

**International AIDS Society:
2nd IAS Conference on HIV Pathogenesis and Treatment
Main Plenary – New Antiretroviral Drugs and Therapeutic
Strategies
July 15, 2003**

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GIUSEPPE PANTALEO: Good morning ladies and Gentlemen, dear colleagues. My name is Giuseppe Pantaleo and I am co-chairing this plenary session with Christine Katlama. There are two topics that are going to be covered. One is antiretroviral therapy and the other is vaccine.

The first speaker is Professor Patrick Yeni. Patrick Yeni is Head of Infectious Diseases at the *Hopital Bichat* in Paris. His main interests are antiretroviral therapy in clinical research. He's also Chair of the International AIDS Society, USA, Parnell, producing international accommodation for antiretroviral therapy.

Patrick?

PATRICK YENI: Good morning. Thank you very much for the scientific program, for this invitation to address new antiretroviral drugs and therapeutic strategies at this conference.

What are the challenges for antiretroviral therapy in HIV infected patients? You could summarize them into three challenges. One is an improved convenience, second one is decreased obsessity (misspelled?), and third one is increased activity both on wide-side virus (misspelled?) and on drug-resistant virus. And the question is, how new drugs and new strategies can help to meet these challenges.

In terms of new drugs I will give you some examples -

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for improved convenience, for decreased toxicity, and essentially for increased activity on drug resistant viruses. But this does not summarize all the effort in drug discovery for HIV infection.

So the first drug I'd like to summarize for you is T-20, and I report here that 48 weeks full results of thorough one and two studies. These were - I'd also say three studies where patients failing a number of - high number of prior - prior antiretrovirals and with a low CD4 cell count and a high viral load, were given the best therapy possible, which was optimized background, OB, and half of the patients had T-20 added to this regimen.

And the results show that in the presence of T-20 the percentage of the patients with undetectable viral load was significantly higher than in the absence of T-20. And this is at the expense of a relatively high number of injection site reactions, however, these reactions are not severe and do not lead to treatment interruption in most of the patients. And obviously there's also the financial cost of this treatment.

Now when a patient is failing T-20 one can identify mutations in the GT41 (misspelled?) envelope gene, which are associated with resistance to T-20. Therefore one important question is, do these mutations preclude further activity of next generation fusion inhibitors?

T-20 49 is one of these next generation fusion

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inhibitors. And a study was performed evaluating the activity of this drug in patients failing T-20. The results were reported at the Boston conference. At baseline there was more than a hundred-fold increase in the IC50 to T-20 when the patients switched to T-12 49, whereas there was no increase in the IC50 to the new T-12 49 fusion inhibitors.

And in fact when patients switch their failing fusion inhibitor to T-12 49 what was observed was 1.12 log HIV (unintelligible) decrease within 11 days.

So this raises hope that it will be possible to sequence drugs within this class of drugs. In a way we hope that false resistance will not be absolute within this family of drugs.

Another example of a new drug is in a very different setting. It's the - it's Atazanavir. Atazanavir can be given - it's given once daily and is given without an incement (misspelled?) with Ritonavir, at least in treatment naive subjects.

And the - all 54 studies was a bivertal phase three study where naive patients were given Combivir plus either Atazanavir or Efavirenz. And this summarized the 48-week results of this study showing that both for 400 copies and for 50 copies, the antiviral activity of Atazanavir and Efavirenz were similar. And the reason why Efavirenz doesn't give results as good as one would expect in this trial is currently

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under evaluation.

In terms of side effects, one noticeable side effect is increase in free bilirubin in patients treated with Atazanavir. And this is actually related to an inhibition of weaker inundation of bilirubin. It's like a (unintelligible) disease and in fact it's not toxicity in the sense that it's not correlated with an increase in ALT or AST in this study. However, in some patients this results in clinical jaundice.

But there is - there was in this study no effect of Atazanavir on LDL cholesterol as opposed to Efavirenz. And I don't show here the results but there was also no effect on triglycerites related to Atazanavir.

At this conference there will be several presentations. One on the lipodystrophy in this study. And there will be also presentations soon on the activity of Atazanavir in treatment-experienced patients.

Tipranavir is also protease inhibitor but which is very different from Atazanavir because it's essentially - it's main property is that it's active in vitro and in devo (misspelled?) viruses which are resistant to many currently licensed protease inhibitors. The drug has to be given twice a day and must be enhanced with Ritonavir.

And this - Phase II dose ranging study has been performed in three class experienced - two PI experienced patients having mutation in the protease gene. And three

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different combination doses of Tipranavir/Ritonavir was tested.

At baseline there was an increase of the IC50 to all licensed PIs, but not for Tipranavir. And after 15 days of functional mono-therapy where only the protease inhibitor was changed in these patients for Tipranavir/Ritonavir, one sees that for the three combination doses that were tested there was approximately one load decrease in HIV RNA within two weeks. And there was no real difference between the three arms in terms of activity.

But based on these results and also on the TK interaction results and on tolerance, it's the 500/200 milligram dose combination that was further selected for Phase III evaluation, and you're aware of these resist studies currently undergoing.

This slide is to show you that Tipranavir is not the only drug with that purpose. A little before and on the clinical evaluation is TMC114. This is also a drug which is active in vitro against viruses with resistance to many PIs.

And I show you here the results of the proof of concepts study where patients - multi-experienced patients and actually patients that three-quarters - for three-quarters of them had only one or even none active PI available at baseline. And these patients were switched to TMC114, million (misspelled?) full-change susceptibility to TMC114 was not increased. And what you see here is that for all combination

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doses that were tested there was more than one load decrease in HIV RNA within 14 days of functional mono-therapy with TMC114.

So I have shown you some examples of new drugs, and for protease inhibitors I have addressed three of them. But please be aware that other drugs are currently under development. Some of them in the first clinical stage.

For entry inhibitors I have addressed fusion inhibitors but I will also say a few words for receptor and co-receptor inhibitors, and I didn't even address the other class - drugs from the other class, either in existing classes such as nucleoside analogs - and as you know there are many drugs in development, but some of them I could have switched to late development because in fact they've just been licensed. And the same holds true for NNRTIs and for integrate inhibitors, and also for other drugs.

So I'd like now to address in a few slides receptor and co-receptor inhibitors because it's amazing to see how strong the discover research in this class of drug is now.

These are drugs that inhibit the binding of HIV either to the CD4 receptor or to core receptors. In terms of CD4 receptors there are at least three drugs in development from three different pharmaceutical companies. Some are small molecules, other are not. Some are (unintelligible) available. And the activity in patients is already demonstrated in proof of concept studies for some of these drugs.

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There is at least one drug in development that inhibits the binding of HIV to the CXCR4 co-receptor and we don't know yet its activity in patients. But there are many drugs that are in development for inhibiting the binding of HIV to the CCR5 - 4 - 5 co-receptor. They're coming from different drug companies and most of them are small molecules. All of them bind to the CCR5 co-receptor but probably not at the same site. And for some of them there is clinical activity demonstrated in patients and for others we just do not yet have the results that clinical studies are currently ongoing.

So this is interesting because there was initially some concern with the activity and the toxicity of drugs that would inhibit the binding of HIV to the CD4 receptors - all the four receptors, however, this did not present a very strong effort in drug discovery in this class of molecules.

I will now turn to new strategies. How can new strategies help us to meet the challenges that I described in my first slide? For convenience it's certainly cued to regimes, and as you heard yesterday, induction (unintelligible) strategy might need to be reassessed with the new drugs we have.

In terms of toxicity, can NRTI (unintelligible) regimes, STIs, TTM, help us to decrease the toxicity of our RIV (misspelled?) regimens? And in terms of activity on wide-top (misspelled?) virus, (unintelligible) regimens -- and we've

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seen examples again yesterday -- can improve the activity at least initially. And on drug resistant viruses megahart (misspelled?) HTI question mark, and TDN question mark might also help us to increase the activity in multiple - in patients failing multiple therapy.

So what I'd like to do is give you two examples of these strategies by addressing first NRTI-sparing regimes, and then STIs on drug resistant viruses. Why NRTI-sparing strategy? Because there is a large intraclass plus class toxicity that also cross-resistance between this class of drugs.

Now if one wants to move to an NRTI-sparing strategy, this means essentially to choose between an NNRTI plus PI combination therapy or a double PI combination therapy. Because other regimens are either disappointing, such as the double NNRTI combination -- we have the example of the two NN study -- or extremely preliminary in terms of single boosted PI regimens.

I will first discuss the NNRTI plus PI combination therapy. The first example we had of that came from the DNP06 studies released a few years ago. In this study naïve patients were given ZDV plus 3TC plus either Indinavir or Efavirenz and you hear of the results in these two arms of the study, but actually there was a third arm combining Efavirenz with Indinavir with antiviral activity somewhere in the middle

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between the two other arms.

However at that time the class toxicity for NRTIs was not so much of a concern and therefore this type of toxicity has not been in-depth evaluated in this - in this study. Furthermore, we will not use Indinavir the way it has been used in this study. And you've probably heard there is also the easier study yesterday showing that Ritonavir/Indinavir plus Efavirenz may also show activity.

So for obvious reasons other combinations have been studied for PI plus NNRTI without NRTI. And there are a lot of studies - you've heard the big study yesterday, but there are other studies and essentially most of these studies are not comparative with the exception of the - of the Nikka (misspelled?) study. And they have addressed combinations of either Efavirenz or Nevirapine plus Lopinavir or Indinavir or Saquinavir.

And these studies were performed in very different settings and essentially what they have shown is that there is a substantial activity of such combination therapy but sometimes they're also toxicity. And the effect of NNRTI class toxicity - for this effect there can be various trade off conclusion with these studies.

However, these studies have set the stage of further large comparative trials to give a clear answer to the value of NRTI-sparing therapy and there are several of these studies

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which are ongoing or planned. There are large studies, randomized, more than 100 patients. And rather than describing them one by one I just would like to summarize their - the population and the, uh, the end points of this - of these studies.

There are studies performed either in naïve patients or in patients treated in having undetectable viral load. And the regimens are either comparing NRTI-sparing versus NRTI-containing regimens, or (unintelligible) patients switch studies, either continuing versus switching for NRTI-sparing regimens, or comparing different switches to NRTI versus PI-sparing regimens.

And what's interesting is that in terms of end-points, obviously the activity will be evaluated, but also there will be an in-depth evaluation of the potential toxicity, especially for nucleoside - nucleoside tide toxicity in these studies, both for lipodystrophy, metabolic complications, and the ratio of the mitochondrial to nuclear DNA content.

So within a few months to one or two years we will probably have a clear answer of how to use these PI plus NNRTI-sparing regi - NRTI-sparing regimens.

The second option is a double-PI combination therapy, and here again we have results from at least two large studies and I will here give you the example of the prominent studies, the results of which were reported in 2000. In that study

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patients were - naïve patients were randomized to receive either Ritonavir to Saquinavir with Ritonavir at 400 milligrams VID, or the same drugs plus D4T. And in (unintelligible) 48-weeks there was actually no difference in terms of antiviral activity. However, at 12 weeks patients may - were allowed to add D4T in the - in the arm without D4T initially.

And when you look at the results at 12 weeks there might be a difference there and if you focus on the patients with very high viral loads there was actually a difference at 12 weeks.

Now at the other side of the study, at nine to six weeks, actually only 24% of the patients initially on their - the Ritonavir/Saquinavir only regimen could remain on this regimens, whether - 60% of the patients being randomized for the D4T continuum (misspelled?) could remain on the regimen.

Therefore it's not very clear in my mind that double PI combination therapy without NRTI is as potent as can be the more conventional therapy.

What is clear however is that in the compact regimen with Ritonavir/Saquinavir only, the prevalence of lipodystrophy - no, I'm sorry. With D4T - in the presence of D4T the inc - the prevalence of lipodystrophy was much higher than it was observed in the compact arm in the absence of D4T.

So here again we have new drugs and we have more concern with this type of toxicity, therefore several studies

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are being performed to address the - the - to address the - the use in the patients of double PI combination therapy, essentially enhanced with Ritonavir.

I will just mention one of the most popular event, which is the Saquinovir/Lopinavir combination therapy, and the results have been presented last year at TCAC by Spescetsi (misspelled?) et al.

In these patients - this is not a comparative study. In these patients who were failing therapy they were given the option to switch to Saquinovir/Loquin - Lopinavir, but they had not NNRTI - NRTI given because actually the patients ran out of options either for reasons of toxicity, either for reasons of resistance.

And what you see here is the activity. There was treatment interruption for some of the patients and what you see here is the change in HIV RNA showing that there is a significant activity of this combination therapy in these patients, and also in ni - an increase in CD4 cell count.

What is not shown here is that there was no negative interaction between - pharmacology speaking between Saquinovir and Lopinavir and also there was no unexpected toxicity with this combination.

Coming back to the activity, in fact the long responders with this combination were essentially the patients with a high number of primary PI mutations or low CD4 cell

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count. So these are interesting results that need now to be compared with other options.

But in fact if you look at all the options that are - that you can imagine, it's important to be aware that there are many lacking data or discrepancy between data as concern only TK interaction. And I've shown this as question marks in this slide. And this is also true, of course, if you consider new PIs like Atazanavir or Tipranavir.

So not even speaking of clinical activity one should be aware that there is still a lot of work to do before we can use with confidence this type of double PI combination therapy.

The last strategy I'd like to discuss with you this morning is the STI strategy, and I'm not going to address the segment of patients with undetectable viral load, but only patients with multiple treatment failure (misspelled?). There one can consider either a full treatment interruption before salvage or a partial treatment interruption in the absence of (unintelligible), which is a rather newer concept.

You're aware of these results of the INRS 097 (misspelled?) study where patients failing high number of previous therapy were switched to multi-drug rescue therapy either immediately or following an eight-weeks treatment interruption. And what you see here is that the antiviral activity of Salvage 30 in terms of decreasing HIV RNA was there in the patients who had undergone a treatment interruption than

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among patients who were switched to salvage 30 without treatment interruption.

And when you look at the primary end point in this study, there was a significant difference both at week 12 and also at week 24, although the difference was narrowing somewhat.

But the CDCRA 064 study gave a very different results, showing, in fact, no difference in antiviral activity whether a patients at STI or not - four months STI or not before switching to - to salvage therapy.

So why are these studies showing so different results? And - and I forgot to say that moreover in the CDCRA study there was an increased estimated incidence of progression of disease or death among those who had - were in the STI group as compared to the new STI group.

So why are there so much - so many difference in - between these two studies? It may be that one of the explanations is - can be understood if one considers patient characteristics and type of salvage therapy. And we probably hear more about that in the CBCRA 064 presentation later this morning.

In this - in this slide you can see that in fact there is no real difference in terms of treatment history between the two groups. However there is a very large difference in terms of the CD4 cell count at baseline before treat - STI is

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initiated. And also there's a large difference in the type of salvage therapy, with multi-drug rescue therapy in the NRA study versus conventional therapy in the CDCRA study.

Therefore, whereas it is clear to me that patients in this situation should not be given an STI opportunity before going to salvage, it's not yet clear that such restriction would apply to patients at the very late stage of HIV disease.

Now what about partial treatment interruption? This concept has been studied by Dixon (misspelled?) et al and presented at last retrovirus conference in Boston. These are patients who take the drugs, who failing the therapy, but they still have the recommended treatment they get the benefit, both in terms of degrees in HIV RNA from set point, but also in increase in CD4 cell count.

And these patients were given the opportunity of interrupting either all PIs from their treatment, or all STIs. And the choice of which segment of the treatment to be discontinued was essentially based on toxicity.

And what Dixon (misspelled?) et al have shown is that in patients interrupting their protease inhibitor, there was actually not much change in HIV RNA. Only three out of 18 patients had an increasing viremia, but in the population the mean change was no.

But this was not the case among patients who interrupted their reverse transcriptive (misspelled?)

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inhibitors and in all the six patients here there was an immediate - immediate and durable increase in viremia.

We're here speaking of a very small number of patients and obviously these results have to be confirmed in large studies. However, they're interesting because interruption of the protease inhibitor segment in this population of patients may prevent further toxicity also prevent the accumulation of resistant mutations that may jeopardize the use of future PIs that we hope will be available on drug resistant viruses.

So in conclusion the STI strategy in patients with multiple treatment failure has shown for full interruption increased risk of clinical progression and also discordant results that we have to better understand. Partial interruption is interesting but we lack data here.

And in patients with undetectable viral load - I didn't address that question but there are many questions here in terms of the effectiveness, of risk of adherence, risk for emergence of resistant viruses, and there are still studies ongoing to address this issue, including the CD4 cell count based treatment interruption.

Considering all this, STI should be used with caution and probably essentially in the setting of clinical research only.

And in my last slide I would like to acknowledge all my colleagues and friends who provided me with their results, as

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well as the slides.

Thank you for your attention.

CHRISTINE KATLAMA: Thank you very much, Patrick.

Everyone here in this room was moved yesterday by the very powerful words of Nelson Mandela. Some of us thought yesterday night that it was time for an HIV scientist and physician to move more actively.

This is why. On behalf of the organizer of the conference I would like to invite you to sign this declaration of support. These are the words of Nelson Mandela. I'm very proud and honored to wait for you.

We are saved to translate our scientific progress into action where it is most needed - in the communities of the developing world, the poorest region of the globe. This is the global injustice which cannot be (unintelligible). It's a travesty of human rights on a global scale. The world must do more - much more on every front in the fight against AIDS.

Of course this means dramatically extending our prevention efforts. But the most lacking in equality is our failure to provide the lifesaving treatment to the millions of people who need it most.

It is our belief that the single most important step we must now take is to provide access to treatment throughout the developing worlds. There is no excuse for delay.

Our HIV scientist, physician, and health practitioners

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attending the seven-day IAS conference, we share Mr. Mandela's view that science has given us powerful tools - tools to stop HIV/AIDS and that the world should be using these tools where they are needed most. We reaffirm our commitment to these goals and express our support for AIDS work.

If you agree on that, on behalf of the organizer I would like to invite you to sign this declaration of support. To sign it you will have papers distributed. Give it back to the staff people with the red t-shirts. Your signature will be gathered and presented at the closing ceremony, and also at the support conference of the Global Fund.

For those of your friends who want to commit it there will be possibility to sign all during the day. Go to the people with the red t-shirts.

Thank you very much.

It's now my pleasure and a big honor to welcome Larry Corey for the second talk on vaccine in this conference. Larry Corey is a Professor of Medicine at the University of Seattle and Head of the Program of Infectious Disease at the (unintelligible).

Larry has led an active research program in the pathogenesis and treatment of viral infections for over two decades. From '87 to '91 he was a Chair of the ACTG -- the AIDS Clinic and Trial Group -- during which both the 076 trial - the (unintelligible) addiction in mother and fetal

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transmission, and the trial of combination therapy.

In 1990 Larry turned his attention to vaccine developments and has been involved in both the discovery and the clinical trial aspect of vaccine for both (unintelligible) outbursts in HIV.

Larry has been the principal investigator of the HIV vaccine trial network since its establishment in '99. The (unintelligible) supported (unintelligible) initiated a global vaccine program and he's at present the largest and most comprehensive clinical trial in the world for testing and evaluating (unintelligible) HIV vaccines.

FEMALE VOICE: Ladies and Gentlemen, as you exit we will be - we'll be giving you the declaration of Nelson Mandela. Please sign the paper and return it to the information desk, which is located in the lobby.

If you didn't yet get a copy additional are available at the information desk. Thank you for your attention.

LAWRENCE COREY: Oh, okay. Well, that's a hard announcement to follow.

Dr. Katlama and Pantaleo, it's an honor to present at this conference in this beautiful city and venue. There have been many references in the conference on the need to develop a globally effective HIV vaccine. The science behind developing such a regimen is perhaps the ultimate synergism in our field between molecular virology, structural biology, human

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immunology, clinical trials, public policy, and healthcare economics.

One could discuss all of these but what the organizers asked of me is to provide some over-arching scientific review with the field.

I will start with what I think is the clearest part of the field - unequivocal safety of recombinant proteins and vectors of candidate HIV vaccines that have entered clinical trials.

Dr. Peter Gilbert and Sharon Frye (misspelled?) have recently reviewed the safety data from over 51 Phase I/II trials involving 3,189 volunteers followed for a median of 5.3 years. Except for one small Phase I trial involving 20 subjects who received a peptide vaccine with incomplete Froins (misspelled?) adjuvant (misspelled?), HIV vaccines exhibit no significant severe short or long-term adverse events. In other words the recombinant vectors and proteins have proven to be safe.

The critical issue for the field of HIV vaccines is developing the highly immunogenic vaccines or vaccine regimens that will be required to achieve benefit. The good news is that there is increasing growth in the field in developing novel immunogens. In the last 30 months nine new vaccines involving 925 subjects entered clinical trials.

There were two Phase II trials involving 570 subjects

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that were studied. One, a canary prospector (misspelled?) in combination with gp120 and plate BE will advance to Phase III in a Phase III trial soon to start in Thailand.

Two Phase III clinical trials of gp120 were conducted, but succeeding in their trial design and their conduct, and involved over 7,221 volunteers.

Unfortunately, the bad news during this time period was the failure of monomeric gp120 to interrupt sexually transmitted HIV in a trial of predominantly men who have sex with men in the United States. And in addition, in recently presented data, no effect on modifying disease host acquisition.

This slide synthesizes the results of this trial, involving over 5,000 persons, randomization of two vaccines to each placebo. And one can see, unfortunately, the infection rate of 5.8 to 5.7% - no difference between the vaccine and the placebo group.

Fortunately, the field of HIV vaccines is a resilient one. In fact I think there is more optimism among scientists in the field today than previously. As reviewed by several people in the meeting yesterday, several novel vaccines are under development, especially those that elicit T-cell responses to HIV proteins.

In fact in the next nine months, just within the HBTN itself, nine different vaccines will be tested and these Phase

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I/Phase II studies will involve over 1,450 subjects.

The three leading approaches at the moment that are - that have been leading approaches with respect to candidate vaccines utilize attenuated or non-replicating vectors such adenovirus replicons, pox virus vectors whether they be NVA, canary pox, or fowl pox, or modified vaccinia in and of itself. Or alpha virus replicons such as VEE Sindbis or Semliki Forest virus.

I will first review the adenovirus replicon story. Here two major approaches are under study. Both are based on an adenovirus type five backbone. One approach, developed by Merck, is based on inserting gag genes, and more recently a gag poll neff (misspelled?) genes into the replicon.

The other is a multi-valen (misspelled?) approach developed by Gary Nable (misspelled?) at the Vaccine Research Center at the NIH, using the envelope of clay (misspelled?) A, B, and C consensus envelopes and the gag poll neff (misspelled?) fusion of a clay (misspelled?) B construct.

Now the advantage of the adenovirus replicon system has been so far the ability to produce vaccines that up to 10 to the 11th particles per ML, which at the moment is two to four logs higher than what one sees with the canary pox vectors that (unintelligible) studied extensively in the last five years, which are usually at around 10 to the 7th. Or MVAs, which appear in most publications to be 10 to the 8th and 10 to the

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In non-human primates these adenovirus replicon vaccines control viremia post-acquisition against hitidership (misspelled?) challenge.

And they have a longer ability of protection. In fact, according to some data presented back to (unintelligible) today over 900 days of protection, and bre - and essentially no breakthrough from escape variance in most of the studies.

Dr. Emilio Eminni (misspelled?) reviewed the early Phase I program of the Merck program yesterday. As such I will only highlight a few concepts. These adenovirus replicon vaccines appear substantially more immunogenic than prior canary pox vaccines. However, this immunogenicity is influenced by the host prior adenovirus antibody responses as well as the concentration of the vaccine.

This latter point is illustrated in the next slide, also given to be by Dr. Eminni (misspelled?) and Shiver (misspelled?). This slide illustrates the immune response as measured by gamma inter-(unintelligible) producing T-cells by pre-existing adenovirus antibody tider (misspelled?).

I would like you to focus on the third column, person to receive two doses of the 10 to the 10th dose of the vectors. Now I would like you to note, even though the numbers are small, the decreasing percent of responses to the vaccine with pre-existing high antibody titers to adenovirus - from 88% down

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to 29%. All these numbers are small. It appears these trends appear to be continuing in - in continuing studies.

The next slide shows another important concept. These vaccines produce cross plate T-cell responses. This slide compares plate B versus plate A and C responses among those who received the gag adenovirus by vaccine.

One can see that whereas there is a decrease - somewhat of a decreased response, these are people who received the plate B tanogen (misspelled?) and looking at their immune CTL responses against plate A and plate C antigens. One does see some decrease and also some slightly loss of magnitude. But the response in cross plate T-cell responses is substantive, a concept that has also been established with other pox virus systems.

The next concept in vaccine design comes with the issue of breakthrough recur - CTL escape as - and expand the breadth of the immune response. Conceptually this has been accomplished by adding additional HIV vaccines to - or HIV genes to the vector.

As mentioned earlier, for the Merck vaccine, this is adding poll and neff (misspelled?), and for the vac - PRC program it is add - adding comple (misspelled?).

The Vaccine Research Center has developed perhaps the first substantive multi-valen (misspelled?) vaccine, which constitutes a mixture of GP140 envelope from consensus strains

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of both plates of plates A, B, and C, combined with a gag pol
neff (misspelled?) fusion protein from plate D.

The VRC adenovirus replicon is designed to suffous
(misspelled?) after a DNA prime with a similar immuni - with a
similar gene products. The DNA vaccine enters human Phase I
clinical trials at the Vaccine Research Center in May of 2003,
and expanded Phase I trials could be started in September of
2003. The adenovirus replicon boost is scheduled for January
of 2004.

Now, the potential issues with the adenovirus
replicons, I think, are that populations in many regions of the
world have a much higher prevalence of high targets of adeno-
five than either the U.S. or Europe, which is split about a
third, a third, a third into people with no adenovirus titers,
modest adenovirus titers, and reasonably high adenovirus
titers.

But there's some preliminary data suggests both in
Thailand and in African-American many persons have adenovirus
five titers greater than one to 1,000. There would be concern
about the immunogenicity of these vaccines in such populations.

Will the vaccines be immunogenic at doses that can be
administered and manufactured? Or will other strategies have
to occur? There are two trials that are set to start -- HBP
and 050 -- with Merck that are set to start this summer, and a
trial that's planned with the Vaccine Research Center for

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construct - design for early next year that are designed to answer this.

Now what are the strategies to overcome this issue? The obvious one is to either prime or boost with another vector. Whether that's a DNA prime and an adeno boost, or an adeno prime with a canary pox or poxvirus boost. And the other one is to design alternative adenovirus serotypes. Adenovirus 24, 34, and 35 have a low seral prevalence in nearly all populations. The issue is can you make these backbones express HIV genes sort of tighter in the consistency and manufacturing ability as you can to adeno five?

This slide, again from Dr. Shiver (misspelled?), illustrates the concept of boosting with a poxvirus after (unintelligible) previously primed with an adeno five virus vaccine. The blue is the CTL response to the gamma interferon producing cells after the adenovirus prime, and one can clearly see both with (unintelligible) canary pox gag and an NVA bag - gag, afford a full increase in T-cell responses after boosting with essentially a heterologous construct.

The next slide is another interesting piece of data, which indicates that - and shows the issues that what we've primed with versus what we boost with, the sequence, influences the immune response and compares priming with a pox virus vector and boosting with adenovirus vector, versus priming with an adenovirus vector and boosting with a pox virus vector. And

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at least in this McCack (misspelled?) experiment one clearly can see that the overall response is better with an adenovirus prime followed by an NVA boost than a poxvirus prime followed by an adenovirus boost.

So the concepts to start taking away is what vaccines given first may matter. Now both the Vaccine Research Center product and the Merck product offer some very interesting approaches to some important complementary strategies, which I think are critical for the HIV vaccine field to answer, which is one reason that we would like to try and hope that these vaccines would move forward both at the Phase III clinical trials.

They will answer does the addition of envelope offer an advantage over just internal structural proteins, in both acquisition of infection and against post-acquisition. The plate specific vaccines really make a difference. Cross plate T-cell memory is elicited by plate B vaccines. Is there substantive increase by having plate specific vaccines and does a DNA prime make a difference.

I'd next like to turn our attention to the poxvirus vector system. Twelve to fourteen such vaccines are under development and about to enter clinical trials. This slide just gives a listing in which both the background of the vectors and the inserts differ enough to call each one a separate product.

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There are vaccinia using envelopes. There are canary pox vaccines. There are a series of NVAs that differ in their inserts both in respect to plate as well as whether they have full genes or CTL apotopes (misspelled?). There are vaccines that have plate B, plate A, plate C and whether they have fowl pox or NVA or modified vaccinias.

The list is long. At the moment the data in humans are short. There is questions whether one can manufacture these vaccines at high enough titer (misspelled?) to continually be safe and consistently immunogenic. And for the field, how will we define concepts concerning how to optimize the vector versus the insert that's not.

As I look at this there must be a shakeout in the poxvirus vaccine field. I'm hoping that this will be data driven and decisions will require an open evaluation and sharing of specimens in the various clinical trials between the ven - clinical trial groups evaluating this vaccine and an open evaluation of the comparative safety and immunogenicity to define which one of these products or series of products are worthy of moving forward.

The questions of does the insert, whether the plate or the string or the vector and its promoter influence the immunogenicity. And for us working in this field, can we develop the tools to measure differences if these things do matter.

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As with the adenovirus replicons, will enhanced immunogenicity be achieved by altering the prime of DNA or by using a heterologist boost, for example and NVA versus a fowl pox? And will the human data be like the primate data and will all these vectors be better boosts than actual primes?

Will the combination of two pox virus vectors, such as an NVA fowl pox or a DNA prime followed by an NVA boost essentially be as good as a DNA prime and an adenovirus boost? Or and adenovirus prime and a poxvirus boost?

These questions will need to be answered in Phase II programs. Rational combinations need to be conceived and efficient clinical trials will need to be conducted. And the parochialism of each inventor and manufacturer will need to be acceded in my opinion to the greater good.

Now, there are a couple other additional viral vector approaches. The leading ones are the alpha virus vectors, whether they be VEE replicons or Semliki Forest virus or Sindbis virus. And there is also another vector, rapid (misspelled?) virus VSB vectors that are being developed.

I'll briefly discuss the alpha virus replicons because they offer some interesting concepts. Alpha viruses replicate exclusively in the cytoplasm and won't alter the host geno, similar to the poxvirus vectors. One interesting aspect of the replicon is that high levels are expressed so the heterologist gene by inserting it downstream of the viral genomic RNA

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promoter, and hence high copy numbers and expression of the HIV genes of interest that are packaged are expected.

Alpha virus lipoproteins target dendritic (misspelled?) cells and there are low levels of preexisting immunity to these agents. So they offer potentially attractive vectors. The issue is, how immunogenic will they be?

HBUTM protocol 040 is the first human trial of the VEE concept as a replicon using a gag plate C insert. It is also an important trial because the trial that's simultaneously taking a vector for the first time use in humans and doing studies both in the United States and in South Africa. Ninety-six patients are - subjects are scheduled to enroll. This trial is starting next week in the United States and we expect in the next three weeks in the Republic of South Africa.

What's happened to DNA vaccines? Certainly the first iteration of DNA vaccines were somewhat disappointing. They've been essentially largely inert. There's been redesign of these - of the second generation of DNA vaccines and they are just entering clinical trials. Like pox vectors there are considerable varieties, differing in their platform, the genes, multi-(unintelligible) plasmids, CTL epitope vaccines, and plasmids containing cytokines.

So far DNA vaccines have been immunogenic mainly in animals and not in humans. They seem to have inefficient - inefficient uptake in muscles and APCs. And while the data are

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few what is available in human suggests better priming of CD4 than CD8 memory from DNA vaccines. That's not to say that that's bad. That's just - is what the data seems to be showing.

At the moment the field is concentrating on developing adjuvants (misspelled?) to enhance the immunogenicity of DNA vaccines. Some of them are - use physical micro-particles and the other ones are adding cytokine genes.

My own feeling is that DNA vaccines are unlikely to be a sole immunogen. Their utility may be in combination either as a prime for a vector-based vaccines, or really perhaps as a boost after vector-based vaccines. And the question is can they be used to add breadth or durability to viral vectors?

DNA given with cytokines such as IL-2, IL-12, and IL-15 or other adjuvants (misspelled?) have enhanced immunogenicity in animals. There is, however, concern about long-term toxicity of giving DNA with these human cytokines. And while clinical trials programs are occurring, they will occur in quite, I think, a step-wise and pretty cautious fashion.

There are other ideas in the field using live attenuated factors such as replication competent adenoviruses and bacterial vectors. These are really very early issues and we do not have time to follow them now.

Now, I've been talking about CTL vaccines, vaccines essentially that we do not expect to prevent infection, but to

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modify viral replication. It is perhaps conceptually easy to see that a vaccine that reduces viral set point would help the individual. It would increase the time to AIDS, it would reduce the need for the number of antivirals, it might improve the efficacy of antiretrovirals and reduce the frequency of transmission.

Now this cartoon clearly showing that our - showing that - what would happen if this kind of post-infection amelioration of what one would change the set point of a vaccine that does this.

But this is a new concept for vaccine design and licensure. They offer a number of new challenges for us as clinical investigators and for public policy and regulation. What level of set point viremia would be adequate for licensure of a vaccine? How long must we observe this effect?

The durability of viremia control is the major determinate in clinical as well as the epidemiological effects of such vaccines. Late breakthroughs associated with low-grade replication and escape mutations from CTL control have been documented in non-human primates, and we certainly see late breakthrough in humans all the time.

The key issue is would such a vaccine reduce transmission? There are certainly indirect data that suggest the case but we probably will need to directly observe and conduct such studies.

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Now what about neutralizing anaphines (misspelled?)? There certainly has been major frustration in developing vaccines that elicit broadly reactive neutralizing antibodies for circulating strains of HIV I. The vaccine Phase III trial tells us that for sexually acquired HIV I vaccines that elicit only high (unintelligible) of binding antibodies are not going to work.

Now there is one idea actually in the bottle - and oligomeric TP140 that has been made both from plate B and plate C by recombinant technique by Chiron (misspelled?). It's a recombinant envelope protein that is designed to unmask cryptic conserved neutralizing epitopes by deletion, not detection, of the second variable loop and has (unintelligible) the envelope.

This slide, given to me by Susan Barnett (misspelled?), shows the neutralizing antibody response to this oligomeric gp140 as compared to a monomeric gp120 and shows much greater cross plate neutralizing responses pretty comparable to some of the monoclonal (misspelled?) antibodies.

In the Kapp (misspelled?) experiments this gp140 also looks protected in combination with DNA. And this will start clinical trials in the next year.

The issue is can we develop vaccines that produce neutralizing antibodies to primary isolates? There are several concepts out there. One is to stabilize gp120 or gp120 cell binding in way that exposes vulnerable or broadly reactive

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neutralizing sites.

The problem is is that not that many broadly reactive antibodies are available for study. The good news is a few are and sterilizing immunity can be achieved in non-human primates with combinations of broadly reactive monochronal (misspelled?) antibodies. Concepts you'll hear about with Rupert's group.

One approach is to look at gp120 CD4 complex. This complex forms a viral attachment and is anesthenically (misspelled?) distinct from 3gp120.

Antibodies with a complex generally - generated in animals can neutralize primary isolates, and immunization (unintelligible achieves pretty broad neutralization, both CCR5 and CXCR4 viruses. Although antibodies with specific (unintelligible) of CD4 do occur. And the issue of safety has been raised and will again be an issue in human clinical trials.

There are other concepts out there for developing neutralizing an - immunogens. One is to - for them to delete the glycosolation sites. The problem is, which ones. HIV averages 21 to 30 glycosolation sites and removal of two to three sites heals new envelope configurations that result in escape and neutralization.

One concept would be to study this, learn from what the virus needs, and then back out those glycosolation sites and see if you could produce immunogens that are more immunogenic.

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One can remove variable regions of the envelope. One can talk about constructing trimeric gp120 or manipulate gp41 to expose its critical determinates, like the entry inhibitors.

So in summary there has been a perceptual awakening and rumbling in the HIV vaccine field in the last 12 months. Several novel vaccine designs are entering clinical trials and will generate provocative data on what primes best and what boosts effectively. The field will enroll more subjects into Phase I/II clinical trials in the next six months than in the prior 30 months and the diversity of candidate vaccines being studied is much greater.

How will these divergent products differ in immunogenicity by dose, by breadth, by magnitude, by preexisting immunity to the vector and the populations in that will be of major importance to the vaccine field?

And I'll say, finally, the scientific community involved in HIV vaccine trials will have something really fun to do.

We have made enormous strides in a large number of countries in overcoming the I must wait for my own country specific vaccine mentality. I think people are - health authorities are recognizing that waiting for country specific vaccines may be happily waiting for Godot.

Recognition that CTL responses between strains of HIV may not differ greatly and even if there are some differences

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the influence these will have on overall vaccine effectiveness in controlling viremia is a scientific question worthy of answering.

We have also started the process of developing a global HIV vaccine trials program. Phase I/II trials of candidate vaccines have been initiated simultaneously in the U.S. and Africa, the UK and Africa by - and the U.S. and South America. And a Phase II global vaccine trial of the Merck adenovirus five vaccine enrolling subjects from the U.S., Haiti, Thailand, Brazil, Peru, and Sub-Saharan Africa, will actually be initiated in the next 30 days.

The dialog between treatment and vaccine research has also been open. HPTN International investigators led by Bill Poplin (misspelled?) from Haiti, Linda Gray (misspelled?) from South Africa, have initiated a policy and designed a program to provide antiretroviral therapy for persons who develop HIV on vaccine trials in resource poor settings.

Current HPTN Phase III trials utilize standardized ART as part of the design for CTL based vaccines. And this policy has made it possible to start initiating vaccine trials in low resource settings.

There is, however, much to be done. Developing a global effective HIV vaccine requires more resources. Answering questions requires experiments. Performing experiments requires reagents. And producing more reagents

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requires changing some of the structural inefficiencies in the current system for developing vaccines.

A wide spectrum of persons involved in HIV vaccine development have been concerned about these issues and have initiated discussion about how we might substantially quicken the pace of HIV vaccine research. While I have outlined field that is clearly moving forward, this pandemic waits for no group or scientific insight.

Developing effective vaccine strategies, especially ones designed to elicit neutralizing antibodies, requires several different structural alterations in our current approach. In my opinion the public sector must markedly increase the investment in vaccine discovery and development. We need more vaccine discovery centers and programs. In my opinion they are best bricks and mortar vertically integrated, scientific communities and designs and buildings, similar to the original cancer centers and essentially modeled after the NIAD Vaccines Research Center. We need to increase the number of vaccines entering into the pool.

Second is to engage private industry in expanding its knowledge and resources in vaccine manufacturing. We need manufacturing facilities totally committed to creating HIV vaccines. We need to create enough immunogens to stop calling each product a vaccine, but to call it a reagent. A reagent designed to answer a specific scientific question, to refine

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the grid of immunological assays and studies needed to success
- to make successful vaccine development.

We currently are too dependent upon gamma interferon producing cells of some breeder mark-out of differentiating between vaccines. Other immune responses, proliferation, chemokine induction, and innate responses are clearly salient to vaccine development.

The entire iterative process of designing tomorrow's experiments on today's data needs to be quickened. We should be generating enough products and studies to strain our clinical trials network. That is a vision I'd like to see.

In closing, it is clear we must all work together to maximize our efforts in developing a globally effective vaccine. It is gratifying to me to see these issues being discussed and ways to coordinate our efforts globally being initiated.

I'd like to thank the many, many people who helped me in constructing this talk, especially my colleagues at the ATTN and work research labs, uh, Emi - Dr. Amenian Shiver (misspelled?) from Chiron, Dr. Barnett (misspelled?) from the BRC, Dr. Nable Graham (misspelled?), (unintelligible). So thank you very much.

GIUSEPPE PANTALEO: On behalf - on behalf of my co-chair also, Dr. Katlama, I would like to thank the two speakers for your outstanding contribution and to thank also the

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delegates for attending this session. Thank you.

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