Prevention of Mother-to-Child Transmission: Maternal Health and Elimination of Pediatric HIV/AIDS
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ROSLAN MALYVTA: Dear ladies and gentlemen. I would like to welcome you to the session "Prevention of Mother-to-Child Transmission: Maternal Health and Elimination of Pediatric HIV/AIDS." My name is Roslan Malyvta and I work with UNICEF in Eastern Europe and central Asia regions as PMTCT Pediatric HIV/AIDS Advisor. I will co-chair this session together with my colleague, Dr. Yin-Ro Lo, from World Health Organization in Switzerland.

Today we have a panel of four outstanding scientists and public health professionals—Dr. James McIntyre, Dr. Nathan Schafer, Dr. Gabriele Fischer and Dr. Nigel Rollins.

As you may have already heard from previous presentations during this conference, a significant progress has been made in delivering prevention of mother-to-child transmission globally in low and middle income countries. More than 1.5 million pregnant women were benefits from PMTCT's intervention in 2008; however, much work remains to be done.

More than 400,000 children were newly infected with HIV in 2008, the vast majority from mother-to-child transmission. In the year 2010, WHO recommendations for antiretroviral treatment of pregnant women, PMTCT and infant feeding provided an important opportunity and public health approach to

implement highly effective interventions in resource limited settings and promote health for both mother and child.

In non-breastfeeding populations, the risk of mother-to-child transmission can be reduced to less than two percent, and less than five percent in breastfeeding populations. Major gaps and obstacles need to be overcome to achieve this.

These are also challenges of health-related millennium development goals. Many women give birth without a single antenatal visit and outside healthcare facility. Maternal and infant mortality in many countries remains unacceptably high. Scaling up the PMTCT coverage and reaching the goal of elimination of mother-to-child transmission should go together with [inaudible] and improvement of maternal and child health platforms.

We need to better understand why women don't attend antenatal care and deliver a child without getting assistance from qualified professionals. We need to identify early enough high risk pregnancies to prevent mother-to-child transmission, infant and maternal mortality. We need to change the attitude of society and health communities towards HIV positive women and their children.

Elimination of mother-to-child transmission and reduction of infant and maternal mortality in countries with concentrated epidemics will not be possible unless enhanced and

equality of services and better outreach to more generalized and most at-risk women. Pregnant women who use street drugs often tend to be missed by antedelivery care and PMTCT services.

Programs need to be tailored to meet their needs and go beyond clinical care, and should include a rate of social support and protection issues, both in health institutions and in the community. Today we are funding an operational mechanism. We have leadership to build AIDS-free generation. The target of elimination mother-to-child transmission by 2015 is agreed by measure stakeholders and government. Together we could heed this call and make it real.

With this, I would like to move the microphone to our first speaker, Dr. James McIntyre from Hanover Health Institute from South Africa. James McIntyre is an Executive Director of Hanover Health Institute in Johannesburg, and the International Vice Chair of the U.S. National Institute for Health Funded International Maternal, Pediatric and [inaudible] AIDS Clinical Trials Network, the leading global collaborative network on HIV in women and children.

Dr. McIntyre previously worked for 25 years in the Chris Hani Baragwanath Hospital in Soweto where he was a co-founder and Executive Director of the [inaudible] HIV research unit. Dr. McIntyre, please. [Applause]

JAMES MCINTYRE: Thank you very much and congratulations for finding you way through to this room. I'm not entirely sure what background music we'll get, but I'm sure it'll be appropriate as the slides change. And I do need to point out, of course, that I must have started work very, very young in Soweto to have done it for 25 years.

I'm going to try and contextualize before we get into some of the more detailed presentations just where I think we stand with regard to HIV and the millennium development goals, particularly four and five, to reduce child mortality, and to improve maternal health. And I really think that, if we're serious about addressing MDG's four and five, we also have to realize that MDG six and, particularly, the combating of HIV and AIDS is completely central to achieving these goals, especially in the countries of highest prevalence.

So if we look at the scale of the problems, we know that there are 33 million or more people living with AIDS globally, two million dying, and nearly three million newly infected in 2008. We know that nine million children die in the developing world every year and that about two-thirds of these deaths are from preventable causes. And we know that around half a million mothers—although recent data suggests that this is dropping—die from complications of pregnancy or childbirth.

And if you look at this—and I love these maps from World Mapper because they just, for me, help me visualize what's going on. This is a map that shows you what the size of the continents would be if they were in proportion to the thing that we're looking at. So if you look at world population in general, you can see that Africa, for instance, has relatively few people, India has a very large population, so it would become bigger. But if we now do that for infant mortality and maternal mortality and HIV, you can see the areas of overlap.

So infant mortality and maternal mortality are exactly the problems in the same places where HIV is a problem. And so WHO's four prongs that we've heard about throughout the conference and which remain the mainstay of our approach to this become really important for addressing both four, five and six of the millennium development goals.

And we've made progress; we have, undoubtedly made progress. You've seen the slide, you've heard it mentioned, we've seen coverage rise from around 10 to 15-percent in 2003/2004 up to about 45-percent and in east and southern Africa to 58-percent, but we don't often see the reverse of this slide. We don't see the number of people who are not getting ALVs that they need in pregnancy and that remains, probably, more than half of women.

We do have this remarkable increase in treatment. We've seen treatment across the globe extended by millions, and that will have some impact on what we're talking about. We have the statements from our leading international agencies and politicians. There is no reason why a mother should die of AIDS; there is no cause for any child to be born with HIV. We can virtually eliminate it.

And so, we're hearing a lot of the eliminate word; we're hearing eradicate around mother-to-child transmission and I think that that's a wonderful goal. It worries me a little bit that we're almost perceiving that because we say we can do it, it's done, and I don't think it is done. It worries me to some extent that PMTCT is going down the agenda of all of our industry here to the extent that you've been relegated to this tiny room in a tucked-away hot corner. But I think that we can move towards that, but I do think that there are some things that we have to recognize have to be done.

So let's talk about appropriate treatments and care. PMTCT services now should be gateways to treatment. Women who need treatment should start it as soon as possible in pregnancy; we've just seen more data again from this conference around that, and we have to recognize that HIV is an underestimated-so far-cause of maternal mortality. This is from this recent article in *The Lancet* that shows what's

happened to maternal mortality since 1980. And if you take the non-HIV causes, you can see this quite dramatic decline. We are having an effect on reducing maternal mortality, but what is keeping it up-although there is some decline from here-what is keeping it higher than it should be is the HIV effect.

And if we look at my own country, in South Africa, where we have a confidential inquiry into maternal deaths, we look at that data from 2002 to 2007, non-pregnancy related infections were the most common cause of death in the first trianium-37.8-accounted for 46-percent of deaths between 2004 and 2007, and AIDS was the single biggest cause of death of mothers, 22-percent higher than any direct obstetric cause.

And if you look at this data of institutional maternal mortality, you can see that the maternal mortality rate in HIV negatives was one-tenth of the maternal mortality rate in HIV positives. So I think that that shows exactly their interaction. But, I think we shouldn't forget about TB. HIV and TB are both independent risk factors for maternal mortality. TB is more common in young women and high prevalence HIV settings in Africa than in older men or in older women.

A South African study showed a ten-fold higher TB incidence in HIV-infected mothers as HIV non-infected mothers and maternal mortality in this study was 121.7 per thousand

with co-infection compared to 38.5 with TB alone, so I think it's just a reminder that we have to do that. [Inaudible] and colleagues recently published this in *The Lancet,* "To say that reducing maternal mortality in women with HIV will also require improvements in antenatal care and obstetrics services, as well as specific attention to the management of conditions that are aggravated by underlying HIV infection."

And I want to say something about the need for treatment, compared for the need for prophylaxis, and Elaine Abrams referred to this data again this morning in her plenary, but I think it really helps us to focus our mind. This is data from Luis Cunnen [misspelled?] Colleagues from the Zeb Study in Zambia and its based on just over 1,000 women who either had follow-up to 24 months. And if you take a CD4 count of less than 350, our current entry point of ALV treatment in the guidelines that we'll hear about, you can see that in this study, 54-percent of women-of these pregnant women would have qualified for ART under their condition.

If we add in the clinical staging, it goes up to 68-percent. So I think that that's, again, a reality call. So when we talk about providing antiretrovirals to women who need them in pregnancy, it may be a large number. But it pays off. And that's shown here by the proportion of transmission and the maternal mortality broken up by those categories. So in those

eligible for ART by CD4 or clinical, you can see those women made up 87-percent of the transmission, both by six weeks and after six weeks; and 92-percent of the maternal deaths, whereas those fewer women who were not yet eligible for ART were at much lower risk contributing only 12.5-percent of transmission from the third of them who met that criterion, and only 8-percent of maternal deaths.

So getting women on treatment, whether it's 30-percent or 60-percent in our services, those women who require treatment remain an urgent priority that we need to address. We know that for those who don't get required treatment, they should be receiving the best possible prophylactic regimen and Nathan will go through the new guidelines, but I think we also need to acknowledge that in this day and age-in 2010-single dose Nevirapine with breastfeeding that is unprotected by antiretroviral prophylaxis is not an appropriate PMTCT strategy other than in emergency settings. It's time to move on. And moving on we are. [Applause]

This is another slide from Elaine Abrams that shows the use of PMTCT drugs in NTCT Plus programs and you can see in blue the drop-off in single dose Nevirapine. You can see the increase in dual drug therapy, but we're still far from achieving the number of women who should be getting ART.

And just to reinforce this yet again, the Pearl Study published this week by Elizabeth Stringer and her colleagues presented at a number of conferences last year that just shows that even, again, with our most simple regimens, the drop-off between women who are provided single dose Nevirapine and those in who it could be shown in cord blood that they've taken it, so there are many slips along the way.

There are remaining research questions in PMTCT. PROMISE, the very large trial planned by IMPACT will provide many of those answers and will particularly start to investigate whether it's safe to stop triple therapy for prophylaxis, or whether it should be continued.

I want to move to child health. We know that HIV is closely linked to the failure of many countries to be on track for MDG IV, we know that child health outcomes are completely affected by the health of the mother and the family and that maternal illness or death worsens child outcomes and increases child mortality, and that's why we still see AIDS orphans in high prevalence areas.

We also know that there's been slow progress in improving access to ART for children in need. HIV is a major cause of death in high prevalence settings. Half of all deaths of children under five occur in Sub-Saharan Africa. Africa accounts for 90-percent of HIV infections in children; 90-

percent of HIV-related deaths. And HIV is the underlying cause of one-third of deaths in children under five in the countries of Sub-Saharan Africa. These are projections from the U.S. Bureau of the Census for this year to show that what under-five mortality would look like with or without the impact of HIV, and I think they speak for themselves.

South Africa also shows that and in the [inaudible] study across South Africa, if you look at the number of neonatal deaths from infections, if you look at many of the related conditions, HIV is playing a major role in child death. We know from the Shure [misspelled?] study that early diagnosis and early initiation of treatment in children saves lives; that in getting children on to care rapidly with PCRTs done in the first four to six weeks cuts mortality completely, but we also know that access to treatment for children with HIV is less than optimal.

We have gone up to just over 355,000 at the end of last year and that had increased from 276,000 estimated in 2008, but we know that more children's lives can be saved if treatments are started earlier in line with the new recommendations. And that's partly because of the availability of testing. Expanding the availability of early infant diagnostic testing remains a critical need. WHO's calling for greater access and without that diagnose, without prompt initiation of treatment,

one-third of HIV-infected children will die before their first birthday and half will die before two years.

We've seen data presented at this conference from my colleagues at the Africa Center that also shows that treating mothers helps to save babies, and in the work from the Africa Center, the incidence of death by five years of age in children of untreated mothers was 9-percent, compared to 5-percent in those where their mothers received therapy. And after adjusting for other risk factors, antiretroviral therapy reduced the risk of children's death by 75-percent.

What can we do in order to achieve this? We know that the effectiveness of our PMTCT programs is probably even more dependent on providing access and coverage than it is on the right regimen. Regimens are important, but reaching them is equally so. HIV-infected women need to be identified, they must have acceptable interventions and those interventions must be in place. And they must particularly be in place to prevent breastmilk transmission if we are going to achieve success.

But prevention of mother-to-child transmission will fail if we focus only on the narrow role of women and their biological role in transmission, and reaching MDG's four, five and six, I think, requires a much broader view and much increase coverage of strategies that we know to be effective.

We should be measuring indicators beyond just infected children. Have we used the most effective drug combinations? Are we providing them? Were mothers evaluated for the initiation of full and ongoing antiretroviral treatment? This would be as much of an indicator as how many women receive prophylaxis. Are other sexual and reproductive health services being provided? Is family planning in place? Were other members of the family targeted through that woman for the provision of service? Has counseling taken place on infant feeding and on future contraception? And has there been exploration by the caregivers of possible special support services that may be necessary?

We need to link the PMTCT programs to everything else that goes on around them. I suggested somewhere the other day we should circumcise all the fathers while the mothers were pregnant, but I got a strange reaction from the men. That linkage may be integrated linkage, it may be to other services that exist, but either way, we need to link it. And we have to realize, though, that PMTCT does not exist in a vacuum.

The resources for treatment are under siege. Nine million three people worldwide still lack access to ART, and two-thirds of those are in Sub-Saharan Africa. Public health decisions on PMTCT programming and regimens need to be made as part of broader country HIV programming. And as we talk of

elimination, as we target elimination, as we talk about getting to zero, and virtually eliminating-I'm not quite sure what the difference is between virtual elimination and elimination, so I think let's aim at elimination by 2015-I think we have to think about what that means.

UNAIDS in the book that they provide in your conference bag lay some of that out: "Virtually eliminating of HIV among babies will cost a little over $610 million a year in low and middle income countries, but the return on that investment is high." I would say the return on that investment may be priceless, a little bit like the MasterCard ad. If programs go to scale according to plan, the world could avert two million child infections between 2009 and 2015.

That's our challenge. I hope the next speakers are going to tell us how to do it and I look forward to hearing how we've achieved it by the next conference. Thank you.

[Applause]

ROSLAN MALYVTA: Thank you, James, for your very nice presentation and overview of the trend relation between maternal and child health and PMTCT. We know from the developing world where maternal child health services are strong, but PMTCT mother/child transmission is virtually eliminated. And let's hope that interventions we do today for prevention of HIV infections in countries with low resource

settings will help also to improve maternal and child health and achieve other millennium development goals.

With that, I would like to move to our next speaker. I would like to introduce Dr. Nathan Schafer from World Health Organization Switzerland. Dr. Nathan Schafer is a leader of the PMTCT Team in WHO. He joined WHO one year ago as a PMTCT team leader and in his capacity, he led the revision of PMTCT guidelines. He coordinates PMTCT's approach with other departments and help lead the PMTCT's inter-agency task team.

Previously he led PMTCT group activities for CDC and PEPFAR and led the original short course AZT trial in Thailand. Dr. Schafer, please. [Applause]

NATHAN SCHAFER: Roslan, thank you very much. I hope you can hear a little bit better than we could hear on the platform; I feel like we're in a maternal child health clinic somewhere. It's crowded and hot and people screaming all over the place, so maybe some of you are used to this already.

I'm going to give a similar talk to what I gave in the symposium on Monday night, but I hope I have a little bit more time to walk through some of the issues. I think that many of you have picked up the new guidelines for PMTCT and Infant Feeding. There may still be some in the back and, if not, please-there were still copies at the WHO booth as part of the UN booth, so please be sure to pick those up.

My talk which I hope that you will have a clear idea of what the new PMTCT and Infant Feeding guidelines are about as an overview, why they are so important and why this is a tremendous opportunity moving forward within the context both of elimination and improving and attaining the MDG goals. So the key messages for the talk are that the new guidelines really represent a major paradigm shift for PMTCT and HIV infant feeding. They provide the normative basis for the elimination of vertical transmission that we're hearing so much about at this conference.

But the challenge, truly, is to implement and scale up the new, highly effective regimens. James outlined the comprehensive issues and the different prongs that are needed in terms of prevention of infection in women and avoiding unintended pregnancies, but for the purposes of this talk on the guidelines, I'll be focusing on the prevention of mother-to-child transmission from an infected pregnant woman to the exposed child.

While much progress has been made globally as of 2008, really we've only, by estimates, are only averting relatively few infections. From nearly 500,000 probable likely infections, we're preventing about 70,000. We think that there will be a significant improvement in this figure as the 2009 calculations are made, based on the rapidly expanding coverage.

If we're talking about achieving elimination, or virtual elimination, we're talking about trying to get down to-at least down to this area of less than 50,000 global infections a year, which would represent a 90-percent decrease in infections.

In November 2009, WHO launched three harmonized, or coordinated, Rapid Advice documents: one on adult treatment; one on PMTCT ARV interventions; and one on HIV and infant feeding. And this was important for several reasons. First of all, the guidelines and other related guidelines, but these specifically are very much inter-related with each other and, too, I think there was real-a real urgency by the-and excitement-by the scientific community to rapidly move to new guidelines based on new evidence, and countries that are scaling up programs were really demanding and expecting new and better guidelines as the basis—more effective guidelines for their programs.

So there's been a tremendous amount of work already based on the release of the Rapid Advice. At this conference, we've launched the full guidelines, and as I mentioned copies may still be available at the door, the Adult Treatment Guidelines, the PMTCT, and the HIV and Infant Feeding guidelines.

The rationale for developing the new guidelines were based on new evidence on what is the best time to start ART

interventions in pregnant women, when to start ARV prophylaxis, what are the best ARV prophylaxis strategies, and most importantly, the very impressive evidence that emerged since 2006 on the benefit of different prophylaxis strategies to prevent transmission during breastfeeding.

I want to remind you that without interventions, the risk of transmission is approximately 15 to 45-percent. We use a point estimate of about 30 or 35-percent. It obviously depends on local factors and, most importantly, on breastfeeding.

With the 2006 guidelines, even under the best of programmatic circumstances, we could expect-we were working in the range here in blue-of approximately trying to achieve transmission rates of 15-percent at best. And we had tremendous dilemmas in terms of guidance on breastfeeding and what was safe and what might reduce the risk of infection.

The new guidelines-to jump ahead-are clearly targeted-based on the new evidence-on reducing transmission to less than 5-percent in the presence of breastfeeding, or even lower, and reducing transmission to less than 2-percent without breastfeeding. The guidelines are based on two major principles and James has alluded to that. One is lifelong ART for HIV positive pregnant women in need of treatment and the second is prophylaxis, or the short provision of ARVs to

prevent transmission from mother to child for women not eligible for treatment. And this is both during pregnancy and during breastfeeding, if breastfeeding is deemed to be the best and safest option for the child's health.

I want to just briefly mention that going into the discussion of the revised guidelines, there's really increasing complexity about the drugs that we're considering using during pregnancy and during the breastfeeding period, so there are a lot of considerations about toxicity. And one of the issues that still makes our guidelines somewhat complex is the different considerations of available drugs that could be used during pregnancy or the breastfeeding period.

Ultimately we would like, of course, to have one simple fixed dose combination of drugs that could be used for pregnant women; that could be used for women with low CD4 count and high CD4 count, but we're not at that stage yet.

Now for women who are eligible for ART, the basic principal is that women who are eligible should receive ART for their own health for lifelong treatment, and women should be initiated similar to the adult guidelines. Pregnant women should be started and, indeed, prioritized for ART if their CD4 count is less than or equal to 350 regardless of clinical stage, or if the CD4 count is not available, if they have

clinical stage three or four, ART should be started as soon as feasible.

We know that CD4 counts, or CD4 testing is much more sensitive than clinical staging, so the new guidelines clearly put increased importance, and stress the need-the critical need of CD4 for decision making on ART eligibility. And there's been important discussion, exciting discussion here about different strategies to make CD4 counts more available, to do pointive care CD4 testing, and to pursue other strategies. So this is a schema of what the eligibility for ART looks like in the new guidelines.

And here's the schema of the basic table for the ART regimen that is recommended. The first line regimens are the same as the adult first line regimens and what also should be emphasized on this slide is that the mother is receiving ART; the exposed infant should also still receive four to six weeks of prophylaxis during the immediate newborn period.

A lot of data supported the new recommendations. This is one set of data from the ZEV [misspelled?] Trial that James referred to already showing the extraordinarily high risk of transmission and the important contribution of transmission and maternal deaths and postnatal infections in women with low CD4 counts. So the guidelines really emphasize the importance of targeting women who are eligible for treatment and treating

women lifelong for their own health and for the benefits of interrupting vertical transmission.

Women with CD4 counts less than 350 represent about 40-percent of HIV pregnant women; account for about 75-percent of all of the MTCT risk; account for 80-percent of postpartum transmission; as much as 85-percent of maternal deaths within two years of delivery. So, clearly, there will be a very strong benefit from initiating ART for maternal health and PMTCT throughout the course of the pregnancy and postpartum.

The second part of the strategy is ARV prophylaxis to prevent mother-to-child transmission, and this is for women who are not eligible for ART or with unknown eligibility. And the new guidelines recommend starting as early as 14 weeks gestation. We're moving the start time from 28 weeks, beginning of third trimester, to 14 weeks. We realize that, in most settings, women will not be starting at 14 weeks, but we hope that they will be starting sometime during the second trimester. There have been tremendous missed opportunities from the old guidelines of women targeted to start in the third trimester, but, in fact, not starting until very late in the third trimester.

And in the new guidelines for prophylaxis, two equivalent options in terms of effectiveness are recommended. Option A based on maternal AZT, or Option B based on maternal

triple ARV prophylaxis and I'll speak a bit more about those in a minute. And what I want you to focus on is that the intervention to the mother must be coupled with an effective intervention during the breastfeeding period. So it's a package. It really extends our whole concept of what PMTCT is about; it no longer at all stops PMTCT, which never should have stopped at delivery, but now our interventions and our follow-up certainly do not stop at delivery, but must continue throughout the follow-up and support and interventions for the exposed child.

And again, there is a substantial body of data to support the new recommendations on Options A and B and prophylaxis. This schema summarizes some of the many studies-tremendous amount of work was done on extended Nevirapine prophylaxis up to six months and ARV triple prophylaxis to mothers. So this is the schema that summarizes the two options in the new guidelines. Option A which starts AZT-there is a recommendation to continue to use single dose Nevirapine and the AZT 3TC tail, especially if the mother starts the AZT late, and then the infant will be put on daily Nevirapine from birth until one week after the end of breastfeeding.

Option B is based on one of several different triple ARV prophylaxis regimens and the mother would continue the triple prophylaxis throughout the period of exposure to

breastfeeding. The related companion guideline which my colleague, Nigel Rollins, headed up is the HIV and Infant Feeding guideline, and I'm just going to briefly summarize two of the considerations here.

From a programmatic point of view, the guideline recommends strongly that it's really now up to national programs to decide on the best feeding option that the national program will support. Certainly, individual mothers still need to make a choice about infant feeding options, but in terms of program support and general support for the infant feeding strategies, this should be part of a national program decision and based on the strategy that will most likely give infants the greatest chance of HIV-free survival.

The question of how long to breastfeed, I think, is still going to be a complicated one. The evidence showed that certainly breastfeeding should continue up until 12 months and then mothers could safely wean from that point. I know that this is going to continue to be a difficult choice in terms of the duration in countries that choose breastfeeding as the best option, but the basic principle would be that prophylaxis should be provided throughout the breastfeeding period.

The cost of the regimens is important and we've heard some very good analyses already of the potential cost benefit and cost savings of the new guidelines strategies. The Option

A is clearly much less expensive than Option B. We estimate that right now, it costs about $50 for the mother/baby pair. Option B costs approximately $200 to $800, so there's a wide range based on the regimen and the price availability in countries. Certainly, we hope that these prices will come down and this is going to be an important part of the decision making in country.

So in terms of the adaptation of guidelines, countries need to face the decision of whether to choose Option A or B for prophylaxis. There are advantages and disadvantages of both options in terms of feasibility, acceptability, safety for the mothers, as well as the cost as I've just mentioned, and this will be important to make this decision at the country level.

In this slide, I've just shown a couple of the advantages and disadvantages that might be considered for Option A. Clearly, there's a cost difference for Option A. it may be easier for Option A in many countries, and high burden countries in Africa are choosing Option A because, essentially it's an incremental increase from the current program of short course AZT plus Nevirapine. And so, now the AZT is extended antenatally and the Nevirapine is extended postpartum.

I think we should point out that in areas where it is unlikely that women will have access to CD4 testing, and many

women would be receiving prophylaxis instead of treatment because they can't be judged to be on treatment, it's plausible to argue that Option B might be more effective in a program setting.

So this schema summarizes where we've moved from the short course strategies of the 2006 guidelines, the darker blue bars show the coverage during the periods of risk for the Option A and for Option B and emphasizing the importance of maternal ART treatment for women that are eligible for treatment covering throughout the risk period for mother-to-child transmission.

In the guidelines, we have a section on research questions because there are not only operational challenges, but there are also important research questions that need to be addressed and answered and, hopefully, would provide the evidence base towards further revisions of the guidelines that we anticipate in a couple of years. I think foremost among these are issues of starting and stopping the triple prophylaxis, the safety of the extended prophylaxis options, the critical issues of the access to CD4 testing, and also, the assessment of proposed strategies to provide ART to all HIV-infected pregnant women.

There are, as we know, important implementation challenges. I think that we should absolutely-while there's

been tremendous success in PMTCT programs on the entry point of testing and counseling, we still need very much to focus on universal provider-initiated testing and counseling as the entry point. We can have the most effective regimens in the world, but if we can't test and identify women in need of the intervention, we will have a program of limited effectiveness.

I've mentioned the issue of CD4 testing and availability. James just talked about the integration of PMTCT and maternal child health services. I would just focus at the end on the great importance of enhanced monitoring and evaluation including impact assessment of the new guidelines. This is an important new opportunity and my colleague, Nigel, will be addressing this in a lot more detail.

WHO has moved ahead with many partners to provide support for country implementation of guidelines and, indeed, I want to emphasize again that countries themselves are really providing the leadership and moving ahead quickly to adapt and begin to plan for the implementation of the new guidelines.

So, to summarize, the guiding principles of the new guidelines are that women in need of ARVs for their own health should receive lifelong ART; that CD4 count is critical for decision making about ART eligibility, intervention should maximize the reduction of vertical transmission and preserve future treatment options. We need to have a unified view of

the antepartum and the postpartum approaches and different options may be appropriate in different settings.

So, in closing, the revised guidelines, we feel, provide an important opportunity, a very exciting opportunity, as we move towards looking to the elimination of mother-to-child transmission. The guidelines provide the new norms and standards for highly effective interventions in resource limited settings to improve the health of the mother, decrease mother-to-child transmission and improve HIV-free survival. With the effective implementation of these guidelines, transmission clearly can be reduced to less than 5-percent in breastfeeding populations and less than 2-percent in non-breastfeeding populations. And the guidelines and the effective program implementation will, indeed, make an important contribution towards the elimination of pediatric HIV.

So I'd like to thank my colleagues at WHO, the many UN partner agencies that provided support and, most importantly, the expanded IATT partners and the countries and ministries of health that are actively working on-that had input into the guidelines and are actively working on implementation. Thank you very much. [Applause]

ROSLAN MALYVTA: Thank you, Nathan. We have time for two questions from the audience. No questions? Okay. Please.

FEMALE SPEAKER: Thank you both for wonderful presentations and for your inspiration throughout. I wonder how assessment of survival of women is going to be carried out when we have no baseline data available. The longest maternal survival data that we have is Dr. Kune's [misspelled?] data, as far as I know, from Africa. We have none in the developed world and I would just mention our poster from this meeting about our experience in the Bronx where we found that seven-year survival was 75-percent in a resource-rich setting with women with lots and lots of visits to the doctor. We don't know what the sources are, what the reasons are, but we do know that we don't know and I'd like to hear of implementation of just assessing where we are right now. Thank you.

ROSLAN MALYVTA: One more question? Please.

LORRAINE SHUR: I'm Lorraine Shur [misspelled?] from London. I'd like to ask a question about compounds that permeate the blood brain barrier. We do know in adults where there's HIV dementia and cognitive delay that that's really important. Is anyone looking at that in children and in pregnancy?

ROSLAN MALYVTA: I'll take one more question from the gentleman from the back.

MALE SPEAKER: Thank you, again, for an exciting presentation on the part in the shift, but one of the things

you mentioned in the paradigm, both speakers, was primary prevention, which is absolutely critical part whether there is any real reports, whether there is any trend downwards and how that's going to be monitored parallel to the paradigm shift that we are preaching [misspelled?].

ROSLAN MALYVTA: And the last question.

TIM: It's a very quick question, just to Nathan. You mentioned when you were discussing Option A versus Option B. Option A, I think is the single AZT and then extended Nevirapine for the baby during breastfeeding. You mentioned that in order-and Option B is the triple ARV prophylaxis. You mentioned that Option B requires CD4 testing, but I think Option A requires CD4 testing also in order to sort out those women who require therapy rather than prophylaxis. Maybe you could just clarify that point. Thanks very much.

ROSLAN MALYVTA: Thank you. Nathan?

NATHAN SCHAFER: Thanks. Fortunately I wrote those questions down a little bit, because I don't remember any of that, but let me work backwards. First, maybe I misspoke a little bit. I know what I was trying to say. Tim, you're absolutely right. To decide on prophylaxis, the whole idea with the guidelines is that Option A and Option B are for women that are not eligible for ART and that's premised primarily on the CD4 count. What I was trying to say was that in the

setting where women are not effectively assessed for eligibility, then Option B arguably in a program setting might have more effectiveness because it will be providing a triple suppressive regimen for women that have low CD4 counts.

In terms of the paradigm shift with primary prevention, that's a great question. We've had other sessions that are looking and emphasizing on prevention and we heard a plenary on combination prevention this morning. I think that we need, in the PMTC-broader than the PMTCT area, we really need more focus on what are the effective strategies that are actually going to be decreasing the numbers of infected young women who may ultimately become pregnant. That's much more than what the PMTCT program can take on.

There are effective strategies with partner testing, male testing, working with discordant couples and trying to do primary prevention in settings where there's enough capacity for women that test HIV negative. After all, pregnant women are the largest group that are routinely being tested. It's a tremendous missed opportunity not to intervene with more effective prevention strategies for women that test negative as opposed to just a 30 second or a three second information.

But I think that we need to focus on that as the speaker suggested. We also need to have better data. I'm actually not so sure that we even really know what are the

trends in countries, and this is an opportunity as we move in the next five years towards the goal of elimination to really look at the number and in different age groups, particularly young women, at the numbers and the trends of prevalence and, to some degree, incidence of HIV infection in women so that we can focus on the prevention efforts.

We certainly hope that the overall denominator is going down as we hope that our effectiveness of programs is going up. On the question of the compounds in the blood brain barrier, there was a very nice session yesterday on pharmaco [misspelled?] vigilance and very important presentations by the antiretroviral registry-pregnancy registry-on long-term monitoring of the effect of different compounds during pregnancy and postpartum. And I think that one of the messages from that session was that we need enhanced pharmaco vigilance as new products are introduced. Clearly, if we're talking about longer term effects in later developments of children, then that's going to present big challenges. I know that there are long-term cohorts that have been set up in the U.S. and some other developed countries, but that's a big challenge, but we need to be thinking about that and look for any potential signals to trigger our focus of interest.

On the issue of maternal mortality, I might ask James or Nigel, perhaps, to comment on that. I think that, Karen,

you pointed out rightly that we really have very limited data in terms of maternal health and survival. One of the opportunities among many of the new guidelines with the follow-up and the expectation of follow-up of the mothers and babies is that is provides us the opportunity, at least first with short follow-up of mothers and to help that transition into care so that strategically we can begin to think about the follow-up of mothers.

There's been so much talk about the MDGs, but we need to develop strategies for how are we going to get the real data. James, do you want to add?

JAMES MCINTYRE: I think just to agree and to agree with Karen that we don't have data. Antiretroviral treatment started in pregnancy is absolutely novel to most of these high prevalence countries. We don't have women, in general, in long-term follow-up, and so, I think it's something-you raise a really good point that we need to collect the data and start to see what's happening.

ROSLAN MALYVTA: Thank you, thank you, Nathan.

[Applause]

YIN-RO LO: I would like to introduce the speaker for the next presentation on pregnancy, HIV and drug use. It's a very exciting topic; we don't hear about that very often in the usual PMTCT circles, so I think that's a very important

presentation by Dr. Gabriele Fischer. She is a Professor of Psychiatry and Neurology at the University in Vienna since 1994. She's the medical director of the addiction clinic.

She's involved in various scientific studies in the field of substance use disorders. Substance dependence during pregnancy has become her special research focus. She's a [inaudible] and very valuable resource person for several international and national institutions including UNODC, which is the United Nations Office on Drug and Crime, the World Health Organization and the European Parliament. Gabriele, the floor is yours.

GABRIELE FISCHER: Thank you very much. As I'm one of the few Viennese people being actively involved in this major meeting here, I want to give you a special welcome in Vienna, and also, I want to refer that it's not only the AIDS conference we have now; we also-it's also the place where Sigmund Freud used to work. And Sigmund Freud also had a lot of experiences by himself and wrote a lot of essays in regard to the dangers and the features of drugs.

I want to thank very much UNICEF and WHO for inviting me to be part of this panel and I would, actually, start off with the topic of addiction.

There was a very interesting presentation in the morning in the Key Lecture, "Looking into the Prevention of

Mother-Child Transmission," and I felt kind of embarrassed because the world of addiction and drugs never was mentioned. And you will see-if you do not know so far, but I don't think-is one of the key reasons, but there is a high mother-child transmission, and if you do not consider addiction-it's a severe disease-and treat this disease, we will lose the battle of reducing the transmission rate for the neonates.

This is very, very well known to the audience here, the figures of how many HIV infections do we have worldwide. We find here the figures about 50 million HIV-infected women, 1.6 million gave birth to children and .4 million children were born with HIV. And just to picture you the dimension of addiction, we find here the data with one billion suffering on tobacco dependence, two billion on alcohol and if we've taken every range of illicit drugs from cocaine, amphetamines to opiates, it adds up to about 50 million worldwide. And opiates are the major drug—shooting heroin is one of the major reasons why women get infected with HIV.

You find here a very interesting ratio between women and males suffering on substance dependence disorder. Ten years ago, it was a ratio of four to one; now we got this ratio, it's about two to one. Women are actually increasing in these figures of suffering on addiction. It used to be about 10 years ago, a key publication in science pointing that

addiction is a brain disorder in these matters and the most effective treatment approach, as in many psychiatric diseases, includes biological, behavioral and social context treatment approaches. And this actually-these approaches from biologically, behavioral and social context relate as well to the context of treating HIV/AIDS.

We also have to bear in mind that addiction is a chronic relapsing disorder with high somatic and high psychiatric [inaudible]. And addiction and the treatment course-the treatment of substance dependence does not differ to any other chronic disorder; it's no different to diabetes, hypertension or asthma. So we always have to keep this in mind, we're talking about a chronic, relapsing disorder.

And if we move on now to a healthy pregnancy, what are the ingredients? Good genetics. We do know that in our population very often there is already a genetic loading of substance dependence. We do know that there's a high inheritability. And still some people think you have to just say no. That's actually the wrong approach and if you're not facing the issue of a chronic, relapsing disorder, we're unable to treat this condition sufficiently. And we won't need all the other ingredients to have a healthy pregnancy.

So the field is broad if you look in our target population of the injecting heroin-dependent women who are

pregnant. If you're not treating addiction, there is ongoing shooting, it's putting a high risk on the pregnant women. There's a lot of infection, it's HIV, it's Hepatitis C and many, many more infectious diseases. And these women are going to be exposed extendedly very often to a violent environment. So we know by now that about 30-percent of the opiate-dependent women are in the childbearing age.

We do have improved treatment approaches for a long, long time. We do know-and this is quite different from publication to publication-about 30-percent and higher of HIV infections are related to IV drug use and to under treatment of the possible opiate maintenance therapy in many areas.

And what is very, very interesting for our treatment, opiates are not teratogenic so we actually can treat these women with opiates like methadone and buprenorphine.

And what we also have to bear in mind, that about 50-percent of our target group is having a co-dependant and, very often, a co-infected partner, so we have to treat, of course, both of them. And what I think is very obvious, is that we not only have opiate-dependent people-or women, pregnant women who are infected-they use many, many other drugs. And what we have to be, actually, very careful, we have to treat them adequately, as pointed out now with antiretroviral treatment

and what kind of drug interactions are going to be occurring with our medication we offer for the treatment of addiction?

Continuously, we need to think how is actually the outcome and we've got to develop mental aspects. This is a slide pointing you out, it's from *The Lancet* which is actually- it was available here. They write, "The proportion of IV users in Russia, China, Ukraine, Vietnam, Malaysia in relation to the percentages of HIV infections." You see these high figures and, unfortunately, you find these very low figures of having access to antiretroviral treatment. Keep this graph in mind because I'm going to be showing how low the treatment of addiction in these areas is.

There is a general consensus between WHO, UNODC and UNAIDS that maintenance, opiate substitution therapy is the standard of care for treating opiate addiction, and for preventing HIV in IV drug abusers. We don't have many medications, but we have some medications for a long, long time, like methadone.

Methadone, actually, had been first published in 1965 and it's the common standard that for opiate-dependent pregnant women, methadone is the role model of medication for adequate treatment. This has been pointed out by key people in the U.S., Edward Gates, Robert Newman, Mary Jean Break

[misspelled?], Loretta Finnegan, there's a lot of evidence that this is a standard of care in pregnancy.

In Europe, we increased the methadone coverage. In the world, actually, you can read this, very rare is Australia and Spain, but you see here China actually increased very nicely [inaudible] they label this medication because of HIV. And I was recently in China; it's delightful to see that opiate dependant HIV positive pregnant women are on methadone and antiretroviral treatment.

This is the graph I was referring to you, that this is again the proportion of IV drug users and the very, very small proportion you see what is available on opiate agonistic treatment for them in these areas. Even with that, it's very low the antiretroviral treatment available, but we are very, very unhappy that Russia has never been moving in watching these increasing figures in the population.

Opiate maintenance therapy makes a lot of advantages in HIV positive women. We can actually not only provide the medication it's got to be a comprehensive counseling, towards addiction, towards harm reduction, towards antiretroviral treatment, and also toward direct drug intervention. Detoxification would be ideal goal but it's not possible and it's not the recommended approach during pregnancy and not even if we have an infected pregnant woman. There are other drugs,

buprenorphine, WHO just released about a year ago that buprenorphine and methadone are the standard of care of medication also in pregnant women. We do not have that many data on buprenorphine it works similar to methadone but it seems to be very, very beneficial for these women, and again we can administer these during pregnancy because it's a non-teratogenic medication.

There is some research toward trials of buprenorphine, as we have learned, and this question was pointed out right now. I being a drug researcher, I'm jealous. I see the necessity that there is antiretroviral treatment available in HIV positive pregnant women. But for us, in the psychiatric world, are using other drugs, we do need to prove the evidence that it's a fake cure, does it have side effects, and we even are looking in the neuropsychological development of the neonates and children. For there are many, many studies in the meantime that show us that also buprenorphine is a safe medication and it used to be an issue the cost factor of a long time. But more and more generic products are available for developing countries. So it is not either methadone or buprenorphine, it's finally we have methadone and buprenorphine as efficient medication to treat opiate dependant pregnant women.

We do have very rare data so far on the interaction with the antiretroviral treatment and this medication. We are quite nicely educated in regards to methadone, we do know that we need to increase the dosing, we need to divide the dosing, but it seems to be that buprenorphine acts a similar way. So opiate maintenance works, it reduces death, reduces drug use, reduces HIV risks, and saves money. It's cheap, this is the area when I have been consulting in Eastern Europe, many of our patients are in prison, even pregnant women. This is a very, very expensive place to be and certainly not the adequate treatment.

Breastfeeding, yes you can breastfeed on buprenorphine and methadone but it's basically, as Nathan pointed out, the basic recommendation is not to breastfeed except there are some promising studies recently in the *New England Journal of Medicine* for Maladie [misspelled?], where there is no other access to nutrition that under a special medication there is a low transversion rate.

I'm going to show you some data and I'm really grateful that UNICEF and WHO are having this topic covered. To just to impress you what a high risk factor it is if we are not treating opiate addiction in these HIV positive pregnant women. These are all tables referring to HIV pregnant women and I'm not going to be going over every detail, I'm just pointing out

important things. This is a study from the U.S. HIV positive women in pregnancy, 30-percent have been using drugs. This is a study again from the U.S. looking into the adherence and the availability of antiretroviral treatment during pregnancy and after delivery. You see here, prior to this study, about 40-percent were using illicit, between 30 and 40-percent were using illicit drugs.

You'll find another study from Europe looking into the rate of women being HIV positive and pregnant and drug history. 42-percent have a positive drug history.

Now I'll show some slides from the European collaborative study. Looking into some European countries and Ukraine, looking in HIV testing, in intravenous drug users, and in non-drug users, you see before pregnancy and over the years, I think that testing is getting better over the years. If you focus on this, here are the non-intravenous drug users and here are the drug users. You see that 71-percent of the non-drug dependant patients had their HIV test in the beginning in order to improve the outcome. There is only 47-percent. Almost a quarter is realizing at delivery that they are HIV positive. The same is the accessibility of having appropriate treatment. You see here 19-percent of the drug using group did not have treatment during pregnancy, there is 7-percent in the non-drug users, and HAART was available double as often to the non-

intravenous drug users. So it's a highly under focused, under treatment in this population.

Again if you look at the outcome of premature delivery and low birth weight you see that the IV drug users are at a significantly higher risk of preterm delivery, but means not having the adequate antiretroviral treatment during delivery and having diverse outcome in preterm deliveries.

Okay, there are some studies, and I want to point out from December on Ukrainian women, this was one follow-up study by Dr. Wooslownese [misspelled?] having been following this group for many, many years. You see here, just to point out, between the drug users and the non-IV drug users that the transmission rate is double as high in the intravenous not treated drug using group.

What is the model? The model is to have comprehensive care. This is my Mikey Nikuri [misspelled?] in Vienna we have in a disciplinary group, we also do the neuropsychological testing in the neonates and children up to the age of six, and having of course the different disciplines, the infectious disease is an integral part of it. But being connected to all the facilities around Vienna is equally important to have the transfer of these women.

At the end, I want to probably point out being a researcher what would be interesting. If we do research in

pregnant women there are very, very high ethical standards to do this. What would be interesting is adding the impact of HIV into the opiate dependant group, like we did with a NIH funded study between buprenorphine and methadone and looking into the HIV medication. How is the pharmaco generics, how is the pharmaco dynamics over this stage of their pregnancy. So I hope I was able to jump you into the necessity of focusing on drug addiction and the treatment and we can change this outcome by understanding addiction and providing the comprehensive services that are needed for pregnant women, their infants exposed to drugs and HIV in utero.

I thank you very much for your attention.

[Applause]

YIN-RO LO: Thank you Gabriele. We can take one question while Niger is preparing to set up his slide. So do you have any questions for Gabriele on this topic?

FEMALE SPEAKER: Thank you very much for a wonderful talk. I have experience in the United States working with pregnant women with many addiction problems, and I think you kind of skirted past the issue that relapse is much more likely in the absence of psychiatric intervention and I'd just like to observe that most HIV providers are uncomfortable giving psychiatric medication or evaluation and that most psychiatrists are very reluctant to give adequate psychiatric

therapy to pregnant women and that this is a real problem. Thanks.

GABRIELE FISCHER: Well, I completely agree and therefore I just really want to focus again on the interdisciplinary corporation especially in this high-risk group of patients.

YIN-RO LO: Thank you very much. I would like to introduce to the next presentation on measuring the impact of prevention on mother-to-child transmission of HIV. Niger Rollins joined the department of Child and Adolescent Health and Development of WHO in July 2008. Before joining WHO, Niger was professor and head of the center for Maternal/Child Health at the University of Kwazulu-Natal in Durban, South Africa where he lived and worked for 14 years. His work focuses primarily on prevention of mother-to-child transmission of HIV through infant feeding, but also works on health systems research and severe malnutrition. Niger, over to you.

NIGER ROLLINS: Thanks very much indeed, Yin. Thanks very much for staying. It's a hot day and you'll have realized by now that I'm not South African, my Irish roots are probably giving way and I'm perspiring rather a lot up here, so if I suddenly take off my shirt which my kids would do in this weather you can blame the organizers okay?

So measuring the impact of PMTC programs—this is a slide taken from a preliminary version of a document prepared by WHO on monitoring and evaluating prevention of mother-to-child transmission programmers and monitoring and surveillance is very, very important but it's different from impact assessments. So while the day-to-day monitoring of what we do in the grind is critical, there is a difference between that and what I want to talk about today—namely impact assessments. So when we talk about impact we use this data to evaluate the overall effectiveness of interventions, so I want to sort of set the stage of what we're going to be talking about.

These numbers, these one or two numbers are very often used for advocacy, for political purposes, for a whole range of reasons that are quite distinct and different from the day-to-day monitoring that goes on within. It needs to tell the bottom line, it may not always tell the reasons why but it needs to tell the bottom line.

So I went and had a look at all the posters that have been presented on PMTCT and looking at what has been presented as impact of PMTCT interventions and programs and there's a whole series of reports about process or output data. The PMTCT cascade, the slide that I think Nathan or James put up earlier from Elizabeth Stringer on the PEARL study showing how the numbers drop over time, in each of the various steps, we've

seen that time and again. We're starting to see now a number non-HIV indicators of the impact of HIV on other services we're seeing and the health system effects being reported. We're seeing immunization rates for example being reported as a proxy of what happens whenever HIV interventions are implemented within routine services.

But what we want to get to are the real outcomes, and by that we talk about for the infants transmission rates, number of infants infected annually, transmissions averted, and as Nathan was mentioning, HIV-free survival. I have to say now that the majority of what I'm going to talk about is on the infant outcomes. But the point raised earlier about maternal outcomes is desperately important. What we do have at the moment are some data on mortality among HIV-infected mothers. Other ways of putting it are the portion of maternal deaths attributable to HIV and the life expectancy HIV-infected mothers, and this is one set of data that were reported in the women and health report by the WHO in 2009 illustrating that globally HIV is the leading cause of death among women of reproductive age.

You see this being reflected in the maternal mortality trends and the data that James showed earlier from South Africa and the quote that we had from a recent publication of *Lancet*, although he referenced the quote by Coratia [misspelled?] one

of the other striking points in that article was just the absolute dearth of information and data about what happens to women over time when they become pregnant and their long-term survival. And the main issue is that we need to have more data on what happens to women as they become mothers and as they survive beyond pregnancy.

For children, the global impact of ART and PMTCT scale-up has been reported a number of different ways. This is the estimate of the annual number of infections averted, so this is what we're trying to achieve—70,000 as Nathan mentioned. We're still seeing over 400,000 new infections still happening each year. So these things are largely modeled data, raw and counted on the grind.

Transmission rates are the usual way by which we estimate and determine the effectiveness or the impact of what we are trying to do in the grind. This is a report from KEPRON [misspelled?] on the effectiveness of a district wide program from mother-to-child transmission and they reported, which was very good at that time, a transmission rate of 8.8-percent. But if you read into the paper you realize that there were 658 women enrolled into that program in that particular period of time. There was only transmission rates estimated in 410 of those children and that you had an 8.8-percent in that one sub-group. So what happened to the other third of children? Was

the program really succeeding? Because if we simply look at transmission, then there's a problem, particularly in this type of a way. The EAM study was a multi-country study where again, very, very admirable results. We see very, very low transmission rates and it was concluded that ART is effective. ART is unquestionably effective but it doesn't tell us about the effectiveness or the impact of the program on populations.

So there are several challenges and limits on using infant transmissions as a measure of PMTCT's effectiveness. You have problems with sampling bias, in that it only measures those children who are actually brought back to services. You may omit infants of mothers who have become infected after the first test, they're not known to the services. Those who never attend ANC are never recognized. Modeled approaches do not necessarily reflect real life non-adherence. The new guidelines, as Nathan presented, really illustrate the exceptional opportunity that we have at the moment to do things very much better and for that reason, the impact of what our efforts need to achieve become even more important to be able to measure.

So I would say that as a single indicator or target, transmission rates alone do not reflect what we want to measure. They don't tell us about maternal health, survival, the benefits of interventions. It doesn't tell us about the

success or failure of identifying initiating treatment on infected infants and their improved survival. It doesn't tell us anything about the potential of including survival in the general population if infants are able to safely breastfeed.

So another way of looking at the problem or telling the story, these were data presented earlier in the week, trying to understand what has been the impact of PEPFAR on PMTCT outcomes in relevant countries and they reported an infant mortality rates in focused countries against elsewhere and they demonstrated a reduction in infant mortality and there's some issues there and under five mortality, we see a similar story. We saw the data that James was referring to earlier from the Africa Center showing a reduction in under two mortality and they have now at this conference reported an under five mortality impact. This was in the context of comprehensive programs offering ART both to mothers, ARVs for preventing, and also largely breastfeeding practices.

This is another population based set of data from another country—another program in South Africa which has comprehensive ART, ARV prophylaxis and you see that in the past eight to ten years, there has been a 50-percent increase in both infant and child mortality in a setting where formula feeding is the default practice amongst the vast majority of

women, but their transmission rates are less than 5-percent. So are we having the impact that we would want to see there?

And in Uganda, again a population based estimate, amongst women who were receiving antiretroviral therapy in their children, 97-percent of the infants were tested and none were infected. So the program had completely succeeded in getting less than 5-percent for example, but they find that there was a six times increase in mortality amongst the infants that were being formula fed than were being breastfed in the same program. This is another way of presenting data on mortality.

These are from the UNAIDS estimates that in Southern Africa we have seen a modest decrease in the HIV associated or attributable death amongst children from of its 17-percent down to 14-percent which is a good sign, but is it enough? This slide also demonstrates something else; that in countries where HIV prevalence is low that simply using the proportion of deaths that are due to HIV will never be seen. You will never see the benefit of your intervention if it's expressed simply as a fraction of all. So there are challenges on simply trying to interpret mortality as a measure of effectiveness as well.

Demographic surveillance systems like the Africa Center reflect population effects that's the universal rates that we're after, but they cannot be generalized as a measure of

national impact, because you don't know whether that particular environment is true everywhere. You can look at demographic health surveys as reflecting the national story but they're difficult to repeat on a regular and frequent basis in order to assess progress. They're only done every four or five, six years. The prevalence of HIV in the population of infants in HIV reflected mortality will ever contribute significantly to national mortality rates.

So we get back to the problem, that HIV-free survival which is what we're really after to have children of mothers known to be infected survive, while remaining HIV uninfected. That's our priority but it's hard to assess.

So now we say what should an impact assessment be able to do? It's got to be meaningful. So it's really got to tell the story that we want to understand. It's got to be measurable, and HIV-free survival is difficult to measure. It's got to be population based because we're wanting to understand are we achieving universal coverage. It's got to be robust. It may not tell us the precision that we find in research studies but it's got to be good enough so that over time we can see trends towards progress or regression. It's got to be replicable within reasonable timelines both with in-country or within district health systems and between countries

to make those comparisons, and it has to be relevant for both high and low prevalence settings.

UNICEF convened a meeting last year on trying to understand methods for evaluating and they concurred that identifying HIV-free survival was the best thing but it was hard to achieve. The PEARL study, as mentioned earlier, they used a novel way of looking a cord blood samples to understand transmission across all births, but it doesn't really go beyond what happens at birth and they also measured transmission rates in the presence of Nevirapine as a particular output of PMTCT programs.

One other block of work that I just want to go through briefly used immunization clinics as a way of accessing children, first of all to assess six week HIV prevalence rates and secondly to estimate trends in infant mortality rates. The assumption was that if there was a high attendance at six week immunization clinics then this would be a proxy and good enough to understand what's happening in the field population.

What they did was that they took dried blood spots from every single child coming to the clinic, they tested the dried blood spots for antibodies. Where there was antibody present it reflected maternal prevalence and exposure. They then did HIV DNA PCR on those same samples where there was antibody present. So they were able to calculate the vertical

transmission rates essentially against a population. Recently they conducted this amongst 347 clinics. They interviewed 38,000 women and they took information about all their other children and were able to reconstruct infant mortality rates. Then they had 8,000 dried blood samples from children who were specifically six weeks old and interestingly, this was funded through the Global Fund.

So this is just to illustrate what these data can tell you and the sort of inferences that you can take, and this was done at district level. They had 8,000 blood samples that 3,237 of them demonstrated antibody which means 40-percent maternal prevalence which is very, very consistent with rest of the national data. They then said of these 3,000 samples where antibody was present, how many were DNA PCR positive, and they found that there was a 7-percent transmission rate over all those children. They were able to break it down by district and interestingly in one district which was actually in the most rural district, it was 4.4-percent, and in the urban environment it was 10-percent. And this really reflects the functionality or the dysfunctionality of those health systems. This is proven to be very, very powerful data within the local/provincial health system.

They were able to break it down by maternal PMTCT regimen. A simple question to ask mothers is what did you

take? They were able to look at infant mortality rates and they reconstructed these amongst those 35,000 interviews and they seen that in children of these mothers who had been born early that the infant mortality rates were 26 and that over about a 10 year period had been a troubling of infant mortality rate. Which is a very powerful story for advocacy. And whenever they broke that down by district they were able to see other differences as well. They applied the same methodology to a community based evaluation, 4,200 households visited, to understand because, as a process, you don't know whether you're missing people that are important. The number of children that were evaluated less than 18 months there was 889 children who had samples taken where there was a valuable blood spot and there was a 6.6 overall prevalence rate in that population which is very consistent with the clinic data and they found there was an infant mortality rate of 67 per 1,000. 36-percent of those deaths occurred at home.

So going back to our starting point, what can we use and what can be used in different prevalence settings? And I just want to leave you with one or two thoughts.

Infant mortality– if we were–and I think it is very possible to do, if we looked at 12 month mortality in infants that are HIV exposed, we can come up with a target that I think is meaningful and that is robust to measure and that will tell

us about the impact of both transmission and also the effect of maternal health and interventions to keep her well and breastfeeding. Coupled with information about transmission rates, those two data provide a very powerful assessment of the effectiveness of ARVs.

In terms of maternal health, a presentation earlier today at the Keshibor [misspelled?] reported on AIDS-free survival. I think that for mothers I think this should be something we should look at to understand what is the impact of these interventions on mothers. I think that is something that we should be really pressing to try and achieve. This is important in terms of money because money counts and it's what a lot of things are evaluated by. If our investment in all the systems and drugs to deliver these interventions is only measured in terms of transmissions averted, then we grossly underestimate the investment. We underestimate the investment in terms of maternal health, we underestimate the benefit in terms of being able to make breastfeeding safer, and we underestimate the value of the interaction between maternal survival and child survival. It strengthens the argument in justification for investment as a contribution to MDGs four and five.

So, in conclusion, impact assessments need to reflect the full scope of what PMTCT aims to achieve. We need robust

simple, combined methods, but we need the investment to perform these. We need these assessments to be repeated in order to monitor progress and to hold ourselves accountable for the investments that are either made or needed. Lastly, just a comment, that WHO is developing a protocol for some of these procedures.

Many thanks.

YIN-RO LO: Thank you very much, Niger. We are at four o'clock and would still like the organizers to permit us one or two questions to the presenters. So please identify yourself if you have a question.

KARIN BICKERMAN: Karin Bickerman [misspelled?] again from New York City. Wonderful talk and really inspiring. I would still like to ask you is the same question I asked you a year ago. Are there any data of the use of single dose Nevirapine in the field, in a community, or in a region that shows increased HIV-free infant survival? Thank you.

SAYED AMED: Hi, I'm Sayed Amed [misspelled?] from Malawi. I think it's really important to understand the impact of PMTCT interventions, but it would also be nice to see what are the problems with individual pieces of the cascade on a program setting, on a national setting rather than just in studies and so I'm curious about your thoughts. I think one of the challenges is linking mothers and babies and being able to

document that and so how we might address that and what are the strategies to sort of measure that?

YIN RO-LO: Okay, last question. Kevin?

KEVIN DECORT: Kevin Decort [misspelled?], CDC. Niger, thanks for a very thoughtful presentation. But in the current climate of spreading out from just HIV and just PMTCT in MDGs four and five. I wonder, and just to play devil's advocate, whether you're in a world where even basic vital registration of births and deaths is missing and is absent in many countries, whether what you're proposing is too complicated? Because at the end of the day even in very heavily affected countries or moderately heavily affected countries the proportion of HIV attributable deaths in children is low. There are other things contributing. I wonder whether we're in fact not better to go from special studies that are less expensive and less labor intensive to get some of that information that we require for HIV while putting more investments in systems that, across the board, are so, so fragile or even up there at all. I mean in terms of human rights the most extraordinary thing is that you can be born and die and never appear in any official document, which is actually quite remarkable.

NIGER ROLLINS: Thank you very much indeed for those questions. I'd have to say that I am pretty confident to say

that there are no reports on HIV-free survival in a program level where Nevirapine has been implemented. The reason I say that is that outside of research settings, I don't know any programs that have reported for example 18-month HIV-free survival, but that requires cohorts to be established and followed up over a prolonged period of time and that's the fundamental problem of it. So I think that single dose Nevirapine 10 years ago we were celebrating having something to reduce transmission by 50-percent. Whenever the microbicide data was presented yesterday as the authors were coming up on stage people were applauding, when the results were presented they were applauding. It was the same response whenever things happen with Nevirapine 10 years ago, longer 15 years ago.

So I think in that sense the biggest limitation as with the maternal data is that we have new way methodologically of determining HIV-free survival even if that is the gold standard of whether we are doing the right thing or not. For that reason I think we need to look at proxies of HIV-free survival and that's why I was saying a simple way of determining transmission early and infant mortality at 12 months either in the general or in the HIV exposed children I think is, for me, if I was a program manager or a minister of health, I think those two numbers I would be very satisfied with.

The second question about needing to understand the steps, I can't agree more. But it's different from if you have a Minister of Health or if you have five minutes with the Minister of Health. They won't understand the cascade, they won't know the cascade, what they will want to know which is exactly what happened with this data from KZM [misspelled?] when they say with the very first assessment in 2004/2005 that transmission rates were sitting at 20.8, they just said we need to do something. When the same data 20.8 was presented to the local community leaders, they just said we need to do something. A single number is very powerful in terms of advocacy. It's not a substitute and it doesn't tell you the reasons why, but it is the number in terms of an impact that is needed. It's not the same thing as what you're referring to, and I agree that they are needed.

Kevin, thanks for the last point. The one thing I would say is that births and death registrations is an absolute necessity if we want to see public health improve across the system. Forget HIV, can't agree more. The assessments that I referred to were special assessments. They were not dependant on those data from Kwazulu-Natal were not from standard birth registrations; those were special exercises conducted. The last one in those 347 clinics was conducted over a 12 month period. Interestingly, they used essentially community health

workers who were extensively trained to collect that mortality data. But to me to see infant mortality rates collected by that they may be out by some points here and there but they tell the story of HIV in those communities that I think is very compelling and I would say if that particular exercise were conducted again in two years' time, infant mortality rates should be very, very responsive to the interventions that Nathan described earlier on. My excitement would be in two years' time to repeat that specific survey and to see whether we've made an impact, because then, I think in terms of moving towards MBGs we would have a real cause for celebration.

The last comment I would say is that we need to remember settings where HIV is not the dominant cause and HIV accounts for 17,20-percent of all child mortality in southern, the most heavily affected countries globally, it represents two percent in all of Africa it represents four percent. So, contextualizing that, whereas for maternal health, HIV is the leading cause.

[Applause]

YIN-RO LO: Thank you very much for staying with us at this advanced time of the day. I will refrain from concluding remarks and wish you a good rest of the day. Goodbye.

[END RECORDING]