the specific subpopulations and look at the question, is it possible to eliminate HIV in a specific MSM population or in a specific population of injecting drug users if you have the data available to parametrize the disease progression and the treatment availability. So yes, the model can of course be also used for subgroup analysis and we could then go back and try to piece the picture together into a picture for the total population.

GEOFF GARNETT: Thank you, Mirjam. So the next presentation is hopefully going to address some of these issues of model structures and the sorts of influence they can have. The presenter is going to be Jan Hontelez who works at both Eramus University in the Netherlands and the Africa Centre in Hlabisa, South Africa. Jan has been working on this area of elimination with mathematical models of HIV spread for a few years and has some interesting results to show us.

JAN HONTELEZ: Thank you, thank you, Geoff. Good afternoon everybody. Like Geoff said, I'm going to take you through a mathematical modeling study over the next ten minutes. It's also going to be on test and treat intervention for HIV in South Africa.

As already introduced by the previous speaker, Reuben Granich and colleagues suggested in a paper in 2009 that the HIV epidemic in South Africa could be driven into an elimination phase which could be they define as an incidence below one new infection for 1,000 person years in South Africa in about six or seven years with decline in incidence. However, many other models investigated this primaing intervention, yet there are as many different results as there different models that examine this.

Incidentally, recently assessed the amount of agreement between the different models in the field by having those models calculating a standardized set of interventions and see what are the models that agree in the depicted outcome. They found that although models agreed that ART could have a substantial impact on incidence, the models agree on the mode of impact, in the long run the predicted impact of the intervention is essentially different.

As models continue to be important in developing guidelines and performing health policy, it is important to determine why these models differ so much in their predictions. That’s why we wanted to examine the impact of different model structures and parameterizations of predicting the impact of universal test and treat in South Africa using a highly controlled experiment. We developed a total of nine

structurally different mathematical models and here you see outline of our study.

We start with a very basic model, which is the same model as Mirjam Kretzschmar started with and we then add on a model structures and a step wise approach in order to determine how this model structure affects predicted outcome. With all these models, universal HIV testing and immediate ART for all was tested and we assumed for comparison purposes, the same intervention as assumed by Reuben et al. which was a 90-percent coverage and we start the intervention in 2012

Now I don't have time to go into detail regarding all these individual models, so I will focus on the main models, A through G, tell you a little bit about our structure and show you the results.

First of all, model A, like I said, this is basic underlying deterministic model of the Granich paper. For comparison purposes, we also assumed the same ART defectiveness, which means ART reduces infectiousness by over 99-percent and we assumed to say the same survival of benefits as in the Granich paper.

This model also has a so-called prevalence density function, which is a bit of a complicated word, but it means that HIV probabilities decline as HIV prevalence in the model increases. Now such a function is necessary in these models in

order to simulate the South African HIV epidemic as we observe flood lining HIV prevalence over the last couple of years.

Also we modeled the simulated model using an event driven micro simulation approach instead of a compartmental approach which allows us to more easily extend the model with other components later on.

Here you see the predicted impact of the intervention. As the solid lines show the impact of the intervention in terms of prevalence and incidence, and the dash line shows you no intervention counter effectual. The stars represent data points from UNAIDS in term so HIV prevalence and the gray areas around the line show the 95-percent confidence interval based on the statistical variation within our model.

We see that the model predictions are very similar to what Reuben Granich showed, incidence declines rapidly to below the 0.1 incidence threshold and is achieved by about six or seven years. We also looked at the overall incidence of infection by the intervention in terms of the number of lives here saved per anti-treatment year, which gives you an idea of the cost-effectiveness predictions that these models give. Here we also see a massive impact of the intervention as about six life years saved. The six life years are saved by every administered ART treatment year by about 2050.

In the next step, we expanded this model by adding an age structured population, so we implemented birth rates and

death rates from South African data and we also included [inaudible] interest by HIV states, also similar to my previous presenter allowing for a higher transmissibility during the acute stage.

Let me just jump to model B, the results. Here we see that the picture is slightly different in terms of the impact of the intervention. We see again a rapid decline in incidence when the universal doesn't treat intervention starts, however it doesn't go as far as in the previous model and we see that the inclusion of early infection into the disease progression keeps the transmission going under such an aggressive test and treat intervention.

We do see that test and treat is declined slightly and that around 2055, incidence reaches the threshold of 0.1 incidents per year. In terms of overall effectives, again which gives you an idea about the predicted cost effectiveness, we also see a massive difference whereas we saws 6 life year saved in the previous model, in this latter model, which includes more researchers, we see that the predicted overall effectiveness is reduced by about half, which is important for the basics of predictions of cost-effectiveness between these two models.

In the next step, we added three more assumptions and structures to the model. First of all, we added [inaudible] to the model by implicitly modeling sexual relationships and

sexual networks. We actually removed this so-called prevalence density function, which I mentioned earlier which was needed to arrive at this leveling off of the HIV prevalence by now explicitly modeling male underlying dynamics such as male circumcision.

We add other STIs that are co-factors for HIV transmission, such as HSV2 and we assume an increase in condom use rates over the late 90s and early 2000s, which is consistent with data from South Africa. We also assume more up-to-date ART effectiveness assumptions, so we no longer issue an over 99-percent effectiveness of reduction infectiousness, but only a 90-percent reduction in infectiousness and we issue more a survival benefits, based on this recent literature.

Here we see the epidemiological impact in this model and if you look at that bottom graph, you see the predicted incidence in the account effectual is different from what you see in the previous models. This is because we now remove this so-called prevalence density function and modeled the underlying dynamics, which actually caused incidence to slightly decline in the future, even though there's no further scale up of prevention interventions.

Therefore, if we look at the impact of the intervention, the epidemiological impact is also a little more profound that we saw in the previous model as we reached the 0.1 incidence at the threshold at around 2035. However, if we

are going to look at the overall effectiveness of the intervention, again, to look at cost effectiveness, we again see that this is substantially lower compared to the previous models as we had only three life years saved per treatment year in 2015 model B, now we have about 1.7.

Finally, we had a detailed health systems component to the model to accurately simulate the current ART treatment scale in South Africa. I don't have time to go into detail, but we assume two sub models. One model models the health seeking behavior of individuals that are infected with HIV, which increases over the disease progression and the other sub model deals with the health systems capacity to meet this health seeking driven demand.

Let me show you the epidemiological results for this model and here was strikingly picture from that the previous model showed. Because the current ART treatment rollout is starting to get very effective in South Africa and because of the effective ART on incidence that is already occurring with this rollout, we see that incidence before the intervention has already started and is already declining.

This makes sense as ART is scaled up, you would expect that prevalence would increase because of increased survival, however we see that prevalence is flat lining which could mean that incidence is declining. If we continue on this trend and we assume that access is scaled up to universal access for all

at 350 cells marker into the future, we see that incidence declines to below 0.1-percent at around 2040.

The test and treat invention still has a substantial epidemiological impact and ART structural is achieved at around 2030. Again, if we look at the overall effectiveness that we see that this is lower compared to the previous models.

Our analyses has some important conclusions and implications. First of all, we confirm the results by Reuben Granich and colleagues that the HIV epidemic in South Africa can be driven into an elimination phase through expanded ART. Of course this elimination phase is a little bit of an arbitrary threshold of 0.1-percent incidence, which does not portray actual elimination.

Since it's pretty complicated to look at our mode in our model, we try to look at whether the disease actually dies out by continuing the simulations far into the future. We see that every model that predicts that incidence will drop below 0.1-percent incidence, the disease will eventually die out into the future.

We find that the models differ substantially in the predicted time until incidents threshold is achieved and also in the predicted impact of the intervention and because of our structured approach, we could determine which of the modeled structures actually make that these models differ so much. We found that especially the inclusion of sexual networks is very

important in the predicting impact of the test and treat intervention because when you include the sexual network, you will have high risk individuals that will continue spreading on the disease, even in an under section aggressive intervention.

We also found that this prevalent density function compared to including the dynamics that underlie the South African HIV epidemic determines the predicted impact of your intervention. Of course taking into account current ART scale-up is important and as my previous presenter showed, [inaudible] HIV transmission accounted for high transmissibility in the acute stage is also highly relevant.

The predicted effectiveness of ART declines which is important of the underlying dynamics of the epidemic are taken into account, which I showed you these lines predicting the number of life years saved per ART treatment year and this has important implications for future modeling studies as models that ignore these structures, these simplified models, tend to overestimate the impact of the intervention.

Furthermore, current treatment rollout may have such a substantial impact that the epidemic will reach the 0.1 incidence threshold if current scale-up is maintained and universal access is achieved, which raises questions regarding the value for money for intensive test and treat intervention.

We did a bit of cost effectiveness analysis that I didn't show you. Sorry, but we found that although these

positive impact of the current rollout of universal test and treat is cost effective and of course the assumptions of the programmatic effectiveness of this test and treat program are rather optimistic and it's likely that treatment uptakes as well as treatment adherence are going to be less effective as assumed under this program.

So we think that a detailed incremental cost effectiveness analysis with more realistic assumption of programmatic effectiveness is treatment as prevention is highly needed given the positive impact the current rollout has already having. We also think that detailed cost effectives analysis for uniform policymakers and guidelines should be performed models doesn't allow sufficient for levels of detail and the underlying epimdemci as I showed that predictive cost effectiveness differs substantially if you exclude all these dynamics. I'd like to acknowledge my co-authors and my funders which is seen listed here. Thank you very much.

GEOFF GARNETT: Thank you, Jan. That was fascinating in terms of what's happening in South Africa with current treatment programs, but my understanding is that that depends on you expecting to see an increase in prevalence because people are surviving longer for treatment which means incidence must have gone down.

Do you think we're at the stage yet and the data is sufficient to be sure that that increasing prevalence isn't

happening with improved survival. Have we got there yet, do you think? Or is this in doubt about it?

JAN HONTELEZ: Yes, I think that's an important question and of course, there's still some doubt because the scale-up only started at around 2004 and we need a long time to see whether the effect I showed is actually happening. However there are some studies that show that incidence in young people in South Africa is actually declining and condom use rates are increasing.

On the other hand, we do see and I'd like to point to a late breaker presentation somewhere tomorrow from a rural area in South Africa that prevalence is actually increasing because of the current ART treatment rollout, which implies that incidence is not going down that much. So we performed a scenario analysis in which we also looked at what would happen if prevalence was increasing instead of stabilizing as was observed by the UNAIDS data and there we find that be it later, this same effect of treatment at 350 occurs in the end.

RON HATTIS: Ron Hattis, Beyond AIDS. First question was your definition of prevalence persons living with HIV or persons with an infectious level of viral load? Because I'm surprised at the promptness of the decrease in prevalence. One of the first things that happens with treatment is people live longer and the prevalence of people living with HIV actually

goes up before it comes down. You have to have a whole generation, a whole cohort die off which takes decades.

The second thing is somewhat facetious, but I wish there were a model to incorporate Murphy's Law, which is that if anything can go wrong, it will. Has anybody in your team or any others taken into account the prediction of increased resistance, drug resistance of disorder, civil war interfering with various nations' programs? The parallel is tuberculosis.

Not only do we not have to treat for life with tuberculosis, but we've had a test and treat policy for many years and the best that we can hope for is generations not to ally free of TB, but generations with gradually lower prevalence and incidence rates of over a period of maybe 100 years and we're not even getting there because of the resistance strains, the civil wars and disorders leaving the interrupted programs, political changes, recessions, etcetera. Could you comment on those?

JAN HONTELEZ: Yes, thank you for those two questions. First of all, the prevalence issue, the models I showed are people infected with HIV, so people living with HIV and it's not necessarily people who are infectious and this is all people aged 15 years and older.

What you see is that prevalence is declining rapidly and we have fitted our predicted survival of people on treatment to survival observed to clinical cohorts in South

Africa based on CD4 cell count on treatment intimation and other things as well. We are fairly confident that this is accurately captured in the model and of course if incidence is declining already in the pre-intervention period, you're going to be have this spillover effect of declining prevalence a few years later on in the prevalence curves.

Regarding the Murphy's Law, as you put it, of course that would be very interesting to look at in models, what would happen with disasters or civil wars, our model is not capable of predicting political futures yet, but it would certainly be interesting if we looked at if resources decline or if treatment programs stop, if ART stocks are going down and there's no drugs to provide treatment, so I agree such an analysis could be useful.

JOHN STOVER: John Stover from the Futures Institute. I wondered if you could explain a little bit more between model C and model D. My understanding on what you said was that for the last model, you added some more real life information about treatment saving behavior which would tend to have people seek treatment later in their infection and also some health system constraints, which I thought would perhaps reduce the quality of treatment, yet you showed a big difference in terms of the rapidity of elimination between C and D. Can you explain where that came from?

JAN HONTELEZ: You said health system constraints. We do not health system constraints. We include a health systems component that gives the capacity of the health system to meet the demands driven, the health seeking ART demand in the model. This is used to scale up ART, so we assume that the health system capacity is scaled up during these years starting in 2004 and up to Universal access within a few years.

I think the predicted impact is partly because incidence is already declining partly and that makes the additional kick given through treatment to all affected CD4s below 350 such a associative potential.

JOHN STOVER: But what was the change that made incidence decline more rapidly, even in a historical period

JAN HONTELEZ: It was the treatment rollout. What do you mean? In the historical period? So in 2004, the rollout starts and then you have additional condom use rate consistent with data from South African studies. In the last 90s and early 2000s and together they cause a decline in incidence in the pre-intervention areas. Then if you continue to scale up to universal access to 350, you see that the decline continues.

SEKRIM BELIBENF: Thank you. My name is Sekrim Belibenf [misspelled?] from Rwanda. I was particularly interested on the last model where you proposed the extension of the [inaudible] ART coverage interventions seems to be one of the better models. When you're looking at the Rwanda

program, we have a more than 90-percent, 94-percent of coverage of people needing antiretroviral treatment and when looking at the data, we find that new infection in people needing antiretroviral treatment, that's the decrease, so I am a bit confused about ART's coverage at 350.

JAN HONTELEZ: Yes, thank you for that question. I understand your concerns. I should note that we looked South Africa specifically and not at countries like Rwanda. In South Africa, as I said, incidence was already declining due to increased condom use and we therefore have the additional benefits of ART at 350 that resulted in even more prevention benefits and I think the effect of ART on transmission if you give to people below 350 as has been recently been demonstrated by Granich and colleagues in a population based cohort in South Africa where they saw that increasing coverage of ART resulted in lower incidence rates in these cohorts.

Of course, I don't know about the Rwanda epidemic in order to be able to adequately comment on whether incidence is not declining in your country, so I'm sorry, I can't comment to that.

GEOFF GARNETT: So I assume we have some specific questions for Jan still, but we're within time, we'd welcome general question to any of the speakers as well as specific questions, but I assume the three that are up now are still for you, so you're not off the hook yet.

KEITH MARTIN: Thank you, yeah, Jan, quick question. Keith MARTIN from Canada. What are you using to scale up the seek and treat program, particularly in Zululand where incidence is high and quite a devastation of the primary care system and particularly rural Zululand? Thank you.

JAN HONTELEZ: Yes, thank you and that's also a good question and a key question because we similarly to the whole of South Africa, but of course we ignore the dynamics within the country showing very different epidemics and for instance, KwaZulu-Natal compared to other areas where prevalence is lower.

Regarding the test and treat intervention, we simply assumed that it was scaled up linearly in terms of coverage in seven years, which is similar to what Reuben Granich colleagues predicted. We assumed it's scaled up to 90-percent coverage, the screening within seven years time and then everybody who is found positive is put on ART. That's the whole assumption underlying this treatment as prevention intervention, so if that answers your question.

TOM WONG: Tom Wong from Canada. Very nice presentation. Did you actually examine the impact of drug resistance on the elimination?

JAN HONTELEZ: No, we did not. That's the short answer. Of course, that's another important issue to take into account and our models are not perfect, so there's still a lot

of gaps to be filled and treatment as resistance might be the important one, yet we do still need to see an explosive increase in resistance that might have been expected because I think this morning we saw the presentation by Bernard Hirschel that resistance is not that of a big problem yet in sub-Saharan Africa, but it's indeed an important issue to take into account.

JIM KOOPMAN: Jim Koopman, Michigan. First of all, I'd like to praise the nice approach to the simple model, the relaxed assumptions and see what happens, but of course that job is never done, so as we got through the from your C to you D model again, where you have this falling incidence, in most of the place where incidence has been estimated reasonably well, it hasn't followed that dramatically with the rise in treatment, especially in developed countries and one of the reasons may be another simplifying assumption of the model that you have people constant or at least age related risk behavior rather than fluctuating risk behavior and the reality is how much is from acute infection, they also change that. Maybe those assumptions are what's give you the estimate of the falling incidence. There's further work to be done.

JAN HONTELEZ: Yes, thank you, there certainly is further work to be done. Regarding acute infection, I can tell you that is indeed an important driver of the epidemic under an intensive test and treat intervention and as Mirjam Kretzschmar

showed, it really does matter which values you assume regarding the proportional infections atrophied at acute infections, what the effect is going to be of an ART infection and also for ART 350.

We also did some scenario analyses where we varied this substantially and indeed this as an important impact on the predicted of both the test and treat intervention as the intervention at 350 cells marker here. So in the baseline analysis that I showed you just now was at about 20-percent of all infections coming from acute infection in the year that the intervention starts in 2012, but if we varied that to a range of numbers such as 40-percent or 45-percent, which comes close to what was estimated by Mirjam Kretzschmar, we see that it's a lot harder to reduce indicdence that's substantial, so that is an important point.

GEOFF GARNETT: But as you showed, Jim, there's a relationship between this acute proportion of acute infections and the basic reproductive numbers is the more that there are acute infections, the lower basic reproductive number and that means that there's that tradeoff, so it may not be as bad as Jan may be painting.

MAX: Thank you, thanks for a very nice presentation, Max [inaudible] from Amsterdam. I have a word of caution and a question, which may actually also be education. Your conclusion is basically that the original Granich model can be confirmed,

that there's a tendency to elimination in the long run, but in fact, you still use the rather optimistic coverage rates for testing 90-percent and for treating 90-percent and I think in some research settings, they may have been able to reach that in Uganda and some parts, but in public health practice, these may be unrealistically high, so that's just a word of caution that if you put it very optimistic assumptions in the model and I think you can probably prove that it works.

My second thing is a question, which many also be a caution. Mirjam Kretzschmar showed that the dropout rate after starting ART is of very big importance in predicting that elimination can be reached. I was wondering if your model you used the Granich dropout rate or whether you varied that as well or took a more realistic assumption than Granich holds.

JAN HONTELEZ: Yes, thank you, Max, excellent questions. In my last slides, I don't know which one, I already highlighted the importance of more detailed cost effectives studies using realistic assumptions regarding programmatic impact. You're right, the 90-percent coverage of annual screening an high uptake of treatment together with the whole dropout which is by Granich and colleagues is likely to be way too optimistic.

We chose this intervention simply for comparison purposes because we wanted to replicate the Granich model and then we wanted to see how different model structures impact

change predicted effectiveness and that's why it's key to keep the intervention the same, otherwise you're comparing different things.

But I agree that more realistic assumptions are needed. However the rather optimistic result from the current ART treatment rollout at the 350 cell marker is actually a very accurate replication at least in the first few years of the current set of treatment rollout, which I cannot show you, but we have close fits to data in terms of health seeking and in terms of ART coverage already shows that rapid decline may result in elimination so it makes you wonder whether test and treat intervention is actually completely necessary.

GEOFF GARNETT: Thank you. So we're continuing to torment, Jan, but some of the other talks showed how it's very difficult to go into the real world programs in the UK and the US where we have a lot of resources and achieve these sort of results, so it's an interesting contrast there.

DON BAXTER: Don Baxter from Australia. Mr. Chair, I was wondering if I can ask Alison Brown a question about those lines. Picking up on that point of caution about testing rates and also I think you said among UK men, between 15 and 25-percent had an HIV test in the last 12 months. I'm just wondering in that period which I think was from 2004 and 2010, was that period?

To what degree was there a change in testing modalities, particularly in relation to the introduction of rapid HIV testing, so what extent does that rollout in the UK and is it only at health facilities or community facilities and is that one of the strategies? Are you doing work on the strategies around that modeling in terms of identifying the undiagnosed who are created an ingenerate most of the new infections?

ALISON BROWN: Thanks very much for that question. In the UK, the majority of HIV testing amongst gay men, 95-percent who are newly diagnosed or diagnosed in sexual health setting which are free and open access, and we know that gay men actually go towards STI, sexual health clinics, the offer in the uptake of HIV testing is very, very high. It's just a matter of capturing the gay men who are taxing the sexual health clinics.

We have had a number of strategies that try and improve testing. More recently since 2008, in areas within the UK where the diagnosed prevalence is higher, more than 2 per 1,000, we've been trying to expand HIV testing outside these traditional sexual health settings into the community and we found that that has been a feasible and acceptable, we haven't yet ordered it to be impact of that.

We also have been expanding more into community testing, including rapid testing, which is the case I think in

most of the London settings, but I agree, the issue is to try and make sure that we're capturing gay men outside of the high prevalence areas with the bigger focus on community settings as well.

FEMALE SPEAKER: Hi, thank you for these very nice presentations. I'm from the Cleveland Clinic [inaudible]. I have two questions. One is for Mirjam Kretzschmar. Very nice presentation. I'm curious what you did show the survival during the different integration period and the different stages of HIV, and your data is from the Cascade database of seroconvergence, which I think has a testing of every six months, you can correct if I'm wrong.

Did you do any, what was the assumption regarding the duration of acute infection and what was the sensitivity analysis because the database I think used as a testing end for six months, that's my recollection.

Did you overestimate the duration of acute infection and did you do any sensitivity analysis around that?

MIRJAM KRETZSCHMAR: Thank you for your question. We actually did not use the Cascade data. That detail is used here because simply our model is a compartmental model with three compartments as disease progression and what we used from the Cascade data was information about the mean or average time spent within each infection stage, so that's what we used to parametrize transition rates in the model.

So we didn't, for example, look at the data in CD4 counts and stages in that, but on an aggregated parameter describing duration of the different infection stages.

FEMALE SPEAKER: What was the duration of the acute infection?

MIRJAM KRETZSCHMAR: I don't know the number from the top of my head actually, but I can tell you later.

FEMALE SPEAKER: That's okay. I liked your study, you're working on a similar template, so it was a fascinating study. My second question is for the last presenter and maybe you mentioned that in the Granich paper also took into consideration for the prevention package. How did you deal with that and what were you assumptions? Because it totally used test and treat and there was a prevention package and the deterministic model that was there that took care of 40-percent of prevention.

JAN HONTELEZ: Yes, that is correct. Thank you for that question. In the Granich model, they assumed 99-percent reduction in transmission probability due to ART and then on top of that, they assumed a prevention package to further reduce the transmission probabilities by 40-percent. In our first models where we also used these assumptions used by Granich, we simply assumed ART to reduce infections by 99.4-percent, which actually the same as saying there's ART and a prevention package, so we took that into account.

FEMALE SPEAKER: What are you final models where you were saying stating as this and very optimistic rollout in South Africa? How did you deal with that in the prevention aspect?

JAN HONTELEZ: Yes, since South Africa in the later models, we did not assume any models in the scale up of preventions, it's purely ART that reduces infections by about 90-percent.

GEOFF GARNETT: Okay, so can we just allow Andrew to ask the last question?

ANDREW: Thanks, Geoff. Thanks that's a brilliant session. I don't think Jan's answered enough questions yet, so I've got more. One of the pieces of detail, I agree with you in adding these bits of detail, it's a brilliant presentation.

One of the other bits of detail I think could be important to look at is what monitoring strategies is implemented for people on ART and the extent to which, you used the example of South Africa, which viral load monitoring, but the extent to which this would be different in countries which used borrow line monitoring. I think another important thing to try to study.

JAN HONTELEZ: Yes, thank you, I agree, absolutely, viral load monitoring, also just treatment monitoring and retention and care is vital to the success of treatment as prevention. In South Africa, the dropout rates and adherence

are not optimal, so as you say, it's very optimistic, but it's not optimal and I think in our later model, we assume annual dropout rate, but we do not have any differentiation by poor adherence or anything like that, so take into account for further analysis.

GEOFF GARNETT: So it just remains for James and I to thank all the presenters for really brilliant and excellent presentations. Thank you all. [Applause].

[END RECORDING]

[1] The Kaiser Family Foundation makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.