Use of Antiretrovirals for Prevention: PrEP, PEP and ART
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HELEN REES: I think if you can come in and find any seats that remain as quickly as possible because I think if we can, we should try and get as much, squeeze as much time out of this session as we can because I know some of the panelists want to be controversial and create debate. So, let's try and get some time for that.

So, my name is Helen Rees. I'm from the University of Witwatersrand in South Africa, Johannesburg. I chair a unit which is actively involved in this field of research called Reproductive Health and HIV Research Institute and I also serve on our national AIDS council with a portfolio for prevention research there as well. I'm delighted to be a co-chair of this session which is going to look at the use of antiretrovirals for prevention, PrEP, PEP and ART.

I'd like to also just introduce my co chair as well, who's Dr. Tequest Guerma. She's a director general of AMREF and she was previously the deputy director general of the HIV department in the World Health Organization and later acting director of that department.

So, we'll move straight in to the speakers but I think that the fact that this room is full is because this is actually a very, very topical area. I suspect that this conference is going to be remembered for many things: The humans rights issues, clearly. But it's going to be one

conference where the issue of using antiretrovirals for prevention and some of the challenges that this poses are going to be noted for discussion.

In my own setting, I used to have and still have vigorous arguments with my treatment colleagues as I come from a prevention background about their take which is why don't we just treat everybody and then we can call pack up and go home. I think that finding the prevention and treatment, we really are talking to each other and we really are at a point of thinking about this and I hope that in two year's time what we will be seeing is not discussing proof of concept and whether we think this will work but harder data. We've already had some very good news from tenofovir gel study as we all know.

But actually looking at some of the programmatic challenges that should some of these approaches work, how we introduce them and what that means and programs.

So, the first speaker today is Dr. Frits van Griensven who is with the Thailand Ministry of Public Health and U.S. CDC collaboration in Nanterbury and Thailand where he leads the Silom Community Clinic and the Bangkok MSM Cohort Study. His main interest is HIV prevention research and he's been a long-term proponent of intermittent PrEP. He's also the co-principal investigator of HPT and O67 which is a phase two trial examining the use of different intermittent PrEP regimens in humans, the first of its kind. Frits.

GODEFRIDUS J.P. van GRIENSVEN: Thank you my dear. Yes. Thank you, Ellen. So, this afternoon I will try to highlight a number of issues related to PEP, PrEP and ART for prevention in MSM. Certain that I will not be able to touch upon everything but a few things I think we can address in the 15 minutes that I have.

This slide, actually I show on behalf of all the speakers here. It's just to let you know where we are. We are in 2010. We just enjoyed the results of CAPRISA. These lines indicate the other trials that are currently going on or have finalized here on the left and the ones that are coming in the near future with their results and still being conducted.

So here's the CAPRISA trial; we just learned the results of that. iPrEx multi-country trial and MSM, I'll talk a little bit more about that later, is scheduled to release results later this year. The Botswana trial, CDC trials changed into a safety study, is not looking in efficacy anymore. Bangkok tenofovir study conducted by my own office is also scheduled for completion later this year, come with results. And the extended safety trial here in MSM, tenofovir in the United States, domestic trial will be reported on later this week, on Friday I believe. So the results will be available to us. It's not an efficacy trial but a safety trial.

The other trials here down at the bottom are very often more complicated designs with multiple arms. They will be released in the future as they near completion.

So in this presentation I will address a number of issues regarding non-occupational or sexual post exposure, post exposure prophylaxis or PrEP and a little bit about antiretroviral treatment, particularly from the perspective of what these interventions may mean for men who have sex with men.

Regarding PEP or NPEP, non-occupational exposure, I think there are a number of concerns regarding the efficacy. We do not have good efficacy data that support PEP for MSM and so controlled studies like the one in health-care workers, they are not available to us to support these programs. Observational studies have been conducted. Some very nice studies have been done, particularly the one in South America and Brazil for [inaudible] for excellent study but they show no clear effect in either direction, either protection or enhancing transmission.

The Amal data actually showed that we can expect very little if the antiretrovirals are taken too late. They really need to be taken very quickly, as soon as possible after the exposure to be effective or to have some effect. The problem is that men usually fail to recognize exposure. They only recognize exposure after they've been thinking about it for

awhile and then very often it's too late. Then drugs are taken but they may not help anymore in terms of protection.

So overall, I think the public health impact of NPEP, non-occupational PEP, is considered to be limited and only cost-effective in very specific situations such as when the serostatus of the index gauge is known, when the drugs can be administered immediately then there may be some effect.

In conclusion, I think what we, I haven't talked about resistance and side-effects, etc. It's not so important in this perspective here. I think in conclusion we can say that generally it's felt that PEP is not feasible for programmatic scale up in MSM but it can be offered as an individual service on a case-by-case basis.

Nevertheless, I think PEP in some way led us to PrEP because we learned that the medication needs to be taken very soon, as soon as possible, so people have been thinking well, why not take it then before? If it's so difficult to take it after why not move it to take it before the exposure? So then pre-exposure prophylaxis came into the picture.

These ideas were then followed up with a number of animal studies where the drugs were given soon before exposure and then were extended also by giving more drugs after a different period of times and variations: two hours before 24 hours, two hours after 24 hours, etc. etc. What we just want to focus on is the rectal-challenge models because they are the

most important for the population that we discuss here today: MSM.

The results, actually, of these animals, they are driving the PrEP research agenda of today for MSM and the results of some of these studies are depicted on this slide. As you can see here, Truvada given daily to the animals and here's the number of exposures. You can see all the animals stay uninfected or protected by Truvada daily even though they had a large number of rectal exposures with SHIV, simian HIV, no infection occurred. Here there is an intermittent regimen minus two and plus 22 hours and also this regimen actually protected all the animals. This shows us evidence that daily as well as this particular combination of pre/post is protecting animals against rectal challenge with SHIV.

These are animal studies. For the humans, that may be a whole different matter. But therefore, obviously, we have the trials that build on this laboratory work or this animal work and the example here of continuous dosing or daily dosing is the iPrEx study being conducted by — well the PI is Dr. Bob Grant and I received these slides from him for which I am grateful. The study is currently going on sponsored by the U.S. government, the Bill and Melinda Gates Foundation and the producer of Tenofovir, [inaudible] at Gilead Sciences.

It's conducted in MSM in the Americas, in Asia and Africa. It's, particularly for MSM because the route of

transmission is different. Rectal acquisition of HIV is different from heterosexual IDU transmission. It's the only study currently going on in MSM. It's conducted around the world and there's one site in Thailand, South Africa in Cape town, South America in Brazil and Ecuador and Peru and two, what is called domestic sites, in San Francisco and Boston.

This study is now fully enrolled 2,500 people, 11 sites and we're waiting for the results to be released, hopefully later this year. Maybe next time [inaudible] you know, we may learn the results of this study.

Just a little bit of information about the design. One-to-one randomization, it's a randomized trial. Active arm is Truvada versus placebo, daily oral administration and manual followup for seroconversion and a number of other things that are relevant in this setting.

So while this trial is going on there has been discussion on whether intermittent PrEP would be better as people have been thinking it's more in line with the sexual lifestyle of MSM. Most of them are not having sex all the time and they may not need to take Truvada or another drug daily which would burden them in terms of pill burden as well as drug burden.

Intermittent PrEP may reduce that burden. It may also reduce side-effects, decrease costs, may actually help to increase adherence and coverage of exposures and may also help

men to increase their safe sexual behavior because they need to be aware and need to know when they're taking the pills. They may be stimulated to think more about their behavior which actually may then result in more protection.

Intermittent PrEP is also supported by the animal models and here are some slides from those experiments given to me by Gerardo Garcia, the person who led these trials in CDC. You can see here a number of intermittent regimens that have been tested in these animal studies. Minus 22 plus two hours, minus three days or 72 hours before two hours after, seven days before two hours after and then, this important, two hours before and 22 hours after and then the post-exposure variant, the plus two hours and plus 26 hours.

Here are the results of these experiments. As you can see that all the first three groups that I mentioned, like 24 hours, 72 hours, seven days before, it seems like what we can learn from these studies is that the pre-exposure drug needs to be taken a long time before, preferably 24 hours before and very shortly after as you can see here. Minus 22, minus three, minus seven and two hours after gives the best protection.

The two hours before and 26 hours after are the PrEP module, the protection is less and minus two and plus 22 similarly. So, long before, shortly after, and all of variations on post-exposure or shortly before or long after, they're not as effective.

Now, some behavioral data have been supporting the idea that MSM are not exposed all the time and this is some of the data come from Bangkok MSM cohort study, the study we're conducting ourselves in Bangkok. As you can see here, most of the men in this study actually have only one or two sexual episodes per week so the majority actually has less than 50 percent of the men here have sex once a week. The median is one, so the median time people have sex in this study is one time per week.

On the right side here you see people who have sex seven times or seven days a week, six days, five days, four days. These people evidently would benefit from a daily regimen. For the ones who have two, one or zero times they would benefit from an intermittent regimen or maybe they should not get a regimen at all because the risk is so low. If the risk is really, in this group you may want to target your intervention there and maybe that should be done daily. These are some of the data that support our idea of giving intermittent PrEP.

MSM do not have sex all the time. The majority of the people have just one time of sexual episode per week. So it's a little bit in contract with the overall opinion that MSM have sex all the time at unexpected moments etc. etc. It's clearly not the case here from this data.

If you need to take a pre-exposure dose you need to know when you have sex. So it's important for MSM to know, are we going to have sex then we can prepare either our package of what we need to take or a condom, pre-exposure, any other things that you may need for your sexual events and get on with it. Now here, this data shows us that the far majority or 70 percent of the men actually prepare their sex in our cohort. Meaning they make some arrangement, intentional arrangements to get their sex and they go out to get it. In that sense, they can also take the pre-exposure dose. In 70 percent of these cases in this cohort, people plan their sex and can take their pre-exposure dose if they want to.

Now, the problem is that those who do not plan, so the other 30 percent, are the ones at the highest risk. If you looked at the risk factors for not planning, we see that younger age, lower education, not identifying as homosexual, receptive anal intercourse, are risk factors for not planning. So here we are with a problem, an excellent challenge, that the ones who do not plan will have a problem taking their pre-exposure dose are also the ones with the highest risk for HIV infection. That's an excellent challenge that you have to face when we start implementing these programs.

The next generation of studies will be comparing continuous versus intermittent PrEP. I think that will happen if iPrEx shows efficacy there will be a move towards seeing

that we get regimens that are cheaper, involve less drug, less burden, and can be implemented on a wider scale. So, we have to see, we have to wait for iPrEx to come out, but I think that's the direction where we're going.

One of these studies is HVTN 067 or the ADAPT study, Alternative Dosing to Augment Pill Taking study. It's a three-armed phase two study looking at daily versus pre/post exposure dosing as well as standard dosing two times a week plus a post-exposure dose. So it's comparing continuous versus intermittent and looking at adherence and coverage, pharmacokinetics and risk behavior in these three arms. It's not a study of efficacy and hopefully it will start by the end of the year the beginning of next year.

This data that I'm going to show you now is coming from Kenya and it was reported here on Monday. In Kenya at that site, I thank Dr. Eduard Sanders and my friends from IAVI-Kemri for giving me this slide. They looked at adherence by MEMS caps, an electronic device that registered the times when pills were taken out of the bottle and self-reports. Men were asked, men and women, there's a few female sex workers in this group, men and women were asked to take two doses, Monday and Friday, and a post-exposure dose. Now, the MEMS caps actually show that adherence here, you can see here, the overall adherence is 68 percent for the standing doses as well as the post-exposure dose.

For the fixed doses, the adherence is 55 percent and for the post-coital or the post-exposure dose, the adherence according to the MEMS caps, if I understand the study correctly here, is 26 percent. So the adherence is pretty poor. Now this is a small study and I do not know what all this data means. There is qualitative data, collected here and it all needs to be sorted out but it doesn't look very good.

It looks very good when people are self-reporting because more than 100 percent reported that they had taken the post-exposure dose in time so that's fantastic. It's even better than we may reasonably expect. It just shows you the challenges and the problems that are ahead of us when we start to implement these regimens on a larger scale.

In the shadow of CAPRISA, we still have to work now in the shadow of oral one percent TDF gel. This slide was given to me by Dr. Ian McGowan and it shows you the oral application as well as the topical application and the maximum representation in blood and tissue is in the middle. It may be that in the next studies that we're going to do are going to see that there will be a combination of both topical as well as oral formulations of tenofovir and that may maximize maybe the presence of the drug in the areas of transmission and maybe the most efficacious. I think that's where we are going.

Particularly here is important the CHARM program which is directed by Dr. McGowan at the University of Pittsburg and

that is actually specifically directed to evaluate retromicrobicides among others for MSM. Not only MSM, also for heterosexual women but also for MSM. You're looking to, through this consortium, to produce or to give us the results in the next future that we are all waiting for.

So a number of rectal studies that, in phase one, that have been conducted or ongoing, the number is small and there's more studies that are being planned, particularly with the formulations here with the tenofovir, UC-781 or combinations thereof. That's in the pipeline coming.

For the phase two studies, what would we want to do? We have phase one information, supposedly the safety, everything's okay, we move to phase two. We would look at receptive anal intercourse, to protect men and women, high-risk populations. We move to phase two-B, we would need to have sufficient incidence and we can find that incidence in certain sites in North America, Latin America and Asia-Pacific, in Thailand as well as in South Africa.

Just want to mention a study that we are planning. Antimicrobials trial network 017 is a phase two multi-site randomized cross-over design of oral single, topical rectal and a combination thereof or a rectal application of tenofovir. We didn't plan this study after CAPRISA came out; we were already working on this for several months prior to that we knew that the vaginal application of tenofovir would give that fantastic

protection in women. Possibly, if it all works out, we may roll this over into a phase two-B or phase three efficacy trial.

This is not going to be tomorrow that we'll have these results for the phase two it's probably 2013 that this will be completed, then we may move to phase two-B, phase three. Before that's completed is 2016 before it's being out there for review to 2017, 2018. If we're very, very lucky we may have something that we could use in phase four. So we're really talking about 10 years at least before we're there to have rectal microbicide that can go into the phase four. And then everything needs to work in our advantage so let's pray for that.

ART is prevention, last part, and there's two components, the test and link and the test and treat that are important here. In fact, they don't differ that much. This slide I received from Dr. Masteroff of Family Health International. It shows you how this works. People get tested. If they're found positive they're being counseled for safe sex. They are enrolled in care, linked, or they're immediately given antiretrovirals. Either when it's indicated or immediately, that's the test and treat, or when indicated that's the test and link. That lowers the viral load and that will decrease then the HIV transmission.

So the rationale? I'm almost finished. The rationale is lower viral loads reduces transmission, antiretroviral treatment reduces viral loads, so treatment reduces transmission. Dr. Myron Cohen will review this for us later during this session. However, we do not have any transmission studies in this current MSM couples.

So the impact of treating the HIV infected partner on the transmission in MSM has not been evaluated. Those data are not available. Nevertheless, these ideas, they're now being implemented on a large scale around the world but the supporting data is not there. We need that data and I understand from one of my colleagues in Sydney, Dr. Andrew Grulich, that they are planning to do a 350 discordant couples' study and look at these issues to see if we can find the supporting evidence.

In the meantime, San Francisco in April this year issued the San Francisco guidelines offering treatment to all HIV positives regarding of CD4 and viral load. In San Francisco they have found a strong association between the mean community viral load and reduction of newly identified cases or reported cases from 2004 to 2008; 798 in 2004 to 434 in 2008 so this is an ecological study. It's not a causal study but it's a study supporting the idea that bringing down community viral load will reduce the number of new infections in the community. San Francisco is a very special situation where they have good

surveillance data as well as access to antiretrovirals for everybody.

These are some of the slides. You can see this in the report written by Das [misspelled?] in the *PLUS Medicine*. It's published in *PLUS* so you can go there to see these very nice slides you see. This shows the mean viral load per district, per census district in San Francisco and you can see the poorer areas of the city have higher mean viral loads than the more affluent districts like Castro and Noe Valley where more affluent people live, also more MSM live and they have lower mean viral load.

This is total viral load and this is the effect what I talked about. You see here the decrease in the viral load, the gray bars, and then here in the red line it blocks the decrease in the number of new reported cases and here the decrease in the estimated HIV incidence according to the CDC detuned assay.

There's always challenges. I don't want to go away here with you thinking well that's all very nice and we're almost there. There will always be many, many challenges and there is a number here that I'm listing. I'm not going to go through them; I'm just going to tell you there will be a lot of obstacles, there will be a lot of problems and we're far from there yet.

In conclusion, PEP, what I talked about in the beginning, is not ready for programmatic implementation but can

work on an individual basis. Daily PrEP results are expected soon and if there's efficacy the studies will try to identify regimens that are non-inferior but cheaper and have less drug and pill burden. Those are the next steps. If there is efficacy for daily, there will be many implementation issues and I cannot touch up on them all here right now but I'll tell you there will be many, many issues that need to be resolved.

Rectal PrEP, obviously we're all very happy and positive with the CAPRISA results but the rectum is really another compartment and the male rectum, or the MSM rectum is another compartment than the female one and there's other things going on so that needs to be investigated thoroughly and that's going to take a lot of time. We're not there yet.

ART for prevention: Reasonable. We have ecological evidence but we do not have any supporting studies, transmission studies in MSM and those studies are needed. I'm going to stop here, I believe. I'd like to thank all the people that have supplied me with their slides to give you this overview and there's a disclaimer and I'm finally, I'm finished. [Applause.]

HELEN REES: Because of time, we won't take questions now but I'm sure there quite a lot of questions generated but because the talks all speak so well to each other, if we don't have time after a speaker hopefully we'll have some time at the

end for picking up on any speaker that you'd like to ask a question to.

It gives me great pleasure to introduce our next speaker, Dr. Julio Montaner who is I think probably known, I hope, to everybody here. He is professor chair in AIDS research and head of division of AIDS Faculty of Medicine, University of British Columbia where he's also the director of the British Columbia Center for Excellence in HIV/AIDS and St. Paul's Hospital in Vancouver, British Columbia. He's the current president of the International AIDS Society and he's the co-chair of this very exciting Vienna International AIDS Conference. We're looking forward to hearing from you. Thank you. [Applause.]

JULIO MONTANER: Thank you, Helen. I'm going to update you on the now-published results of the paper entitled *Association of Highly Active Antiretroviral Therapy Coverage, Population Viral Load and Yearly New HIV Diagnoses in British Columbia, Canada: A Population-based Study.* I would like to thank this opportunity to thank, first and foremost, Providence Health Care in British Columbia, the Minister of Health in British Columbia which generously supported all this work, as well as the National Agency of Drug Abuse in the United States which also partially funded the study.

Industry partners included Merck, Viva, and Gilead. The authors for this work include myself, Vivian Lima, Rolando

Barrios, Benita Yip, Evan Wood, Thomas Kerr, Kate Shannon, Richard Harrigan, Robert Hogg, Patricia Daily and Perry Kendall.

As you know, we have abundant evidence that antiretroviral therapy is prevention. We have definitive data indicating that you can stop HIV transmission quite effectively in the mother-to-child transmission setting or the parental transmission setting as we probably should be referring to it. In that setting, the efficacy of this intervention is such that the United Nations AIDS program has called for the elimination of vertical transmission which is something that is long overdue.

There is some data which is actually quite compelling from those original studies regarding the role of antiretroviral therapy in heterosexual, [inaudible] couples. In particular, a recent study funded by the Bill and Melinda Gates Foundation, which nicely illustrated that this arrangement can be as effective as in excess of 90 percent reduction of HIV transmission. We have previously published a cohort study where we looked at the community viral load effect on antiretroviral therapy in the British Medical Journal a year ago and we elegantly demonstrated that by intervening with that antiretroviral therapy in injection drug usage you decrease the viral load and HIV incidents and please note that I am using the word incidents here because in the rest of the paper I'm

going to discuss HIV diagnoses per year which is not exactly the same thing. In HIV incidents, measurements which show that the incidents in IDUs decreased quite substantially.

Mathematical models have been put forward by our group, and a number of others, most notably Rueben Granich, however mathematical models and therefore, there has been quite a bit of controversy regarding various estimates that have been used.

For that reason I think it's quite nice that we can show you real populational data of what happens as we expand into retroviral therapy coverage in British Columbia.

There are several unique study features that I would like to highlight for you. The first one is that this is a true population based study. The limits, the borders of this study are the borders of the province of British Columbia. So every person living in the province of British Columbia who was HIV infected with a non diagnosis of HIV is counted here. Each, for all intents and purposes, an ITT type of analysis. The second thing is that Canada having universal health care system has free access to heart and medical monitoring and everything else that goes with it.

That I am perfectly clear, the province of British Columbia is unique in the sense that there are no copayments, there are no restrictions, there are no deductibles. When I say free access to care, it means 100-percent free. The other thing that is unique in British Columbia is that we have one

center that is responsible for drug acquisition, drug distribution and dispensation throughout the province and data captured, therefore is complete.

We also have a full data capture for viral load because there is one single reference laboratory that does all of the viral loads. All of that is in our center. In addition, we have a fairly comprehensive program of the BC CDC that has kindly given access to us to monitoring blood borne diagnoses and I'll refer to that further.

I want to highlight also that this study composes two distinct faces, in fact there are three faces, but from the mythological perspective the first is a retrospective analysis that took place after the first rollout into retroviral therapy and the second one was a prospective phase which I will refer to in a moment.

Going into the phases of the study, as you all well know, highly active retroviral therapy basically was established at the Vancouver Conference in 1996. The summer of 1996, as we were involved in the conference, and in one of the people at the clinical trials that led to the establishment of ART we had a tip and therefore, on December of 1996, we were already rolling out into retroviral therapy.

The first line that you see here, on the blue, shows you the uptake of antiretroviral therapy in British Columbia.

This is the so called Incas [misspelled?] trial, very small little blip there, but this is the first rollout.

In the summer of 1999 we had a stabilization of the use of antiretroviral therapy, you remember those days, the tension between initiating therapy and stopping treatment and STIs and so on and so forth, so all of this is driven by the guidelines. The first phase starts in 2004, that's concomitant with the first recommendation by the National Aids Society, USA guidelines that advised against treatment interruptions.

Of course the recommendation became very forceful, eventually, but if you look back we were already talking about it at that time. With the support of the government, therefore and with the notion that the treatment was good for the people infected with HIV. Good for the people in terms of public health and good for the public purse we were able to convince the government to allow us to move forward aggressively with the antiretroviral therapy rollout.

You have a unique situation because we have Phase I - Rapid Rollout, Phase II – Steady State, and then a prospective and purposeful expansion of antiretroviral therapy on Phase III so these are three different phases.

I am not going to bore you with this slide. This can be read in the paper, it's important to acknowledge the fact that the viral load asset has changed over time, and therefore, in order to simplify analysis we truncated the lower limit of the

viral load essay at 500 copies per mL. It doesn't really matter how you cut the analysis, all of the analysis basically gives the same results.

Before I show you the data that is in the paper, I'd like to dispel the notion that expansion of antiretroviral therapy invariably leads to increased resistance. This is real data from a real program at a populational level. What it shows here that between 1995 and 2010 we have expanded antiretroviral therapy as I showed on the earlier slide. On the blue line below now using 50 copies as the metric you see that we have increased the effectiveness, this is populational effectiveness of antiretroviral therapy rather dramatically so that we are operating almost at the 90-percent at a populational level.

That includes all comers, second line, third line, whatever line of antiretroviral therapy you want to count. The incidents on a yearly basis of HIV resistance, all of the resistance in the province of British Columbia gets done through our program by Richard Harrigan and so you have here, it is has decreased. Please note that this is a semi-locked scale so we have decreased HIV resistance by 90-percent.

Let's walk to the lines of paper from this week, this is now the first phase of the expansion of antiretroviral therapy, the blue line shows the number of people engaged in antiretroviral therapy, you see the new diagnosis for HIV which

were stable, prior to 1996, decreased significantly after the rollout of antiretroviral therapy. As we reached steady state for antiretroviral therapy coverage, you see that the new diagnoses are on a steady state, and on the Third Phase, as we expand antiretroviral therapy on the blue, you see that new cases are declining.

The slope of the uptake of antiretroviral therapy coverage was significantly steeper in the first rollout. Mathematical modeling done by Viviane Dias Lima and published in the JID a couple of years ago showed actually, almost predicted these results. Again, emphasizing that the speed at which you rollout antiretroviral therapy will have a dramatic impact on the valuable of interests in this case, namely new diagnoses.

We have a special interest in this work regarding hard to reach populations and I will show you here in the green the fact that for the first decade if you want, of antiretroviral therapy we did not have much luck in terms of decreasing new diagnoses of HIV among intravenous drug users. However, in the last three years of the effort, in negotiation with the province, and the Vancouver Health Authority responsible for the care of those most affected by injection drug use we devised several innovative programs outreach targeting intravenous drug users and, as a result of that, quite nicely you can see a 50-percent decrease, five serial is 50-percent decrease in new HIV diagnosis among IDUs since 2007.

In order to estimate what the impact that this is having in our community, Bob Hog actually did these graphics for us, where you look at taking the baseline data points and then you estimate what would happen if things remain stable using demographic variables, and so you expect that the epidemic would remain stable at the following rate.

This is actually what we saw, you can use that line as your baseline if you want, or a new baseline down here so there is no significant decrease in HIV new diagnoses in the second phase, and there is again a significant decrease in the Third Phase all over again.

The last time that Myron Cohen saw these results he wanted to see the CD4 data, so this is dedicated to Myron, that we go, I'm sure he's going to have a couple of requests for the next time I present this, but here you have the frequency distribution of CD4 counts expressed in bars showing in the early days of antiretroviral therapy on this first bars, you see a large number of patients with relatively high CD4s as you know, the guidelines evolve, things change.

We became more conservative so that's illustrated here, the median CD4 decline but as you see here there has been a statistically significant increase in the CD4 counts as a result of this steady expansion. Notice that there is still a lot of room, but nonetheless the CD4 count is going up.

This is the actual table regarding bottle loads and put in here basically for transparency purposes and just to give you the sense that it doesn't matter how we look at it, 500 copies, 50 copies, IDUs, non IDUs, at the end of the day the results there look the same. If you will allow me I'll just show you the bars using one particular analysis.

This is the population, plasma, viral load using percent of individuals less than 500 copies, and what you can see is that we had a very nice effect early on on the yellow which is predominantly MSM in our population, suggesting that most of the benefit for the MSM community in BC occurred early in this regard.

We had a relatively smaller effect on the IDU community but, on the other hand we had a greater catchup effect, if you want in the IDU community later on and that explains the sort of the balancing act between these two communities in terms of the preventive effect of the intervention.

We can use this data multiple ways and a lot of the work is still ongoing. We can stratify them, look at frequency distributions within each one of the cells, and in this case I'm trying to illustrate for you the fact that for the non IDU, although the cases are growing, they're growing largely at the expense of the soft blue here which represents individuals who haven't detective of viral loads.

Now please do remember that this is the people that know they have HIV infection. They are approximately 25-percent of HIV infected individuals in the province of British Columbia that are not aware they are HIV infected and therefore our next phase of expansion is aiming to get better at finding those cases.

The sick as we call it, sick and treat will have a stronger component of sick which is an area that we could do better. The IDUs, as you can see, not much was happening here, but things are getting better, there is a larger proportion of undetectables. In order to give you a sense of how much more improvement we can extract out of expanding antiretroviral therapy and when people who need HIV treatment and I emphasize this is within people who meet guidelines for treatment.

These individuals are all characterized, they're all engaged, and they're all suitable for accessing therapy based on the most recent International Aids Society USA Guidelines that were presented at this conference and now published in JAMA earlier this week, and so we feel that this is some of the low hanging fruit if you want, from that perspective, these people are already identified and we need to go and engage with them in the discussion of whether or not they want to take treatment for their own benefit, and ultimately for public health benefit.

Then there is a more difficult challenge which is to find the 25-percent that is not showing in these graphs and that's where our efforts should go next. Couple things that you need to know, we're finding less HIV diagnoses, not because we're testing less, but we're testing more.

Less cases on the face of more testing, that's a very good background in which we can make these claims. Within regards to other behaviors, these being population study, I don't have an actual survey that I can tell you who is doing what and with whom, but I do have data, province wide for Hepatitis C, infectious syphilis, this is the way they report it, genital Chlamydia and gonorrhea.

I put there Canada data in addition to BC so that I had to accept the fact that Canada, BC is not doing as well as Canada, whereas with Hepatitis C and syphilis, although a little bit better in gonorrhea, but nonetheless what you see here is that the trends are actually not suggestive that they have been dramatic changes in behavior in our community.

Key findings of our study, well, we found a strong correlation between the number of patients on ART and the number of new HIV cases diagnosed per year. For every 100 additional patients on ART, the number of new HIV cases decreased by a factor of 0.97. If you want me to put that in English, or Spanish for that matter, it would be equivalent to a decrease on new HIV diagnoses by 3-percent.

For every one logged in, decreasing viral load the number of new HIV cases decreased by a factor of 0.86, I'll just skip that except to say that we are the delighted to know that Michelle Bachelet has put forward the so called Prevention Revolution at this conference embracing fully these notions and his treatment 2.0 initiative. Thank you.

HELEN REES: We'll take a couple of questions now. If you'd like to introduce yourself.

ANDREW GRULICK: Andrew Grulick [misspelled?] from Sydney, in Australia. Bernard Herschel in his nice review of treatment as prevention in the plenary this morning said "Just because A follows B doesn't mean that B caused A", and that's a particularly possible explanation in an ecological study such as this one.

The immediate other explanation that I can think of that is injecting drug users mainly transmit blood through contaminated syringes and, in my understanding in response to an outbreak in Vancouver in the early 90s there was a very large rollout of harm reduction activities in the 1990s. Isn't that at least an equally plausible explanation for the trends that you're seeing?

JULIO MONTANER: Right, so two things. First, this is not just one ecological study. There are two subsequent phases of rollout antiretroviral therapy that elevates the evidence, at least a little bit.

Number two, this is not the only piece of evidence. We have the recent Gates funded study and so on, and so forth. We're not just basing these claims on one particular study.

Number three is that we use Hepatitis C, syphilis and gonorrhea to actually act as surrogates for background behavior issues, so what I can tell you is that our province has been very liberal in terms of needle exchange all along, and yet Hepatitis C remains very high and HIV did not drop early, actually it dropped over the last three years when there has been no change on needle exchange or other such harm reduction practices.

HELEN REES: If you could, we'll just take these two questions, if you could make them as brief as possible.

BOB GRANT: Bob Grant, San Francisco. The other inter current process that is happening in many cities is zero positive, zero additive behaviors. The preference for zero positives to have unprotected sex, mainly with others who are positives.

This has been noted in both San Francisco and Seattle, and I imagine in British Columbia it's happening as well, and

you know, by some estimates could account for a large decrease in the incidents of new infections to uninfected people. Do you have data on zero sorting in British Columbia?

JULIO MONTANER: Yes, we had looked at zero sorting and I cannot quote a number for you. There is zero sorting going on in BC but obviously it's not working very well because the actual fact is that MSMs, and I think I tried to make that point, in the latter years, the effect of ART predates zero sorting on the non IDUs, most of the effect that we show in the third phase that would be, the second phase of the expansion, is driven by the IDUs who don't do any zero sorting.

HELEN REES: Last question please?

ROBERT REMUS: Robert Remus from University of Toronto. You show the ecological associations between uptake of therapy and, at least a decreasing reported HIV cases which is problematic as a surrogate for incidents.

I don't, one of your slides showed incidents, but we really didn't want to translate it into incidents, but my main point here is that what you really want to look at is the reservoir of infected but untreated which is really the driving force for this transmission, not the number of people you treat, but rather the number of people who are still untreated.

I suggest that, and that would obviously have to be modeled, but I suggest that you add that curve to your slide. I think it would add some weight to see the actual diminishing reservoir of people who are potentially sources of infection, and of course most transmissions are among people who are undiagnosed, are not on treatment.

I think that would add to your argument.

JULIO MONTANER: Thank you Robert. Yes, the, talking to our public health people, they feel that the proportion of people who are undiagnosed HIV infected in the province has remained relatively stable, but we intend to do that. That's a good idea.

HELEN REES: Thank you very much. Just now.

TEGUEST GUERMA: Just now, Professor Geoffrey Garnett, with the Professor in my Microparasite Epidemiology at Imperial College, London his many years of research as epidemiology and culture of sexually transmitted infections, he's the chair of the UNAIDS Epidemiology Reference Group for estimates, models and protection and he has played a part in the developing the methods used in HIV surveillance globally. He will be doing a presentation on modeling potential synergies of PrEP and ART for prevention.

GEOFFREY GARNETT: Thank you, so yes, I'll be doing a presentation on modeling the potential synergies. To model the synergies we have to understand how they work on their own, so I'm going to be looking at the impact of ART in reducing HIV transmission both through treatment of those HIV positive using pre-exposure prophylaxis, and then looking at the combination of the two.

At first I'm going to focus on looking at the potential impact of increased treatment coverage with our previous guidelines and our current guidelines just looking at what would happen if we could reach the people that we currently deem to be in need treatment.

Then I'm going to be looking at some hypothetical examples of the way pre-exposure prophylaxis might work within populations, and then ask the question "When should we be using treatment of positives to prevent transmission and when we should be using treatment of negatives to prevent transmission?"

The way I've approached this problem is, instead of trying to say what's the best model for the spread of the infection with treatment preventing infection, the approach is to ask questions. What factors could reduce the effect of treatment having an impact on prevention, including those factors in our models to try and understand that the limits to what we could achieve through treatment.

There are a number of things that would prevent treatment having an impact on the spread of the infection. The first is if we have really rapid spread of the infection, so by the time we get to people on treatment, the infection's already spread through the population so we're too late.

That's, we're no longer in that situation, the epidemic's been going on for a long time. Next we can think about patterns of contacts of those that are HIV infected. If the contacts decrease as a function of time since infection, then treatment of people later on in that infection has less impact.

There are three ways that that can happen. One is concurrency. Concurrent sexual partnerships lead for explosive spread with primary viremia, leaving less for the later stages of infection. Another is if people have high risk behavior for a while then reduce their sexual activity, and the third, which we haven't got round to modeling yet, is if we have people who only have protected sex with people of a similar age as them, and as they age, their activity decreases.

There's still a little bit of work to do, but I'm going to show you results for the first two adding in concurrency to our models and people reducing their partner numbers over time. The other things that would impact on the success of treatment is poor adherence, poor suppression of viral load, treatment fairly earlier and the evolution of resistance and I'm sure

you're well familiar of the potential for those to reduce the reduction in transmissibility that's achieved by putting people on treatment.

An area that hasn't had much focus is, what rate do people progress to low CD4 counts, and we have contradictory evidence from Sub-Saharan Africa, we've got ART link studies which suggest quite a rapid progress to CD4 counts less than 350, but then some modelers have compared the [inaudible] of CD4 counts in HIV infecteds within populations, for example Kenya, an estimated a lower decline in CD4 counts.

I'll show results for both of those. What I won't show results for is changes in risk behavior, because I think that's fairly obvious, if there's an increase in risk behavior, HIV spread will increase, if there's a decrease in risk behavior, the HIV spread will decrease, so I'm not going to focus on that.

I'm going to be showing results of a model that's being developed by Jeff Eaton and it's, the basis of this model is published in, was in press in AIDS and behavior, and it's really based on a model presented quite a while ago by Miriam Cratchmeyer [misspelled?] and Martina Morris that we replicated and then have developed further.

It's a transmission model and I'm going to be looking at generalized heterosexual epidemic including concurrency in sexual partnerships, heterogeneity in rates of partner change,

so both concurrency and heterogeneity in partner numbers. Transmission risk within partnerships is a function of time sense infection and then this movement for, of people over time from high activity to lower activity groups, and it's a stochastic model so there are repeated runs for a particular population.

What we're putting into the model in terms of parameters, this is an analysis of, it's a reanalysis of a reanalysis of data from the Ranchi and from the Partners In Prevention Study so a recent paper by O'Donnell, where we've estimated the transmission rate per 100 person years of contact, assuming a stable rate of contact within partnerships of those in the primary infection, when CD4 counts are above 350, between 350 and 200, and then below 200.

What we estimate from this observed data is that there's obviously a very high transmission risk in primary viremia which Myron Cohen will talk about, then drops down to a low level for quite a long period, and then starts to rise up as people's CD4 counts decrease.

We have a bathtub type shape where we get higher transmission early on, and late on in the infection. The length of this high CD4 count, when it's above 350, in this graph is taken from the ART link study, but as I said there are other estimates that this is longer. What happens if I'm an HIV infected individual and I'm infecting other people,

cumulatively over my infection, what fraction of those that I will infect, infected at particular stages. On this axis we hae time sense infection, on this axis the proportion of HIV transmissions that take place, and at first nearly a third of my infections take place.

It then stabilizes and I get very low levels of infections and then it accelerates as my CD4 count falls below 200. We can put that in the model, and this is what we get for the different stages of infection, that impact on the proportion of transmission that comes from that stage. We start off early with many infections coming from the primary viremia, fewer infections coming from later on, and it stays, that those with CD4 counts under 100 contribute very little to the epidemic and we're assuming they have lower risk behaviors, but over time the contribution of those between 100 and 200 and between 200 and 350 increases.

This is without treatment in the model, and the contribution according to stage of infection shifts as people move out of the risk group. If people move from high risk to low risk, then more of their infections are transmitted early on in their infection, when they're still high risk. We can then look at the model with incidents over time with the introduction of treatment.

What we're doing is we're assuming different starting points for treatment, getting to 80-percent coverage by the

time people would have died but starting at different points with a constant rate of uptake and this shows you the results when there is a high rate of movement from the high risk group to the low risk group. Here the treatment of those under 100 CD4 count has little impact, treatment of those with less than 200 reduces incidents by about 25-percent, and there's a further 15-percent reduction with a CD4 count less than 350.

To look at that, in another way, I've put it over here, time since the introduction of retroviral treatment with different starting eligibilities, and we see that starting 80-percent of the population with an initiation time of 200 can have a big impact on the spread of infection with about 25, 30-percent reduction in incidents, that's increased by starting people at CD4 counts of around 350 to give us a reduction of around 40-percent.

We can explore what parameters change this. This is that fairly short period to CD4 count of less than 350. If we increase the length of time that people are in the asymptomatic period with a CD4 count greater than 350, then that reduces the effect of the later treatment because more of the transmissions going before people enter treatment, and here with the CD4 counts of less than 350, we're getting about a 30, 33-percent reduction in incidents due to the treatment in the model.

If we look at a totally different epidemic, one that isn't driven by concurrency in a generalized population but one

that's driven by a small high risk group, in this case we're trying to represent sex workers of about 2-percent of the population which achieves a prevalence of 1-1/2-percent, the results are a little less stable, but again, we do get a fairly big impact of the treatment on the incidents of infection. Here people leaving the high risk groups become low risk has more of an effect. So the more people change their risk behavior, the more that reduces the impact of the treatment which is a result we would expect.

So our mobiles are backing up the arguments that putting people on treatment can have an impact on the spread of HIV and quite a substantial impact. Then moving pre-exposure prophylaxis, here we're developing models representing different regions of the world.

And the first model we were working on was for West Africa where we have a detailed representation of patterns of use of the pre-exposure prophylaxis and here we're talking daily pre-exposure prophylaxis looking at it in combination with other interventions in a model, which includes sex workers and regular clients and the general population taking data from Benin to parameterize the model where we have movement between the different populations, the sex workers and the women.

And we've taken a couple of scenarios. One if optimistic that we would get adherence, that we'd have a long duration of use of the pre-exposure prophylaxis and a high

could reach quickly. One's a more realistic assumption where we get good, 50-percent and good adherence five years duration on pre-exposure prophylaxis and it takes us five years to reach that. And this graph shows the relationship between efficacy on the x-axis, coverage of your pre-exposure prophylaxis and your susceptible on the y-axis and then different levels of reduction and infection. So the blue line is 5-percent infections averted, the red line is 10-percent reduction infections averted and between those lines we have a five to 10-percent reduction in infections averted and we can choose an efficacy.

So if for example our PrEP has a 80-percent efficacy and we manage to get 30-percent coverage, we do expect to prevent about 15-percent of our cases of infection. That's a lot of people on pre-exposure prophylaxis and it's quite optimistic with the efficacy. If we are realistic, again with a high efficacy but poorer adherence and longer time to get up to coverage, we get even fewer infections prevented with our 80-percent efficacy and 30-percent coverage.

But that's using the pre-exposure prophylaxis in all susceptibles. If we can target those at high risk, then we can increase our benefits and so this analysis just assumes that 10-percent of the population are using PrEP but compares the number of infections averted when that's used across all the population and with a situation where most of it, nearly 100-

percent is used in with the high risk of acquiring infection and suddenly you make your PrEP more effective and efficient by targeting those at highest risk.

So we need to be thinking if do develop PrEP, how are we going to target and get a high uptake in those most at need. And we can look at the interaction between pre-exposure prophylaxis targeted with other interventions and see that it does add to armory of prevention interventions. The missing piece might be a vaccine that we would want to add or some other new technology.

So what we're doing by developing these multiple tools is we're identifying different ways of intervening, adding them together we can a bigger and bigger effect on the HIV epidemic. Just want to talk a little bit about treatment of those who are infected to prevent transmission versus treatment of susceptible and I'll try and be quick.

What happens is if you look at in a population those that are susceptible to infection, those that have a stable partner and those that are zero discordant, there's not that many. They're an important part of the population for HIV transmission. So it's not that many people to be looking after with the pre-exposure prophylaxis, but their role goes down as we increase the CD4 counts at which we initiate treatment. The more people we're putting on treatment who are positive, the fewer susceptibles are exposed to HIV positives who haven't got

suppressed viral loads because of treatment and so that just illustrates this change. Where the change from CD4 counts greater than 200 to greater than 350 we get a reduction in the percentage of discordant couples that could benefit from pre-exposure prophylaxis.

And we can start to think if you had a discordant couple, would you be better to treat the positive to prevent infection or would you better to treat the susceptible to prevent infection and if we compare the efficacy of pre-exposure prophylaxis on this axis and the cumulative risk of infection on this axis where we have ART initiation at 350, we get a stable reduction in incidents of HIV and as we increase the efficacy of PrEP, we get a bigger benefit from putting the susceptible on the pre-exposure prophylaxis than treating the HIV infected individuals.

This is comparing immediate antiretroviral treatment initiation with PrEP where again if we just put the HIV person on the treatment being fairly pessimistic or fairly optimistic where you have an 85-percent reduction in risk in those who are on the treatment. So Mike and Julio can fight over whether that's pessimistic or optimistic, but what happens is it's only pre-exposure prophylaxis is really highly efficacious, will it do better than the antiretroviral treatment to prevent the transmission within the couple.

What we haven't done yet with this analysis is put the actual costs both in terms of toxicities and also dollars cost of providing the drugs. So I'll stop there. Just a few conclusions, good coverage of both with CD4 counts less than 200 we believe could avert around 25-percent of new infections and you add a further 15-percent with CD4 counts less than 350 in generalized HIV epidemics and sub-Saharan Africa.

Reductions in risk behavior associated with treatment would improve this and that was included in the models published by the WHO in the lands that are targeting for immediate treatment. An increase in risk behavior which I think we have seen in some Western European countries would undermine it. Pre-exposure prophylaxis can reduce incidents but needs high efficacy, high coverage and high adherence and appropriate targeting to be efficient so there's a lot of work to be done if we're going to use pre-exposure prophylaxis as a tool.

And earlier treatment reduces the role of pre-exposure prophylaxis and then you have to consider the relative efficacy of the two interventions. Thank you [applause].

TEQUEST GUERMA: The next presenter is Myron Cohen. Myron is at J. Herbert, very distinguished professor of medicine, microbiology, immunology and public health at the University of North Carolina. He's also the Associate Vice Chancellor for Medical Affairs Global Health and he's the

Director of the University of North Carolina Division of Infectious Disease and the UNC Institute for Global Health and Infectious Disease as well as the Associate Director of the University of Carolina Center of aid research. You have the floor.

MYRON COHEN: Good afternoon. As the last speaker you guys are tired from listening and time runs out, but I talk so fast that this talk is almost over already. This is considered half done. I'll use slides as you might expect and we've already concluded that antiviral therapy can be used for post-exposure prophylaxis, pre-exposure prophylaxis and treatment as prevention. I'm going to focus on treatment as prevention.

Now because I think it's important to give a summary I'm showing a slide, a disclaimer because Julio and I will undoubtedly get in a fight eventually about this. I've been a big advocate of antiviral therapy as treatment as prevention for a very long time through a series of studies, but in our 1997 paper, we concluded the details really matter and so what I hope to do in 15 minutes is provide the details.

So the first is the biological plausibility. This is really important. The drugs you choose matter for prevention so the treatment benefits are very profound and have been explosive and wonderful. We're not 100-percent sure which drugs to use for prevention. This is a summary from my colleague Angela Pashuba [misspelled?] and her group and when

she looks at the concentrations antivirals in the female general tract, we've done the male as well, comparing blood to female secretions and what I want to emphasize here is that not all the drugs actually concentrate in the female secretions.

Some, especially the proteus inhibitors have trouble getting in. That's a special problem in terms of the selection of drugs as we do treatment for prevention in general. Chris Patterson and the group is providing a late breaking abstract tomorrow about truvata [misspelled?] concentrations with interruptive drugs and Raltegravir we've been studying intensely as well as mereveroc [misspelled?] recently.

So this to us is really important and I think the importance of the pharmacology can be emphasized by the fact that when you suppress the blood viral load, and everyone wants to show blood viral load data, you don't suppress the genital tract. So if you look at a meta-analysis by William Brown in our group there are 422 articles about female shedding and 707 abstracts. 18 of these articles have ART in use and they demonstrate poor suppression of the genital tract in the face of complete blood suppression.

Susan Cu-Uvin from Brown has a paper coming out on AIDS that I highly recommend to you studying 59 women and she demonstrates that some women are persistent shedders, they're blood suppressed but they're genital tract you can always

recover HIV and some are intermittent shedders. We see the same thing in men.

Now we're not sure what this means. We don't know how this occurs and we're not sure that the virus we recover, which is measured RNA is an infectious unit. Is that virus contagious? But that's really an important research topic for those of us interested in treatment as prevention. Now, people at this meeting have talked nonstop I think about observational discordant couples and I believe those area really important. W. Dunnell's paper in Atlanta got a lot of attention and I've heard that number, there's a 92-percent suppression of transmission in the face of antivirals over and over and over again.

I would remind you this is an observation study conducted over a very short period of time, so seven or eight or nine months but we're talking about lifelong therapy and partnerships that extend a very long time. So I'm excited about observational couple results, but I think it's important for us to kind of think a little more deeply about what they mean. I also want to emphasize a couple of papers. One hasn't been published by Patrick Sullivan at Emery in which he studied 2,900 couples for 512 days. See that this is a short study. He had 175 transmission events. Some of them on therapy, some not on therapy but the most important thing about this paper is

that four out of 175 transmission events occurred in couples in whom the index case was receiving therapy.

So what's important to us is how are we going to advise patients and physicians about how to manage patients on therapy. So we're looking for a very solid answer to the transmission probability question. There was an 80-percent reduction in Patrick's paper, not a 92-percent reduction. And now there's the really cautionary paper, and I hope you can — I'm going to slow down a little because this is important — our Chinese colleagues from the China CDC led by Wang Ning in a paper presented here tomorrow by Dr. Lio [misspelled?] but it's by Wang Lu studied 1,977 discordant couples in Henan between 2006 and 2008.

There were 84 zero conversion events and they were equally distributed among people on therapy and off therapy. Now, what does this mean? The Chinese have a free treatment program. Our colleague, Dr. Wu who directs the CDC is in the audience, they have an excellent free treatment program, but all programs are imperfect. The infrastructure's imperfect. But the point is, this is the real world so as we start dealing with treatment as prevention, we've got to pay a lot of attention to the things that don't work or aren't perfectly as well as the things that do work.

There can be lots of explanations for why this was imperfect. Most likely the patients were intermittently taking

their therapy, etcetera, etcetera, but it really attracts my attention. This has been accepted as a paper in JAIDS, it'll be published in September for those who are interested. Now, the NIH is supporting a very large study that's been heavily discussed called HBTNO52 and that study is designed to ask two questions, but little bit different than has been presented at this meeting.

The study's conducted in 12 sites in nine countries and the main question is, in 1,763 discordant couples already enrolled now in two and five year study, will we see durable — and I emphasize the word durable — prevention of transmission over five to seven years? We're looking for a number, it's not a population based study, it's not to inform the planet. It's to inform healthcare workers about what was observed under controlled trial conditions about prevention of ART. So that's the main purpose of the study. The study also has the advantage of giving us a little more information in an RCT setting of when to start ART. So we're excited about completing the study and as I said, it's fully enrolled in year two. We'll see how it goes.

Now, population benefit and modeling. Modeling, modeling, modeling, modeling — and no offense to my very good friend Geoff. You know there's going to be more models and people have pointed out what is important to this audience, assumptions provide the answer. Some models have said you tell

me what the answer you want and then I'll fill in the assumptions. So the assumptions provide the answers and I think the people in this audience need to be not skeptical, they need to provide the data that proves or disproves the assumptions because without the data proving or disproving assumptions, we cannot move this field forward.

Dr. Ruben Granich's article and Brian Williams is on the bottom. That's the universal kind of utopian treat everyone and this is going away, it's in green. But I've provided you not all the models because there's more than this. In the red, are all the models that say that treatment will make the epidemic worse. So depending on the assumptions, you can make the epidemic unchanged, you can make the epidemic go away or you can make the epidemic worse and I just think it's the job of the investigator to do this kind of work, to do modeling, but to generate data to support or refute the model hypotheses.

Now ecological studies, and if time's available I am 100-percent sure there's going to be a massive fight about ecological studies. Ecological studies that have shown a population level benefit have been completed by my friend Grant Colfax in San Francisco, already published by Julio in Lancet and a lady from Denmark presented a very nice paper in this meeting. Those are the successful ecological studies. Dr. Andrew Gruelich already stand up sees no benefit even though a

lot of ART is available in Australia. My colleagues in Amsterdam have seen no benefit and the French have to date not seen a benefit.

So ecological studies are complicated to interpret and you already saw people starting to attack Julio. It's just the beginning of the attack looking for a thing called the ecological fallacy. We even have a word for this. It's the assumption that the association is causation where if somebody else introduces an idea that reinvigorates your thinking. A very good example of this is Senegal's epidemic in 2000. In 2000, Senegal had about two or 3-percent HIV prevalence and that was ascribed to a wonderful public health program.

Ten years later, it's primarily ascribed to the fact that 97-percent of the men in Senegal are circumcised. Now, obviously it's multi-factorial but we need to be looking for other explanations of why we see things in the general population. Having said all this, this horse is out of the barn. This is the test and treat movement and it is a good movement. I think most people who want to see ART given at the right time to the right people at the right dose are very excited about this.

So what's the summary of the test and treat movement? We have an NIH supported pilot study by Max Essex in Botswana. We have a HPTN study in the United States being developed by El-Sadr and Ken Mayer. We have a population based study by the

British led by Sarah Fiddler and Richard Hayes called Pop ART expected to be conducted in Tanzania if it comes through.

We have a PTN concept for another trial and treatment seek and care if you want to call it by Tim Mastro and Sally Hodder. Susan Little is leading a trial in Kenya and we heard from Bernard Hirschel this morning about a study he and Francois are doing with ANRS. So we're going to see a lot of people try and introduce ART and see a population benefit prospectively that's exciting. My hesitation is we don't know how to measure population benefit very well and so we can do the introduction of the ART. We can see people taking the therapy, but we need better tools to measure a benefit and I'll leave you with that thought.

Now, there are two inconvenient truths and I'm going to end with my two inconvenient truths. Inconvenient truth one is about acute and early infection. This is not just a little tiny thing that you model away. This is the idea that the person who's recently acquired HIV has a greater transmission probability than a person with established HIV. This is a wonderful review paper by Andrew McMichael in Nature Medicine that shows you what we call Ramp UP Viremia [misspelled?] that lasts for several weeks with a very high peak viremia, hundreds of thousands, if not millions of copies.

My friends who work with monkeys have demonstrated led by Dr. Chris Miller that if you take a tiny little bit of

monkey serum from a monkey newly infected, that little bit of serum is maybe a thousand times more infectious than from a monkey with established infection. That's a virology issue. So acute infection has been modeled or been estimated to be at least 26 times more contagious than established infection. That may be the lower boundary. So people with acute infection can be very contagious.

Now, this is a summary of the 11 – there are 11 acute infection modeling exercises that have been undertaken. What I want to show you on this slide is if you look at the 11 studies you get all kinds of different results. The lower boundary of all these results is that acute infection is responsible for 9-percent of all new infections. The upper boundary is 90-percent. So these are all over the place.

Now, not to be hypocritical, let's do our own study that we model. Kimberly Powers – well we took a lot of data. Kimberly Powers in our group will present a late breaking abstract on Friday that I think is very compelling and in this abstract, she'll provide all of our data from Lilongwe, Malawi for 20 years where we took every acute infection we saw, what their viral loads were, what their behaviors were and we modeled that against the incidents and prevalence of HIV in Lilongwe, especially prevalence.

Now, this is the actual prevalence in Lilongwe, Malawi over a long period of time. This is from Kim's presentation.

You see that way up here you had 27-percent prevalence of HIV in Lilongwe. You see down here in more recent years, the prevalence has fallen to about 14-percent. I want to point out to you ART not started here. We don't know why the prevalence of HIV went down in Malawi. Behavioral changes, government interventions, the natural epidemic itself? But no ART was introduced and this again gets us at the ecology and what our computer data shows us is that we estimate that in Lilongwe, Malawi over time 38-percent of the new incident cases that occur, can be ascribed to acute infection.

So from this point of view, that's a lot of patients we would have difficulty finding to deal with or treat if we knew how to treat them. The upper boundary is almost 60-percent. The lower boundary is 19-percent. I would encourage you to go to hear this talk if you're interested in the contribution of acute infection.

Now, another piece of evidence about the importance of acute and early infection has been led by Canadians Lumma [misspelled?] and Mark Waynberg [misspelled?] in Montreal, Susan Little in San Diego and Art Colley [misspelled?], Cristoph [misspelled?] Hurt in Chapel Hill. These are studies that show acute to acute transmission. They show clusters of people all of whom have the same virus suggesting that these viruses were passed very rapidly forming a cluster.

Some of these clusters are very big, 60, 70 people and they can occur very quickly, that's the best way of saying it. So that's one issue. And these clusters usually use drug resistance to demonstrate the cluster. Now, Julio pointed out that for whatever reason they're doing great in Vancouver, but most of the rest of the planet is very concerned about transmitted drug resistance and most people find about 10-percent transmitted drug resistance and these clusters all are based on transmitted drug resistance.

Sally Blower, who's really the mother of a lot of these modeling experiments over the last 20 years, has this very cautionary model that I'll end with about drug resistance. What she argues is using Ruben Granich's model that if you only have 70-percent adherence of your daily dose of therapy, you'll end up with a very substantial amount of transmitted drug resistance because people will be imperfect in their therapy and their resistant variant will go the next person.

Now, a little disclaimer, resistant variants are probably less transmissible. Mark Wayneberg has done a lot of work in that area. So maybe the resistance problem, while you might see resistance in the next person, it won't be a substantial threat to the health of the next person. This is a thing we need to understand as we roll out the test and treat movement.

So I'll end then as quickly as I can on the last slide. I believe in 2010 that antiviral therapy has the power to reduce onward transmission of HIV but the magnitude and durability of this tool is unknown and it's really our responsibility to flesh this out as we go forward. I think the population benefit of antivirals will depend on one, can we durably suppress transmission from a person who's infected to the next person? What can we reliably tell them with data? That I think is important. Number two, can we prevent transmitted drug resistance? How are we going to do that so it doesn't threaten the use of our drugs.

And number three, how will we deal with the people with acute infection? This is a big challenge because although we're getting better and better tools, we don't know how to do this and I think as we roll out this movement, we need to deal with these issues. Thank you [applause].

HELEN REES: Thank you all for your presentations. We have five minutes for discussion. I'm sorry, so I can take two or three questions. So Renee.

RENEE RITZEN: Renee Ritzen [misspelled?] from Gays Foundation. I have a question for Dr. Cohen. You mentioned that we need some tools to measure population based impact. I was wondering if you could tell us what you think those most important tools are Mike.

MYRON COHEN: Okay. So the most important tools, this might be almost rhetorical because I think Renee knows my feelings about this, there are two tools that I think are really critical. One is a lot of the studies I showed you are planning on using phyla-genetics as kind of a surrogate for understanding how much prevention they're getting, avoiding clusters and the Max Essex' Study Susan Little's. The second thing that is the most critically important thing is the development of a reliable incidence test.

RENEE RITZEN: That's the correct answer.

MYRON COHEN: Thank you Renee [laughter]. The Gates Foundation is absolutely committed to the development of a reliable incidence test. People earlier this week might have heard a talk by Georgia Tamares [misspelled?]. She and the U.S. CDC are working together on a new test. The Gates Foundation is supporting research in this area. We will get a reliable incidence test.

HELEN REES: Thank you. Briefly, microphone number three.

KEN MAYER: Hi, Ken Mayer [misspelled?] of Fenway Health, Brown University. Excellent talk, Mike and the whole panel, superb. But it's sort of leaves people walking away with the idea just take the ART, add water, stir. So I think real plea that when we're talking about combination prevention with ART we have to think not only about adherence and not only

about behavioral disinhibition but linkage to care. There's a lot of presentations at this meeting that you can get people on the drugs, but we're talking about lifetime commitment if we're going to have a public health benefit.

HELEN REES: Thank you. Microphone number two.

KEN NELSON: Ken Nelson from Johns Hopkins. Mike, I really agree on the importance of acute infection being important in transmission, but I wonder how much does symptoms that occur with acute infection, how much does that modify the likelihood that there'll be sexual contact in transmission? We looked in Cheng Mi [misspelled?] at a couple that are in a study for symptoms which some people have reported being very high and we couldn't find the, looking at those who were HIV positive and converted compared to the population, we didn't find a high rate of symptoms but they were fairly high in the background too. Is that important?

MYRON COHEN: I'm going to give two very quick answers to that. One, there is every reason to believe that people with acute infection rarely are sick enough so that they're not going to have sex because in our own setting, we find the people in STD clinics. Now we find them with modest symptoms that they don't construe as severe. They're coming because of an STD not because of those symptoms but they often will have fever, headache, diarrhea, myalgia, sore throat, mild though and not blocking necessarily sexual activity.

I don't believe a symptomatic approach to detection of acute infection is reasonable. There's going to have be some population level approach and I'll put in a plug for again diagnostics. Newer tests introduced all over the world will pick up many more people with acute infection. Our job is to figure out how to manage them, another challenge for the research community. I'm unaware of any guidelines that are totally secure.

HELEN REES: Thank you. Pedro.

PEDRO GAHN: Pedro Gahn [misspelled?] from Argentina. I have two quick questions regarding resistance. I'm not an epidemiologist, I'm just a humble clinician and I try to understand why we are using a combination, for instance, of Tenofovir, FTC and efavirenz with two drugs with very low genetic barrier over time and the guidelines continue recommending those and we didn't see an expansion of resistance, albeit we see more and more people on treatment than any first setting. This is number one.

And second, if we are concerned about resistance in the context of "ART as prevention", why are we not so deeply concerned when we are providing for instance a immunotherapy with Tenofivir as PrEP for people that might be – well those people are at higher risk because they would be the candidates for acquiring primary infection.

MYRON COHEN: I think Julio should answer the first question. I'll answer the second question.

HELEN REES: Yes, Julio maybe you would like to respond also to Mike's question.

JULIO MONTANER: I'm glad to hear that Myron has been promoted to moderator, but in any case [laughter] –

MYRON COHEN: And after you answer – that was nice. Thanks.

JULIO MONTANER: I think Pedro's right and I think I have been advocating for quite some time that if I was to try to reconcile the benefit to the patient and the benefit to the system, the public health etcetera, I would attempt to do clinical trials that will compare say a traditional [inaudible] approach Tenofivir, FTC and efavirenz with something different. Tenofivir boosted PI with something that really could give you simple, easier, long term like [inaudible] type of regimen.

And to be perfectly honest with you, that's the essence of what Michel Sidibe is currently proposing. Now that when these two or three men has a secondary benefit and prevention, despite a fear mongering that year hear that end of the corner, what we have to do is give the best treatment to the people, the simplest the most durable that has both goals, the best for you and the best for public health and it can be done.

HELEN REES: Thank you. Unfortunately we will not have time to take more questions. So too really I have no

pretention also to summarize this very interesting discussion, but what we have heard is that we have some evidence from PMTCT, observational studies and discordant couples that ART for prevention works and all the models are also confirming this, but we still also have a lot of challenge such as durability, acute and early infection, resistance and how to prevent transmission of resistance and so many other challenges.

So the way to go is really to have more clinical trials to confirm that ART for prevention really works and is feasible at the population level and then we come up with a real recommendation on ART for prevention. For the time being, ART for prevention can be used in a combination prevention as an [inaudible] biomedical intervention in the combination prevention strategy. Thank you and I would like to thank all the presenters [applause].

[END RECORDING]