Bringing HIV Cure Within Reach
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June 21, 2017

Slide 1: Title

Mevrouw de Rector Magnificus,
Mijnheer de decaan,
Leden van de Raad van Bestuur van het AMC

The story of HIV cure is the story about people. People like Joep Lange, a visionary who dreamed big and never let anyone tell him it could not be done. I am standing here before you today in very big part because of the door Joep and Jacqueline opened for me. I am incredibly honored to wear Joep's gown, a most precious, lifetime gift from his family.

I would like to share with you the story of people who inspire me to dream big like Joep in bringing an HIV cure within reach. I would like to share with you the advances in science that are exciting and give hope that one day we will have a cure for HIV.

Slide 2: Bua was born in 1991 in a small village in Thailand. She was a happy child who was creative and loved to paint. At age 8, she lost her mother to AIDS. Two years later, she had tuberculosis and rash on her body. People in the village avoided her. They would get off the bus when she got on and her friends refused to play with her. She moved to a school that was far away from home.

Bua painted this picture called "Sad" when she first knew She had HIV. Her father had no money to buy a place to host her mom's ashes so she drew this picture for her mom.

Slide 3: At age 13, Bua was dying of AIDS. HIV medications had just become available in Thailand. She started it and recovered. She painted this picture called "Life" and said "*"I paint brightness into the night, I paint my life to fight weakness"*

Slide 4: Bua designed the cover of my PhD thesis book that was about treatment of HIV in children and adults in Thailand. She showed amazing insight and strength in being alright with growing up alongside HIV within her.

Bua is now a 26-year old graduate of art who is employed and lives in Bangkok.

Slide 5: When I asked her what an HIV cure would mean to her, she answered me with this picture called "Hope", and she said "*I am this bird, flying with others, wishing for a day that we are free of HIV"*

My hope with this presentation is that if you are not already interested in HIV cure research that you will become interested. This is because everyone has a role to play in our quest to find a cure for HIV. This is a multi-disciplinary effort that needs input from the community, social scientists, ethicists, clinicians, basic scientists and others. We need new ideas from people who are not in the HIV field because how to treat other diseases can teach us in dealing with HIV. If you are not in the health or research field, your interest and engagement in causes relating to HIV can help the research and help to inform others who may not understand or have prejudice against people living with HIV.

Slide 6: There are 37 million people in the World living with HIV. They live in all parts of the world but mostly in Africa and the Asia Pacific. They have hopes and dreams like us. So many suffer discrimination because of society's unfounded fear, unfair judgment and false morality. HIV stigma kills and I believe that changing HIV from an incurable to a curable disease will help reduce the discrimination against people living with HIV.

HIV treatment or antiretroviral therapy, abbreviated as ART, is highly effective and people can be healthy and live a normal life span. One pill once a day is what is required for most adults. For children, it is more complicated with liquid and more pills required. Everyone knows how hard it is to take medicines on time everyday and poor adherence to ART has led to resistance that is a major problem requiring expensive medications.

Drug access has been spotty especially in low-income countries. The world continues to face 1 million deaths from AIDS each year including 100,000 children. Tragically, many die undiagnosed in major part because of fear of discrimination. We also know that HIV medications are very effective in preventing HIV spread whether given to people with or without HIV. However, there are 2 million people newly infected with HIV every year.

Slide 7: The UNAIDS set a goal towards the end of AIDS of 90-90-90 by 2020 for 90% of people who have HIV to be diagnosed, 90% of people who are diagnosed to be on treatment and 90% of people treated to have responded to treatment which means having undetectable or very low HIV viral load level in the blood.

The reality is that the world is far from this goal. From 53 countries with available data, we are not even sure what the first number is and the second and third numbers show that we are very much under target. Sweden is the only country that has reached this goal. Thailand and the Netherlands rank 9th and 10th in the world, and we are just about 80-60-60.

How will an HIV cure help us reach 90-90-90?

I would argue that if a cure were available, more people will be willing to come forward for HIV testing and accept treatment. In Thailand, we have seen the

number of people accessing HIV testing and treatment increased significantly with the demonstration that early treatment can control the HIV reservoir to very low levels. People have hope that this would give them a better chance of responding to a cure therapy when it becomes available. People are also more motivated to take medicine regularly to keep their virus in check. With a cure, the period that people need to take medicine regularly will be shorter and more manageable.

Importantly, without a cure, the number of people in this 90-90-90 goal will increase everyday, and everyone will need life-long therapy. In the US Army, the cost for treating one soldier with HIV infection for his or her lifetime is estimated to be 350,000 USD. This is a burden to the person, to the family and it is unaffordable for most countries.

Slide 8: Why is HIV so difficult to cure? There are two main reasons. One is that HIV hides quietly in cells that we call latently infected cells. HIV integrates itself into the DNA of these cells in red. These cells are mostly memory CD4 T cells. They are long-lived and go undetected by the immune system and untouched by the HIV medications.

We also know that virus persists in organs such as the brain, the intestines and the lymph nodes. Sometimes, not enough HIV medication can get into these organs to stop the virus.

Slide 9: The other reason is because HIV is a moving target making it difficult for the body's immune system to get rid of it.

The body makes antibodies shown here as the green Y shaped cartoon to capture HIV and clear it, but HIV changes itself for survival as shown here in the multi color viruses so the natural antibodies are unable to do their job. This is also the case with killer cells in the body such as CD8 T cells that are not able to keep up with the virus.

Slide 10: When we talk about HIV cure, there are two goals. One is eradication or sterilizing cure, which is the ultimate goal we aspire to of getting rid of all cells in the body that is capable of making HIV virus. The other is a more achievable near term goal called HIV remission or functional cure. This means that the person still has HIV but he or she is able to control the virus to levels that are undetectable in the blood without taking HIV medications. The person should also be healthy and have no increased risk of transmitting HIV to others compared to people who are on HIV medications.

Slide 11: Among millions of people living with HIV worldwide, HIV remission and eradication is extremely rare

Here is a graph showing viral load in the blood vs. time off of treatment.

A typical patient who stops medication, the virus will come right back in the purple line. The other spectrum is the Berlin patient who has been off ART for a decade without viral load rising. But this was only achieved by extreme measures of cancer treatment and bonemarrow transplantation with cells that were resistant to HIV.

HIV remission is mostly seen in people who were treated with ART early and subsequently able to control HIV like the Mississippi child and adults in different cohorts.

It is very hard to prove if someone has reached eradication as currently we do not have a way to test all cells in the body. So our goal right now is to stretch the time in remission from months to years to decades that will increase the likelihood of someone achieving HIV eradication like in the case of the Berlin patient.

Slide 12: Through a collaboration between the US Army, The Thai Red Cross and many of you here, we started the RV254/SEARCH010 study in Bangkok in 2009. It has been an amazing operation by the team. We have screened over 200,000 people to enroll over 450 people in acute HIV infection, which is the first 4 weeks of infection. We are able to diagnose people within days or a few weeks from when they contracted HIV, sometimes even before the standard test becomes positive. Our team works very fast in confirming the test results and have the patient start ART the same day or the next day.

Slide 13: In this graph on the left, you can see that if HIV is left untreated during acute HIV infection, the viral load in the blood goes up very fast and very high and people have symptoms like fever, sore throat and rash, the number of infected cells or the HIV reservoir also increase rapidly. The viral load comes down to a set point when the immune system starts to gain some control, but the viral load remains high.

In contrast on the right, when we are able to treat people early, we reduce the viral level to undetectable levels very fast, people's symptoms go away faster and the HIV reservoir is smaller. We also stop the virus from further mutating and damaging the immune system.

Slides 14: These are data from our studies in Thailand showing, in orange, that the HIV reservoir size or cells that have total HIV DNA change very little in people who start treatment late even with successful ART, but the reservoir size decreases significantly over time with ART in people who were treated early by 2-4 weeks in purple and within the first 2 weeks of infection in blue.

In fact amongst the people who was treated so early with such low viral burden, half of them test negative to the most sensitive standard HIV test even years after being infected. This is a huge social benefit for people in Thailand where having a positive HIV testing could restrict many life options like getting a job.

Slide 15: I would like to share with you a short movie clip of a young man who is in our acute study in Bangkok. He will talk about what being part of a research study relating to HIV cure means to him. **Movie**

Slide 16: The field is actively studying strategies towards an HIV remission. Early treatment reduces the HIV reservoir and preserves the quality of immunity. However, because the ART suppresses the HIV viral load so quickly, there was not enough time for the immune system to build up enough immunity against HIV.

So what else can we do to help the immune system work better in clearing infected cells. I would like to share with you some exciting research in trying to find ways to improve immune clearance of HIV.

Slide 17: The idea of the shock and kill model is that we give drugs called latency reversing agents that could wake up the latently infected cells to start making virus and show the virus on its surface so that it could be seen and targeted by HIV medications and the immune system.

So far this has not been enough to get rid of cells infected with HIV and future strategies include using more than one drugs and using new classes such as the TLR7 agonist which also works as an adjuvant to boost the effects of vaccines and antibodies. Importantly, we need immune therapies to boost the immune responses that will provide the kill component. This could include antibodies, vaccines and engineered cells.

I would now like to talk to you about promising research on immune treatments that could help us get closer to an HIV cure.

Slide 18: As you have heard that the body makes natural antibodies against the initial virus but then cannot keep up with the changing viruses.

We know now that some people can make antibodies to a very wide range of different viruses. These antibodies shown here in the multicolor Ys are called broadly neutralizing antibodies or bNAbs.

These antibodies are now being produced and used to capture virus in the blood and it can also attach to an infected cell that has parts of HIV on its surface and clear those cells by the natural killer cells through mechanisms such as ADCC shown here

These antibodies have been shown to suppress HIV viral load in people. Studies in monkeys have shown that bNAbs given early after infection can induce remission and even eradicate the infection in one study.

It appears that giving bNAbs very early improves the way the immune system handles the virus. For instance, the immune complex generated by the antibody

attaching to the HIV virions might help stimulate CD8 T cell responses to HIV that is important for killing infected cells.

Our group is doing 2 studies in Thailand and Africa of VRC01 bNAb during acute infection and after early ART to see if it can reduce the reservoir and help people reach a remission. There is also a study by the IMPAACT group that will look at whether giving VRC01 to young infants with HIV could help to reduce their HIV reservoir size.

The future of bNAbs is in using combination antibodies to improve potency and lessen the chance of resistance. So far the bNAbs have to be given monthly. In the future, we will likely have antibodies that can be given just 2-3 times a year. There are also new innovations like mRNA delivery system that would only need 1/50 of the dose to achieve adequate blood levels, which will reduce the cost significantly.

Slide 19: In a given person with HIV who is on ART, out of all the cells in the body, the ones that are infected with HIV are actually rare. The CD8 T cells that could kill these infected cells are even more rare. So how does the immune cell finds its target when it is like sending 1 person to look for 3 specific people in Amsterdam and surrounding areas with 3 million people.

What we need in the future is a way to generate persistent immune surveillance that could immediately eliminate any cell that becomes reactivated and starts to produce virus.

Slide 20: One way is to use a genetically engineered viral vector that could be given once and it would persist in cells and keep generating antibodies. It would be injected into the muscle and then the muscle cells would make the antibodies for as long as the life of the cells. The vector could also be engineered to transduce the liver cells to make antibodies that could induce tolerance or lower the chance of the body rejecting the treatment. It would need to have an off switch to turn off the activity if there are side effects. This could be a game changer if only one shot is needed for long-term treatment.

Another way is to use bispecific antibodies. One is called DART. One arm of the antibody binds to HIV and the other arm binds to T cell. The beauty of this is that it can grab any T cell and bring it to an HIV infected cell without the T cell needing to be HIV-specific. So this increases the chance of killing by several magnitudes. Monkey studies have also shown that bispecific antibodies can improve killing of infected cells in sanctuary sites like the lymph nodes.

Slide 21: One of the best ways to boost long-term immunity is through vaccines. Here the vaccines could be used to generate antibodies, both neutralizing and non-neutralizing, and immune cells that target HIV-infected cells. There are a number of HIV vaccine trials around the world. The field has learned so much from the RV144

vaccine trial in Thailand that is informing the development of both preventive and therapeutic HIV vaccines.

In our Thai acute HIV cohort, we are now studying an Ad26 prime and MVA boost vaccine. Our goal is to see whether it would generate HIV-specific immunity that would help people control virus after they interrupt their HIV medications. With the same objective, we are also planning another vaccine trial that will use the person's own dendritic cells that will be loaded with conserved HIV peptides and given back to the same person to boost the HIV-specific CD8 T cells to eliminate infected cells. This type of immune therapy has been effective in treating cancers.

Slide 22: What is also very exciting is that the discoveries of bNAbs are informing the design of HIV vaccine for both prevention and treatment. This is an enlarged picture of the outer surface of HIV. We now know the different areas on the outer surface that bNAbs target and researchers are using this knowledge to design proteins that look like these targets to put into vaccines. The goal here is to produce vaccines that would help the body make bNAbs. Several novel molecules are now identified such as SOSIPS.

Slide 23: The engineered T cells or here what is called CAR T cells have been used successfully in treating many types of cancer. This is now being looked at for HIV.

Here we have a CD8+ T cells that the T cell receptor has been engineered to express part of a bNAb on the surface of the cell. This allows the CD8 T cell to be redirected to an HIV infected cell that is showing HIV envelope on its surface. It basically makes these CD8 T cells into a better killing machine.

Slide 24: Another way to eliminate HIV is to make cells resistant to HIV by taking away the CCR5 receptor. Basically we are trying to close the door that HIV needs to get into the cells like what happened in the Berlin patient.

This is done by taking out a lot of cells through a machine called leukapheresis then the cells are modified using gene therapy zinc finger nuclease to break the CCR5 gene then these resistant cells that do not have CCR5 are given back to the same person.

New gene therapies using CRISPR Cas 9 show promise for curing HIV. With new technologies, these types of therapies will likely be safer and easier to give in the future.

Slide 25: In addition to diagnosing and treating HIV early and keeping patients virally suppressed on ART, what might be possible in the future that could help us get closer to a cure?

In infants diagnosed with HIV, the best thing in my opinion is to give passive immunization with broadly neutralizing antibodies that could work immediately in

limiting the reservoir seeding and clear infected cells. It is preferable if this can be given in just one shot with adenovirus vector that could continue to produce the antibody for years.

We could consider adjuvanted vaccines that not only improve CD8 killing of infected cells but also reactivate latently infected cells making them more susceptible to killing.

The antibodies and adjuvanted vaccines would be the mainstay of treatment for children and adults. In long-term treated people, we might also need potent latency reversing agents and additional methods to look for the rare target cells with DART or other antibodies as well as cell-based and gene-based therapies.

Slide 26: In this early stage of cure research, we are asking enormously from our trial participants who do not have personal benefits but face risks.

This 35 year-old Thai man was treated early then joined our treatment interruption study and was interviewed as part of a social science study.

At his first visit just before treatment interruption he said "*I might be the first person to be cured. It's also a benefit to others. However, it's okay too if I cannot be cured. The researcher was also not sure whether it would succeed. But it is a reasonable risk."*

While he was off treatment, he said *"I do not have to hide from everyone when taking the drug like I did in the past. I have a positive attitude. Whatever happens, I will be fine."*

About a month later, his viral load rebounded and he had to restart his treatment. He said *"I wish I could have stopped it longer. I wanted to stop the drug for my entire life. Being off drug became normal. But if there are other studies I can try, I want to try."*

Although we never use the word "cure" when communicating with trial participants, you can see that there is so much hope for a cure. People like this man inspire us to try harder and do better. It is also important to have social, behavioral and ethics research so we can conduct these studies as best as we can and are able to effectively communicate such research to trial participants and the community.

Slide 27: It is the young people who inspire me the most. They are so brave and resilient. They retain a positive outlook despite such adversity in life. They are doing so much to help others learn from their experience.

Nut is a 26 year-old young woman. I have marveled at how she deals with living with HIV since a young age, and now after finishing university, she has become an incredible counselor for children and families living with HIV.

She said "*I was able to cope with having HIV by meeting others like me. I am so proud that now I can help other children know that it is alright to live with HIV. I am now their idol who is available for them. I am glad to be able to support young parents as they find out their new baby has HIV*."

Slide 28: MikeQ is a 23 year-old young man who is in his last year of engineering school in Chiang Mai. He is the president of the Thai Network of Youth Living with HIV. MikeQ started ART when he was 8 and learned about his HIV at age 12. He became more involved in camps and group activities for children and youth with HIV and when he decided to no longer hide his HIV status, his family was supportive.

What an incredible courage to be able to stand in public in Thailand as an HIV positive person and use that platform to help promote the general public's understanding of HIV and advocate for better treatment and rights for people living with HIV. One major issue he is fighting for is to accept people with HIV into the work force and stop the requirement of a negative HIV test to get a job, which is a common practice in Thailand.

Slide 29: It is a very exciting time with so many scientific discoveries that have given rise to new technologies.

For prevention, there are now dozens of trials testing bNAbs and vaccines, as well as long-acting antiretrovirals.

For treatment, we are getting better in our diagnostic tools to detect HIV infection very early giving an opportunity to intervene immediately, we will have highly potent ART with some that could be given just a few times a year.

Learning from people in HIV remission and the Berlin patient with a possible eradication, we now have many novel interventions that are being studied.

I believe that together we can push for continued scientific discoveries that will make HIV cure a reality and take us to the end of AIDS.

Slide 30. If Joep and Jacqueline were here today, I would thank them profusely for welcoming me into the AMC and AIGHD family. I would tell them how grateful I am that they saw my potential before I did, from doing a PhD to mentoring other PhD students and to this professorship. I am amongst many people who were fortunate to be mentored by Joep and I intend to carry his legacy forward.

Slide 31: I am grateful to Professor Peter Reiss who tirelessly helped me at every step of the way from the initial paper work to translating various documents to advising on every detail in getting me to this day. He does it with such calm and wisdom. I have also been fortunate to co-mentor several PhD students with him, and Dr. Stephen Kerr and Dr. Ferdinand Wit.

I would like to thank Professor Marcel Levi for being so supportive of my professorship. Professor Hans Romijn for continuing to welcome me in the AMC, and Professor Frank Cobelens and Professor Constance Schultsz for welcoming me in the Department of Global Health. I thank Professor Fransje van der Waals, Dr. Henriette Scherpbier, Ms. Linde Nieuwenhuys and many many others who are listed here, I am so grateful to all of you for your help.

Slide 32. I have been fortunate to have wonderful mentors through out these years who shaped my career in HIV research. From Dr. Anthony Fauci at the NIH to Professor William Shearer at Baylor College of Medicine to Professors Praphan Phanuphak and Kiat Ruxrungtham at the Thai Red Cross, Professor David Cooper at University of New South Wales and Professor Bernard Hirschel at the University of Geneva who is here today. I am fortunate to have such supportive directors in Professors Nelson Michael and Merlin Robb at the US Military.

Slide 33: I would like to thank the teams in Thailand. The SEARCH clinical team who care so deeply for our trial participants. They are like a family to me, and leaving them to go to the US was one of the hardest things for me.

Slide 34: The many people at AFRIMS with the laboratory teams shown here. They work so hard with such commitment to make our studies a success.

Slide 35: Today is so special because I have family and friends who have traveled from many places around the world to be here, from Japan, Thailand, the UK, the US, Switzerland, Italy and Ireland. I thank you so very much.

Slide 36: I would like to dedicate today to my parents who passed away almost 15 years ago. My father, a Thai physician who devoted his life to public service and helping the poor. My mother, an Irish woman with a sunny personality, who followed my father to Thailand at age 18. She became a key member in the Thai and expatriate communities and was so loved because she saw the best in everyone. I know they would be very proud today and my mom would be so happy that her sisters, Breda and Frances could be here for me. I am grateful for my sisters, Natalie and Lisa, and having Lisa here makes me so happy.

Slide 37: Any success I have is also my husband's success. Andy left his career in the US as a chemical engineer and moved to Thailand with me 17 years ago. He is the calm and loving force in my life who supports me in everyway. He is a stay-at-home father for our two children, Gavin and Nalyn whom I am so proud of.

Thank you so much to all of you for being here.

Finally, I have spoken. Ik heb gezegd