XVII International AIDS Conference
Plenary Session, Day 3
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MALE SPEAKER: Welcome to the Wednesday session. It is my pleasure to be here together with Dr. Linda Sussman, Director of HIV/AIDS for Development for the International Center for Research in Women.

We are very pleased to be here to deliver the Young Investigator Prize on the topic of Women, Girls, and HIV/AIDS. The ability of women and girls to HIV infection and accelerated disease progression is well recommended. As HIV incidence continues to increase among women and girls, particularly in research limited settings. Research and gender are really the issues including community based intervention and investigations, will provide clinical evidence and information on which to base our response.

This Young Investigator prize, women, girls, and HIV/AIDS is offered by the International AIDS Society, the International Community of Women Living with HIV, ICW, and the International Center for Research in Women, ICRW, and will be awarded to a young woman investigator from a limited setting who most demonstrates excellence in research and/or practice that these women, girl, and gender issues related to HIV/AIDS.

The prize is a certificate and a $3,000 check, it is funded by the IAS and the ICRW, and supported by ICW. Linda?

LINDA SUSSMAN: Good morning everyone. It is my great honor to present this award to Paola Elizabeth Perez Montonado [misspelled?]. Her abstract is entitled [Spanish spoken],

"Taking HIV Information and Prevention to the Most Vulnerable Mexican Women." Paola? [Applause]

MALE SPEAKER: Good morning, and first, congratulations to the award recipient, and it is my pleasure to introduce the first speaker for the plenary session this morning. Dr. Robert Siliciano is a member of the Howard Hughes Medical Institute and Professor of Medicine and Molecular Biology in Genetics at the Johns Hopkins University School of Medicine. He completed his undergraduate work at Princeton University and received his M.D. and Ph.D. degrees from Johns Hopkins. After a post doctoral fellowship at Harvard Medical School, he joined the faculty at Johns Hopkins.

He is the recipient of a distinguished, clinical, scientist award from the Doris Duke Charitable Foundation, as well as two NIH merit awards. Dr. Siliciano's research focuses on the dynamics of HIV replication in vivo, and mechanisms of HIV persistence in patients on highly active antiretroviral therapy.

He will speak today on "HIV Persistence on Patients on HAART: Reevaluating Prospects for Eradication." Dr. Siliciano.

ROBERT SILICIANO, M.D., Ph.D.: Thank you. Good morning. I would like to first thank the organizers for the kind invitation to speak.

It has not been 11 years since the introduction of highly active antiretroviral therapy, or HAART. And the dramatic reductions in viremia experienced by patients on HAART

led initially to hopes that the infection could be cured with two to three years of continuous treatment. However, to date, not a single patient has been cured, and the initial hopes for eradication have given way to a pessimism that is so profound that eradication has almost become a taboo subject.

What I would like to do today in my talk is to try and take an objective look at the steps that we need to take in order to find a cure for HIV infection, and review the progress that has been made.

So in my opinion, there are three steps that we need to take. First, we have to stop the virus from replicating. This is the critical, initial step. This takes away HIV's main advantage if the ability to mutate and evolve, and it is very hard to see how we are going to cure the infection unless we can carry out this initial step. And, of course, the approach is to use antiretroviral drugs to block specific steps in viral replication.

Now the next step is to identify all of the stable reservoirs where non-replicating forms of the virus persist in the body. And, finally, we need to identify ways in which we can eliminate each of those reservoirs.

So I am going to review the progress towards each of these goals, concentrating on the first critical step. And I will begin with some general background. So when patients start on a standard three drug HAART regimen, the level of viremia falls from the pre-therapy study state all the way down

to the limited protection of current clinical assays, which is about 50 molecules of HIV RNA per mL of plasma. And this rapid decay reflects the fact that the infected cells that produce most of the plasma virus are very short lived, and so if you stop new cells from becoming infected with HAART, the previously infected cells die off quickly and viremia decays.

Now it was originally hoped that the decay would continue until the infection was eradicated. What we see in a patient who is doing well on HAART is this, simply measurements that come back below the limit of detection and so you do not know whether the decay is continuing or not.

Well, it turns out that it is not. And the reason has to do with the unique mechanism of viral persistence, that exploits the fundamental physiology of CD4 positive T cells. Now most of the CD4 cells in the body are in a profoundly quiescent state, and these resting cells include naïve T cells that have not yet responded to any foreign antigen, as well as memory T cells that have previously participated in an immune response. And these cells circulate throughout the tissues, essentially waiting and counter with an antigen that they can recognize. And when one of the cells encounters a foreign antigen that it can recognize, it becomes activated and divides and generates lots of activated effector cells of the same specificity.

Now at the conclusion of the immune response, most of these cells die, but some of them survive and go back to a

resting state as long lived memory T cells. And these memory cells survive for very long periods of time, decades, in fact, allowing future responses to the same antigen.

Now what happens in HIV infection is that the virus preferentially replicates in the activated cells, and it tends to kill them. It does not really replicate in resting cells, but what can happen, rarely, is that one of these activated cells can become infected as it is in the process of reverting back to a resting state. And this gives you a stably integrated form of the viral genome in a long lived memory T cell, and what is particularly interesting is that as the cell makes this profound transition from an activated state back to a resting state, HIV gene expression is turned off. And that is due, in part, to the fact that HIV gene expression depends on a host transcription factor, NF-kappa B, which is excluded from the nucleus in these resting cells.

So as the cells make this transition, HIV gene expression is almost automatically extinguished, and the end result of this is a stably integrated, but silent or latent, form of the viral genome in a long lived memory T cell.

Now this is almost a perfect recipe for persistence because it allows the virus essentially to persist just as information, and in this form, it is unaffected by immune responses and antiretroviral drugs. And, of course, if the cell becomes activated again in the future, it can begin to produce virus.

So in 1995, we developed assays to detect these cells in patients and we found that they were present in everybody with HIV infection, but only at low frequency. Only about one in a million resting CD4 cells harbors this form of latent HIV. The problem is that these cells persist in patients on HAART, and this was originally shown by Tony Falchi [misspelled?] and Doug Richmond and by our group in 1997. And we measured the decay rate of this pool of latently affected cells in patients who were doing well on HAART, and the decay rate is extremely slow, as you can see. Note that the time scale here is years, not days. And here are the data representing measurements in large numbers of patients who had suppression of viremia to blow the limit of detection for as long as seven years. And at this rate of decay, it would take over 70 years to clear this reservoir.

So we know that HAART can reduce the level of viremia, the level of free virus particles, in the blood to below the limit of detection. And we also know that HIV can persist in these resting memory T cells.

And the next important point is that everybody on HAART is actually viremic. That is, with an especially sensitive assay, it is possible to detect free virus particles in the blood of patients on HAART who have a clinically, undetectable viral load. And we call this residual viremia. This was first demonstrated by Roger Pomerantz [misspelled?], and confirmed

very elegantly by Sarah Palmer, who has developed an assay that can see a single virus particle in the plasma.

So what this means is that what HAART actually does is to reduce the level of viremia to a new plateau that is just a little bit below the limit of detection of current, clinical assays. Now the explanation that is usually given for this residual viremia is that it reflects ongoing cycles of viral replication that are occurring, but just at a lower level due to the presence of the drugs.

Now this is a very disturbing scenario because ongoing replication in the presence of the drugs will inevitably lead to the evolution of resistance and treatment failure. Fortunately, there is an alternative hypothesis. We believe that in the optimal situation, HAART actually stops all ongoing viral replication and that the residual viremia that patients experience is simply a reflection of the release of the virus from stable reservoirs, cells that were infected prior to the initiation of therapy. For example, those long lived memory T cells that I mentioned. And you might imagine that every day some of those cells become activated and they begin to product virus, and that virus cannot go on and infect other cells because of the suppressive effects of the drugs. However, it can be detected as HIV RNA in the plasma.

Now this is actually a much more optimistic hypothesis because it says that HAART actually stops viral replication. In other words, we have accomplished the first step that I

mentioned. So this hypothesis makes a number of predictions that we can test. First it predicts that the viruses in the plasma, the free virus particles, should be genetically similar to viruses in the latent reservoir.

So here is a phylogenetic tree of viral sequences from a single patient, here are the sequences in the latent reservoir, and now I am going to add the sequences detected in these free virus particles in the plasma using an extremely sensitive sequencing technique. And, as you can see, the two populations of viruses are phylogenetically intermingled, and in some cases, identical. And this is consistent with the idea that at least some of the residual viremia is derived from this latent reservoir.

Now a second prediction is that the residual viremia should continue without viral evolution. In other words, we should not see progressive, evolutionary change in the residual viremia, or the appearance of new drug resistance mutations because the complete cycles of replication that are necessary for evolutionary change are not actually occurring.

So if you look at this phylogenetic tree, you can see that the free viruses in the plasma, the colored triangles, have not diverged significantly from the other viruses in this patient, and furthermore, sequence analysis does not reveal the presence of any new drug resistance mutations. And this absence of new resistance mutations is also characteristic of the free viruses in the plasma of patients during blips, these

transient elevations in viremia that many patients on HAART experience. In fact, blips are likely just a reflection of the fact that everybody on HAART is viremic due to the release of virus from stable reservoirs, and that there will inevitably be some biological and statistical fluctuation in the level of residual viremia that is occasionally captured as a blip.

Now the third and most important prediction of this hypothesis is that intensification of HAART should not further decrease residual viremia. That is, if we add a fourth drug to a potent HAART regimen, we should not see a further decrease in the level of residual viremia. And that is because there are really no ongoing cycles of replication for the drug to inhibit.

So we carried out an intensification study in collaboration with Frank Maldarelli and John Coffin at the NCI, and John Mellors at the University of Pittsburgh. And I would like to present results from a subset of patients who are on an optimal, efavarinz based regimen and had measurable levels of HIV RNA in the plasma. And for these patients a boosted form of the potent protease atazanavir was added to their regimen for eight weeks.

So here are the mean levels of HIV RNA prior to intensification. And you can see that they are below the limit of detection of current clinical assays. But they are readily measurable with Sarah Palmer’s [misspelled?] single copy assay.

Now what happens when you add atazanavir for eight weeks? What happens is that nothing happens. The level of viremia does not change. And here are the levels post intensification. We have seen this same result in all 15 patients studied with three different intensification drugs. The result is that intensification of HAART has no effect on residual viremia. This result strongly suggests that the residual viremia is derived from the release of virus from stable reservoirs of long lived cells infected prior to the initiation of therapy.

Now we cannot exclude a small contribution from ongoing replication, but it is clear at this point that the major problem is the release of virus from stable reservoirs. So before I turn to how we find and eliminate those reservoirs, I would like to present some new research into the basic pharmacology of HIV drugs that helps us understand how it is that HAART can actually stop all ongoing viral replication.

So this is a dose response curve for a hypothetical antiretroviral drug. And what is plotted is the fraction of infection events that remain uninhibited as a function of the drug concentration. And this reaction decreases, obviously, as you add more drug.

Now we can describe this dose response curves with a simple mathematical formula, and I realize it is a little early in the morning for mathematical formulas, but this one simply says that the amount of inhibition is a function of three

things. The drug concentration D, the IC50, which is a standard pharmacologic measure of drug potency, and the exponent M, which describes the slope, or the steepness, of the dose response curve. And this slope parameter is analogous to the Hill coefficient, it is a measure of cooperativity in the binding of multiple drug molecules to a single target.

Now interestingly, the HIV protease and reverse transcriptase inhibitors that we use to treat HIV infection, bind to a single site on the relevant target enzyme, and so this slope parameter has largely been ignored, or has been considered to be equal to one, in which case it drops out of the equation. And if the value is greater than one, the curves simply become a little bit steeper.

Now we tend to use these antiretroviral drugs at concentrations well above the IC50 in this pink shaded range. And it does not appear that in this range, the slope parameter makes much difference. But that is only because the conventional way of plotting these dose response curves does not adequately describe the degree of inhibition produced by antiretroviral drugs. In fact, because viruses replicate exponentially, it does not make any sense to plot the inhibition of viral replication on a linear 1:100 scale as is conventionally done. Rather, we should use a logrhythmic scale so that we can see the fraction of events going down from 100-percent to 10-percent, one percent, 0.1, and even lower.

So if you do this and you take the same dose response curves from the last slide and simply replot them with a logrhythmic Y axis, the result is truly shocking. What happens is that the dose response curves for drugs with different values of the slope parameter diverge dramatically in the clinically relevant concentration range such that drugs with a higher value of the slope with much, much more inhibition of viral replication by orders and orders of magnitude.

And therefore we decided that we better measure the slope parameter for current HIV drugs, and determine whether it was different than the expected value of one, and we did this with a very sensitive assay that can see a single infection event.

So for the AZT like drugs, the nucleoside analog RT inhibitors, the slope values were all exactly one. For the non-nucleoside RT inhibitors, however, the values were around 1.7. For the protease inhibitors, they ranged all the way up to 4.5, for the T20 like drugs infusion inhibitors around 1.7. And for five structurally diverse inhibitors of HIV integrase, the values were all one.

Now this begins to make a bit of mechanistic sense if you consider the fact that the two drug classes that have a slope value of one, the nucleoside analog RT inhibitors and the integrase inhibitors both target an enzyme nucleic acid complex for which there is only a single relevant copy per virus.

In contrast, a multiple copy of HIV protease are simultaneously involved in the maturation of each virus particle and this, we believe, adds to a form of intermolecular cooperativity that gives rise to the steep dose response curves.

Well, what difference does all this make in terms of how well the drug actually works in patients? To address this question, Lynn Shan, a graduate student in our lab, developed a very simple index called the instantaneous inhibitory potential. And what this is, is simply the number of logs, or the number of tenfold reductions in the amount of infection that you get from a drug at some clinically relevant concentration, for example, the CMAC, the peak plasma concentration. So, for example, here are the dose response curves for two drugs that would be judged to be equally potent based on the conventional IC50 measure, but which have different values of the slope parameter.

For a drug with a slope of one, you are getting about a two log reduction, a 100-fold reduction at the peak plasma concentration, so the IIP value is two. For a drug with a slope value of three, however, you are actually getting about a million-fold reduction, a six log reduction, and so the IIP value is six. And so Lynn has gone on to measure the IIP values for current antiretroviral drugs because this index captures the importance of a slope parameter in a number that

is fairly easy to understand and it is just simply the number of logs by which you knock down viral replication.

So for the nucleoside analogs, for the IIP range for one up to four; for the non-nucleoside RT inhibitors, from three up to six; for the protease inhibitors, from two all the way up to ten, with lower values being seen for the fusion and integrase inhibitors.

So the most striking result here is that some of the HIV protease inhibitors can cause a ten log reduction in just a single round of infection. This is a ten billion-fold reduction, and at this level of inhibition I think it is easy to understand how it is that HAART can actually stop all ongoing replication. In fact, it would be surprising if any replication were occurring.

And these results also help us understand, at long last, why it is that the HAART regimens that have consistently been shown to be the most effective in multiple clinical trials always contain a non-nucleoside RT inhibitor, or protease inhibitor. These are the drug classes that have this extraordinary potential to inhibit viral replication.

So now that we have seen how it is that HAART can actually stop ongoing replication, let us turn to the issue of viral reservoirs. How do we find them and eliminate them?

Our approach to identifying viral reservoirs has been to focus on the free virus in the plasma, the residual viremia, which we now know is derived from release of virus from stable

reservoirs, and we hope that by studying the free virus in the plasma, we can deduce the nature of the cells that are continuing to produce virus in patients on HAART.

So, as I mentioned before, at least some of the residual viremia appears to be derived from the latent reservoir. However, in a number of patients, the story is a bit more complicated. For example, in this patient, I have only shown you part of the phylogenetic tree. Here is the rest of the phylogenetic tree. And what is particularly interesting is that in this patient, almost all of the viruses in the plasma are identical to one another representing a single virus species that has been captured in the plasma in multiple, independent blood samples over a three year period. And we have seen this same sort of phenomena in about half of the patients studied, where the residual viremia is dominated by a small number of viral clones. And these clones do not show evolution over time, and most interestingly, we cannot find these clones in resting CD4 positive T cells, suggesting that they are coming from another source. And I should say that Tobenitol [misspelled?], the only other group really that has done sequence analysis of the residual viremia, has seen exactly the same phenomena.

And our current hypothesis is that this represents the rare infection of a stem cell or a progenitor cell, for example, in the monocyte macrophage lineage, and that this cell is able to divide after infection. And so it copies the viral

genome without error into multiple progeny cells, and then these cells go off and produce virus particles for their normal life span.

So the idea that there is a second major source of residual viremia, perhaps in a cell that has some capacity for self renewal, it is clearly a disturbing one and will require much further research.

Now what about eliminating viral reservoirs? For the latent reservoir in resting CD4 positive T cells, the approach that several groups have taken is to use agents that induce global T cell activation and in the course of doing so, turn on latent HIV. Now the problem with this approach is that you also activate all of the uninfected resting CD4 cells, and those cells go on to produce cytokines in such large amounts that unacceptable toxicity results. It would clearly be preferable to find agents that can turn on latent HIV without inducing a global T cell activation. And the viruses that are produced in the process would not go on and infect other cells because of the suppressive effects of the drugs and one would hope that these cells would go on to die, either from virocytopathic effects or from host immune attack.

Now, unfortunately, we do not have such an agent right now, but we can take hope from the fact that several laboratories have developed ways to generate these latently affected cells in the test tube from primary T cells. And this gives us, at long last, a realistic in vitro model for HIV

latency so that we do not have to depend on the transformed cell lines that have been used in previous research. And the hope is that with these really more realistic model systems, it will be possible to identify agents that are able to target the latent reservoir.

And let me just describe how we do this in our laboratory. What we do is to take primary T cells from a normal donor, and transduce them with a gene that promotes survival, the BCL2 gene. This allows the cells to survive for a long period of time in the test tube, and then we can activate the cells and infect them with a form of HIV that is relatively non-cytopathic, it does not kill the cells as readily, and then culture them, and they actually survive long enough in vitro to go back to a resting state so that the virus becomes latent. And this, essentially, recapitulates the process by which a latency is generated in vivo.

And the hope is that with models like this, we will be able to produce enough latently infected cells in the test tube that we can use them to screen libraries of drugs, large drug libraries, to identify novel compounds that are able to activate latent HIV, hopefully without inducing global T cell activation or unacceptable toxicity.

So let me just sort of summarize what I have said. As a result of the efforts of literally thousands of people in universities and in the pharmaceutical and biotech industry, people who have participated in the development of HAART. I

think that we can now say that the first step has essentially been accomplished.

Now it would be a mistake to say that we are one-third of the way there to finding a cure for HIV infection, because the second and third steps may turn out to be much more difficult, although some progress has been made. But the fact that the current HAART regimens can stop ongoing viral replication is really of enormous significance because what that does is to take away HIV's main weapon against us, and that is the ability to evolve. And the fact that current HAART regimens can stop ongoing replication poses a unique challenge for everybody in this room.

What it means is that treatment failure is not inevitable. Even with the drugs we have today or with forms of drugs that are very similar to what we have today, if we could develop forms of these drugs that could be taken for life without unacceptable toxicity, then it is, in principle, possible to offer everyone who is currently living with HIV infection the chance for a normal life. And this is the long term challenge that all of us face.

So, as I conclude, let me just thank the people in my laboratory that did the work that I mentioned. The longitudinal studies on the latent reservoir were done by my wife Janet and Diana Finzi, a former graduate student, and this work would not have been possible without the help of some fantastic physicians in our HIV service, Tom Quinn

[misspelled?], Dick Chase [misspelled?], and Joel Galant [misspelled?]. The work on the intensification of HAART was done by Scott Kim [misspelled?] and Jason Denoso [misspelled?], along with our collaborators, Frank Maldarelli, Sarah Palmer, and John Coffin at the NCI, and John Mellors at the University of Pittsburgh. The work on the slow parameter was done by Lynn Shin, along with Moira McMahon, Suzie Pierce [misspelled?], and Haili Zhang, Brian Jilek, and Marc Callender. The work on the predominant plasma cone was done by Tim Brennan, Justin Bailey, and Ahmad Sedaghat, and Rick Nettles is here. And finally the development of an in vitro model for HIV latency was done by Andrew Yang and Yen Zhou. Thank you very much.

MALE SPEAKER: Thank you, Bob, for the excellent talk. I may just fulfill one of the commitments that I should have done early this morning. This is to introduce our chairs. Our first chair was Jack Whitescarver from the Office of AIDS Research at NIH, a very good friend of IAS, a strong supporter of our conference.

The next chair will be Paul Becker, who is the Dutch Ambassador for AIDS and who has also been very instrumental in helping us to put together these conferences.

And the last chair will be Suniti Solomon, who is a senior researcher from India, and was probably the first person in India that took seriously the research in HIV. So with that, I leave you with Paul.

PAUL BEKKERS: Good morning, ladies and gentlemen. In the field near Soweto of South Africa, two newborn infants were found. They were abandoned, both were boys. They were brought into an orphanage in Johannesburg, run by the Salvation Army. The infants both tested positive after three months. After another three months, one tested negative, the other positive. When all the efforts of the South African authorities to find the parents were exhausted, they were given up for adoption. The boy who tested negative was adopted by a family and is now living a happy and healthy life. The positive boy is still waiting.

Ladies and gentlemen, there are hundreds of thousands of children like these. According to data at UNICEF, 48-percent of all children between 12 and 17 years of age in Sub-Saharan Africa have lost one or both parents. Over 50-percent of the population in Swaziland is orphaned. Not only does this have grave consequences for children's chances for survival, education, and general physical and psychological development, it also affects the very fabric of society. The fact that we do not really know how to deal with this. We are struggling to find answers.

Research is urgently needed on how to most effectively provide support to these children, to see what works and what does not work. The Joint Learning Initiative on Children and HIV/AIDS is currently the leading forum on this matter. In 2006, the Joint Initiative on Children and HIV/AIDS is a two

year network of policymakers, practitioners, community leaders, researchers, and people living with HIV that mobilized research and discussion on the children affected by HIV and AIDS.

The Joint Learning Initiative does not seek to supplant the efforts of many dedicated and effective organizations working on behalf of children, no. Instead, it wants to provide an independent, collaborative analysis of what is working and what needs to change.

Linda Richter is a prominent member of the Joint Learning Initiative and is heading its working group on strengthening families. Allow me to introduce her to you. Linda Richter is the Executive Director of Child, Youth, Family, and Social Development at the Human Sciences Research Council in South Africa. She is an Honorary Professor in Psychology and an elected Fellow of the University of KwaZulu-Natal, as well as an Honorary Professor in the Department of Pediatrics and Child Health at the University of Witwatersrand. For three years, Linda Richter was an Honorary Fellow in the Department of psychology at the University of Melbourne. Linda Richter has conducted both basic and policy research in the fields of child and youth development, and has published more than 150 papers on these fields.

Ladies and gentlemen, Professor Linda Richter.

PROFESSOR LINDA RICHTER, Ph.D.: Good morning, colleagues. I would like to begin by thanking the Conference coordinating committee for giving such an important slot to

children and HIV. In the 23 years since the inception of the International AIDS Conferences, this is the first time that there is a plenary on the well being of all children affected by HIV and AIDS. [Applause]

A focus on children is long overdue. Children have been exploited in photo opportunities and headlines, but they have been almost invisible in the global response to HIV. However, this is changing. In recent years, efforts have been increasingly mobilized to bring children to the fore. Following the XV International AIDS Conference in Bangkok, a co-edition on children affected by AIDS, C. Carver, was formed with the support of a number of organizations, including the Bernard Findley Foundation. And they have successfully hosted for two years now a symposium of two days preceding the international conference. And as Ambassador Paul Becker said, in 2006 the Joint Learning Initiative on Children and AIDS was formed and part of its results are affected in my speech, and in a satellite session that will be held at 6:30 this evening.

Well, laying out and updating the basic facts and figures helps to get a handle on a problem. But in the main, children have simply been too small to count, too minor to matter. There is a lack of good data on children, especially between the period when mother to child transmission occurs, and the time of adolescent risk of infection, where we are now learning of higher than expected prevalence rates. The

information that is available is kept in several agencies and stored in programmatic silos.

They also, this data also does not conform to the definition of a child under the Convention on the Rights of the Child, which is 0 to 18 years. Instead, we largely collect data on children 0 to 14, with respect to HIV AIDS. This makes it very difficult to link to other indicators of child health and well being. Nonetheless, what data we have from UNAIDS, WHO, and UNICEF, indicate the following an estimated total of two million children were living with HIV in 2007, 90-percent of them in Sub-Saharan Africa. The number of these children estimated per year has grown 8-fold since 1990. Both new infections and deaths among children have grown threefold globally since 1990. Again, the greatest majority of them, 89-percent in both cases, occurring in Sub-Saharan Africa.

New infections started leveling off around 2000 with the expansion of prevention of vertical transmission services and have been declining ever since. Nevertheless, some 370,000 new infections occurred last year in children, comprising nearly a fifth of all infections, new infections, occurring globally. In 2007, more than a quarter of a million children, some 270,000, are estimated to have died of AIDS.

Parental deaths have increased significantly, especially in Sub-Saharan Africa with the mature epidemics. In 2007, 12.1 million children in the region were estimated to have lost one or both parents to AIDS. This comprises some 37-

percent of all parental loss. However, an important point to note about this is that about 80-perent of these children have a surviving parent. This makes us consider our response.

Firstly, treatment for adults is imperative for the well being of children. And secondly, we have to think that we are supporting 10 million children with a surviving parents, a vulnerable parent, not 12 million children with no parents. Not only do we lack data on children, but what we have is not well used. For example, population based surveys in many African countries identify only very, very small numbers of child headed households, or skip generation families with only elderly people and children. But many programs, policies, and advocacy efforts continue to focus very large amounts of money and effort on these relatively rare situations.

These extremely vulnerable households are tragic expressions of social breakdown and neglect by state and civil society services. However, to focus narrowly on these groups is to bring to ourselves from seeing the much larger numbers of children and families that urgently require protection and support in the face of the epidemic.

So where have we gone wrong? Children affected by HIV and the families that care for them are enduring terrible suffering and deprivation. This suffering is largely needless. It is needless because it results in the main, not directly from the virus, but from our failure to prevent infection and treat both adults and children. It also results from our

failure to assist the poorest families to deal with the social and economic disruptions produced by the epidemic.

So in what way have we gone wrong? First of all, HIV prevention is failing children. The overwhelming majority of children who are HIV positive are infected through vertical transmission. However, interventions to prevent this transmission, the effectiveness of which have been established for more than a decade, are not reaching enough of those who need them. In contrast, good quality programs in the rich world have brought vertical transmission down to two percent. While coverage of prevention of mother to child transmission services have increased in lower to middle income countries, from 10 to 34-percent over the last three years, this is slow, not fast expansion. Large numbers of pregnant women still do not know their HIV status, and of those who are able to access services, most continue to receive single dose navirapine.

Secondly, how have we failed children? Children living with HIV have far less access to treatment than do adults in the same settings. Early infant diagnosis among exposed children is essential for timely initiation of prophylaxis and treatment. But last year, only eight percent of infants in lower and middle income countries were tested within two months of their birth. Preventable prophylactic trimoxazole has been demonstrated to reduce significantly the illness and death amongst HIV exposed and HIV infected children. However, again, last year fewer than four percent of the estimated 1.5 million

children exposed through maternal HIV started receiving the antibiotic by two months of age.

The number of children under the age of 15 receiving antiretroviral treatment between 2005 and 2007 has practically doubled across all regions over each succeeding year. So we are improving. At the end of 2007, however, less than 10-percent of the estimated 2 million children living with HIV were on antiretroviral treatment. We have to conclude that children have been neglected in the roll out of treatment.

Thirdly, how have we failed children? Not only orphans are affected. Children are infected with HIV and they are affected. Affected, that is, by the devastating impact of the epidemic on their families and the communities in which they live. Children affected often group together with children who are orphaned because of AIDS and then categorized as orphans and vulnerable children. But in reality, orphans, huge as their numbers are, are only the tip of the iceberg of affected children.

The much used term, AIDS orphan, in itself causes enormous confusion. The UNAIDS definition of an orphan, a child under 18 who has lost one or both parents, does not accord with common sense meanings of the word. In western countries, the usual meaning of an orphan is a child who has lost both parents. In most other parts of the world, an orphan is a child without family or close kin. However defined, children who lose their parents are of concern to all of us.

But in HIV affected communities where there is also extremely poverty and deprivation, orphans are seldom worse off than other vulnerable children.

Recent household data in 15 high burden countries indicate a small and decreasing depth between orphans and non-orphans, for example, in their likelihood of attending school, also in growth indices, nutrition. Indeed, experience shows that singling out specific groups of children such as orphans leads to a number of undesirable effects, including their stigmatization. Children may be labeled by families to be able to access desperately needed assistance, while other equally, or more, destitute and more vulnerable children and families as passed by in highly targeted programs.

Most importantly, though, the focus on orphans has individualized the challenge of care and support. It has framed the epidemic's impact on children as an individual matter, rather than as a global, continental, regional, and national social problem. It is also separated our assistance to children from efforts to support their families and communities.

Close to 60-percent of families are affected in the hardest hit countries. This means it is impacting on very large numbers of children. As a result of focusing too specifically on orphans, our efforts to improve the last chances of much, much, much larger numbers of vulnerable

children have been considerably less effective than they should have been.

Fourthly, our failure, families, extended kin and communities, many living in extreme are largely left to support affected children with little or no funding of assistance from governments. The numbers of children affected are increasing against the background of deepening poverty. In most of southern Africa, for example, over 60-percent of children live below the poverty line in already very poor countries. In such situations, support to individual children by local community based organizations, while absolutely essential, is not enough. All children in communities hard hit by HIV are made vulnerable by the epidemic, all of them require our support.

But, to date, very few interventions for children have been formulated, resourced, or implemented on a scale anywhere near commensurate with the impact of the epidemic. Based on the very small number of country reports submitted in 2007, it is estimated that fewer than 15-percent of households supporting orphans and vulnerable children are being reached by either community based or public sector programs. This figure is barely up from the five percent that was recorded eight years ago. In the most severely affected regions, families and communities are simply carrying the overwhelming burden of HIV, including an estimated 90-percent of the financial cost.

The major sources of support for children and families still come from civil society organizations, many of them faith

groups operating in circumscribed areas, often by happenstance. Even if magnified many fold, these approaches cannot hope to address the required needs. By our current approaches we are not getting to those who most need help. While we dither about what can be afforded by the very rich world, the poorest of the families continue to buy what they can and for their children.

For our efforts to protect children affected by HIV and AIDS, to be effective they must be founded on a bedrock of state support for families, and on a public health or systemic approach that has authority, reach, continuity. Such a bedrock would also enable civil society organizations better to reach much needed individuals who need services such as psychosocial and moral support.

In summary, then, we have short-changed children. In addition to achieving painfully little with many missed opportunities to expand our respond and we have often compounded the problems we have tried to address, PMTCT still does not routinely include treatment for mothers. Mixed and uncertain messages cause confusion about infant feeding; child testing and treatment, family support, and the promotion of children's development, including of children who are HIV negative need attention. Our efforts to help orphans to the exclusion of other poor and vulnerable children in the same communities have caused needless deprivation and unwittingly contributed to children's isolation and discrimination. While the global response to HIV/AIDS has accelerated, children lag

behind in all aspects of HIV control, prevention, testing, diagnosis, treatment, and care.

Well, what now needs to be done? The world is beginning to heed the call for more to be done for children, but we now have to be specific about what this might involve. Leadership and a commitment to a rights based approach to children and families is critical. The AIDS struggle has a history of bringing human rights under the spotlight. Examples include efforts to overcome stigma and discrimination, exclusion from school and work, gender power imbalances, and access to treatment. In each case, AIDS has served as the impetus to challenge abuse and disregard of our dignity, and to advance the fulfillment of human rights.

Similarly, in addressing the needs of children affected by AIDS, the rights of the poorest families in the poorest countries to social protection and universal access to services, now needs to be recognized as the next imperative for action on the human rights agenda.

It is with this issue in mind that I would like to offer four main recommendations to refocus our responses so that they could achieve what they should for children.

My first recommendation is that policies, programs, and funding must be redirected to provide support for children to, and through, their families, such an obvious thing that we seem to have neglected. The overwhelming majority of infected and affected children globally are cared for in families. This is

right because families care best for children and here I am defining families in the broadest possible way, taking into account the many different structures that exist across the world, if many efforts to assist children affected by the epidemic have ignored the clear benefit of supporting families.

In generalized epidemics, HIV clusters in families, affecting many related people at once. Families are also critical entry point and a platform for effective and long lasting behavior change. For example, adolescents who are emotionally close to and supported by their families are generally found in many contexts to be less likely to engage in sexual behaviors at a younger age and to be exposed to other forms of risk for infection.

But it is the socioeconomic conditions of families, the resources they have at their disposal, and the services, safety nets, and support that they can access, which largely determines the nature and the effect of the epidemics impact on children.

The poorest families face the worst effects of the epidemic by diversifying their livelihoods to compensate for lost income and labor, by financing the healthcare of those who are sick, by providing home palliative care, and by absorbing affected kit and kin. They have done this by and large by reducing their consumption, quite frankly, by eating less and by spending less on education and less on the healthcare for

other members of their family. All of this critically affects the well being of children.

This response by families has come with some costs. Household dissolution, abandonment, neglect of informally fostered children of relatives, property grabbing, and abuse have all been recorded. These anomalies do not detract from the importance of family support; rather, they emphasize the need for stronger mechanisms of social justice and welfare in highly effective communities.

What is clearly inappropriate as an alternative response is to attempt to provide institutional orphanage and other forms of residential or non-family care for children. Children who still have families, no matter how poor, orphanages produce problems of their own with documented ill effects on young children's growth, cognition, and socioemotional development that also costs up to 10 times more than family care and they diverge valuable resources from efforts to strengthen, rather than replace, families.

Families are the most influential force in the lives of children and adolescent's. Strengthening the capacity of families through systematic pocket sector initiatives has been identified globally as one of the most important strategies of building an effective response for preventing and mitigating the impact of the epidemic on children.

My second recommendation is that a dramatic rethink in policies needed to develop comprehensive and integrated family

centered services. In generalized epidemics, all activities and prevention treatment and care lend themselves to a family focus. By targeting only individuals, many interventions and services are missing critical opportunities to reach out to family and community members as well.

For example, HIV testing amongst couples and even whole households is proving to be a promising approach. Opportunities to reach out to family exists naturally through services such as PMTCT when a pregnant woman presents at a service point. Other entry points include the home care of their very ill person, or the initiation of a family member to antiretroviral treatment.

Family focused studies indicate that treatment for adults provide very significant benefits for children in the household. A longitudinal microeconomic study in Kenya demonstrated that adults in treatment were able soon to resume working and that their return to employment was associated with terribly important child benefits. Children's nutrition and growth improved, child labor was reduced, and children returned to school.

Action for children's well being must address not only their health, but also their basic material needs for food, clothing, clean water, shelter. It must address the psychosocial well being, their cognitive development, and the changing needs of boys and girls at different stages of their development.

Comprehensive approaches to children's well being provide crucial opportunities to reinforce key components of primary healthcare for all, and it also enables us to integrate health sector action with other child focused work in other sectors, and to leverage broad advances in social development.

My third recommendation is that the backdrop to much of the AIDS epidemic on children is extreme poverty, therefore, much greater attention must be given to social protection for poor families. Social protection is a crucial missing ingredient in responses to children affected by HIV and AIDS. AIDS deepens poverty at the household, community, and over time, the country level. Poor families have few resources and reduced capacity to deal with illness and death. They need free or subsidized services, various forms of insurance, and protection and assistance in times of need.

While I have referred to the scale of the problem in Sub-Saharan Africa, a review of 363 papers in low prevalence and concentrated epidemic communities, has shown that children affected by HIV/AIDS everywhere face similar challenges. Exposure to stigma and discrimination, emotional distress, possible separation from siblings, relocation to unfamiliar surroundings, material deprivation and loss of opportunities and entitlements, heightened risk of further HIV infection in the family, illness, and possible death. Everywhere, HIV/AIDS affected households experienced a worsening of their socioeconomic status. They frequently become indebted, sell

their assets, reduce their consumption, especially of food. They spend more on the healthcare of sick members and suffer a loss of income as a result of declining productivity.

In both Uganda and Botswana, households are being found to spend an additional 25-percent of their income on each person in the household living with HIV. Social protection in poor countries is now firmly on the development agenda, evidence from around the world is demonstrating the benefits of social security in these settings. Every developing country, no matter how poor, can afford a basic social protection program for children affected by HIV and AIDS and extreme poverty.

The International Labor Organization has estimated that the cost of a social protection package for low income, African countries, consisting of a small, universal, old age pension, universal primary education, free primary healthcare, and a child benefit of 25 American cents per day, ranges from only 1.5 to 4.5-percent of the gross domestic product. How can we not provide this to all children affected by HIV/AIDS?

A recent, effective, Zambian pilot program provided US $15 per month, to each of the poorest 10-percent of households. If this approach was implemented in all lower income countries in Sub-Saharan Africa, it would cost only three percent of the aid pledge to Africa at Glen Eagles. AIDS activism has increased access to ARV treatment. Now, in the same way, we

must improve the ability of people to claim social protection entitlements.

If citizens are not empowered to reach out, demand, and receive social protection and other rates improvements in services including HIV treatment and prevention will even further divide those that already have from those with little or nothing. But, it is also critical that the more resources we are requesting go directly to the poorest families affected by HIV, not via the many intermediaries that now currently stand between various forms of aid and the children who need it.

This leads me to my fourth and final recommendation. [Applause]. We should expand the use of income transfers. These have demonstrated impressive results in spotting poor and vulnerable families including those affected by HIV and AIDS. A continuum of social protection strategies exist ranging from micro-lending to skilled training programs and work initiatives. However, the degree of incapacity of the worst hit and poorest families affected by AIDS means that they are often unable to take advantage of borrowing and work. In such cases income transfers have been found to be particularly effective in providing immediate relief in averting disastrous dates and sale of assets. Mexico and South Africa are shining examples in expanding income transfer programs to the poorest families.

In conclusion let me express the hope that this plenary presentation both reflects and inspires a greater awareness of children in our response to HIV and AIDS. Children and families have been shamefully neglected. Prevention, treatment, and care for children continue to lag behind adults. Support for all affected children has been left largely to families extended kin and communities although they are the most appropriate groups to help children they cannot protect and care for children without assistance. The current response is composed largely of temporary ad hoc projects with limited outreach.

These efforts undoubtedly alleviate some of the distress experienced by children and families, but small localized projects can only take us so far. To have bigger impact requiring larger and more systemic responses, our technical achievements in fighting HIV/AIDS must be matched by the appropriateness, effectiveness, sensitivity, and respect of our response. This is especially true of children for whom ultimately we have responsibility. Thank you. [Applause]

SUNITI SOLOMON, M.D.: Now it is my pleasure to introduce Elena Reynaga from Argentina, the third speaker of this session. All of us working in the field of HIV/AIDS know very well the violation of human right against sex workers with the police and the government. Elena with her Herculean efforts started working as a social activist in 1994 to denounce the violation against sex workers and became a point

of reference both nationally and internationally with regard to sex work related issues including HIV, AIDS, violence, gender, human rights, and labor rights.

She is the Founder and Executive Secretary of AMMAR, an Argentina Association of Female Sex Workers and its major achievements have been an establishment of the syndicate, which gives the sex workers the status of workers. She is also an executive secretary of the Redtrasex, a network of female sex workers of Latin America and the Caribbean and a consultant on many international bodies. Ladies and gentleman let me present to you Elena Reynaga. [Applause].

ELENA REYNAGA: Wow. [Spanish spoken 1:05:00 to 1:30:12]

[END RECORDING]