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Deciphering the code of ‘Cure’ in the era of HIV/AIDS

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Abstract

A cure for HIV has always been the holy grail of HIV research though ‘Cure do have philosophical, and programmatic connotations in the context of HIV/AIDS. Many developments and strategies have been evolved to tame this virus, since its reporting - some 32 years ago. Medical fraternity is reacting with guarded appreciation and anticipation, more so after the publication of reports of Sterilizing /functional cure of a man (known as Berlin patient’) following BMT from a donor having deficient chemo co receptor CCR5 (vital for HIV entry) gene and one baby, known as ‘Mississippi Baby’ who was infected with HIV at birth but is now apparently free of the virus. through a hit hard, hit early approach taken by researchers and doctors in relation to antiretroviral therapy These findings hold out the hope that treatment during acute HIV infection (ala –Mississippi baby) has the potential to transform the outcome of HIV infection in at least some individuals. The use of early and aggressive treatment could be a paradigm shift in HIV/AIDS treatment in children in the developing world, where mothers are typically treated during pregnancy to lower the risk of passing the virus on to the child. Both long-term survivors and those who have been exposed to HIV but remain sero negative (called Elite Controllers and Slow/Non Progressors) offer a great opportunity to study the mechanisms of resistance to HIV infection and disease. Till ‘Cure’ is not achieved we will have to remain steadfast in working towards it.

Keywords: Sterilizing Cure, Functional cure, CCR5, Mississippi baby, Berlin patient, hit early hit hard approach, reservoirs

1. Introduction

Background:

Cure’ -comes from Latin word ‘cura’ meaning –care, concern, attention’. The current use of word seemingly sprang from the belief that proper and sufficient ‘care’ was tantamount to ‘cure’.

Would that this were so!

The familiar admonition to ‘Cure occasionally, relieve often, console always ‘-- comes from the ancient French aphorism ‘*Guirer quelquefois, soulager souvent, consoler toujours*’. This proverb fits superbly into the natural history of HIV/AIDS leading to its much wanted ‘cure, even it does portray that cure or eradication has a bit of a philosophical content (we keep telling our patients --HIV is now a treatable and controllable illness like Diabetes Mellitus and Hypertension, thougha ‘cure’ is still elusive), meaningthereby that nobody has a clear concept and we are still in a trial and error phase.. Cure may have different meanings in the context of epidemiology, clinical care and programmatic evaluation and could range from ‘remission (cancer model) to ‘eradication’ (Infectious diseases model). *An example may be cited here:* in RNTCP -Revised National TB Control Program in India minimum two sputum negatives(of AFB), out of three done during ‘Continuation phase ‘ are required to declare the person be *cured* of TB.

Evolution of thought of cure

AIDS is a disease of staggering numbers, of tragically recursive devastation. Since the first diagnosis, 30 years ago by Dr Michel Gotleib (reported in MMWR, CDC, 5th. June 1981), HIV has infected more than 60 million people, around 30 million of whom have died. For another 5 million, anti-retroviral therapy has made their infection a manageable though still chronic conditionIn late nineties the two events has shaped the evolution of the thought of Cure ‘or Eradication’ of AIDS With the advent of effective combination ART (cART) in the mid-1990s, some researchers suggested that given enough time, antiretroviral drugs might

eventually wipe out all HIV in the body. At the XI International AIDS Conference in Vancouver in 1996, Dr David Ho from the Aaron Diamond AIDS Research Center proposed that a "hit early, hit hard" strategy using a potent combination regimen could potentially eradicate virus-infected T-cells—and with them, the virus—within two to three years.

Around the same time, however, Dr Robert Siliciano and his team at Johns Hopkins were conducting research that would yield a more sobering finding: In the May 8, 1997, issue of *Nature*, they reported that HIV can hide in a "reservoir" of long-lived resting CD4 T-cells. Because it is not actively replicating, this virus is invisible to the immune system and out of reach of antiretroviral drugs. HIV's genetic blueprint, known as proviral DNA, can lie dormant for years or even decades within a host cell's chromosomes, ready to produce new virus when the cell is activated.

Dr. Siliciano also suggested that the size of the viral reservoir will determine how long the treatment needs to be continued for a functional cure to be possible and how long it may take for a latent virus to recur once treatment has stopped if a functional cure has not occurred. A baby has a tiny (if any) reservoir of latently infected cells, then 15-18 months of combination ART may have been sufficient to reduce that reservoir to allow for a functional cure (as has been unfolded at the 2013 Conference on Retroviruses and Opportunistic Infections –CROI-- as a case report of a "functional cure" in an infant who started a full antiretroviral therapy regimen within the first days of birth., ---illustrating —and putting to the test— the evolving thought about the possibility of curing HIV infection and sparking new interest in the possible implications of this concept for the future of HIV treatment.

History of Resistance

The history of infectious diseases frequently includes people who were resistant to a pathogen. Such a phenomenon helped the Spanish, who had resistance to smallpox, in their conquest of South America, but not the Aztecs or the Incas, who had no resistance to smallpox and were decimated by the virus. Microbial resistance involves adaptive (acquired) immunity (e.g., the HLA sub- type) or innate (natural) immunity resulting from the genetic makeup of the host.

With the human immunodeficiency virus (HIV) and its known destruction of the immune system, resistance to infection and disease was not initially expected. However, certain people — long-term survivors — who have been infected with HIV for more than 10 years, (and sometimes more) and received no treatment yet remain without disease. In addition, some people who have been exposed to HIV on many occasions do not become infected. Both long-term survivors and those who have been exposed to HIV but remain sero negative (called *Elite Controllers* and *Slow/Non Progressors*) offer a great opportunity to study the mechanisms of resistance to HIV infection and disease.

Non-detectability of Virus in plasma is not equivalent to Cure/Remission or Non- infectiousness of the patient

Ultrasensitive tests reveal very low levels of plasma HIV RNA (as little as 1 copy/mL) in most people with "undetectable" viral load. Replication-competent HIV can still be isolated from resting CD4 T-cells from people with the longest duration of HAART use—now around 15 years—and viral rebound almost always occurs soon after treatment interruption. HIV can persist in spite of continuing ART as it hides in reservoirs, some of them becoming latent ones that are not sensitive to current therapies.

Barriers of Eradication and suggested Approaches to overcome it

Despite the significant reduction in morbidity and mortality following combination antiretroviral therapy (cART) or HAART (Highly Active Anti-retroviral therapy), cART cannot eradicate HIV. Recently, there has been a renewed scientific interest in developing new strategies to eventually find a cure for HIV. There have been several significant advances in our understanding of the major barriers to curing HIV. These barriers include long-lived latently infected cells and residual viral replication, at least in some patients. In addition, anatomical reservoirs including the gastrointestinal tract, lymphoid tissue and the central nervous system (CNS) may harbour unique long-lived infected cells and penetration of cART may be limited at these sites. The complex mechanisms of how latency is established and maintained in different T-cell subsets and the major cellular reservoirs that persist in patients on cART have recently been extensively reviewed elsewhere. The most significant barrier to cure among above reasons mentioned is the establishment of a latent or 'silent' infection in resting CD4+ T cells and the persistence of HIV in a latent form in different cellular and anatomical reservoirs. Mathematical modeling suggests that it would require 70 years of treatment with HAART to eradicate latent reservoirs..

Researchers are exploring many approaches for eradicating HIV or achieving a functional cure, which are

- Starting ART very early before viral reservoirs are fully established,
- Intensifying antiretroviral therapy to stop residual HIV replication
- Activating resting T-cells to purge or flush out latent virus,
- Maintaining latency to keep proviral DNA permanently silenced
- Eliminating or disabling HIV-containing resting cells,
- Protecting uninfected cells against viral entry,
- Strengthening the immune system's response to HIV.

Mechanism of Entry of Virus

HIV enters cells primarily through attachment to the CD4 molecule and subsequent binding to co receptors, of which two chemokine receptors, CCR5 and CXCR4, are the most common. R5 HIV types bind to CCR5; X4 HIV types use CXCR4. People whose cells lack expression of the CCR5 gene are markedly resistant to HIV infection despite multiple exposures to R5 HIV, which is the most prominent virus detected after transmission. This mutation is found in 1 to 3% of the Western population. Among people with HIV who have only one copy of the wild-type CCR5 gene, progression to disease appears to be slower than among those who have two. Obviously, such information is of value in efforts to develop new approaches for therapy.

Cure Strategies

Functional or sterilizing cure?

There are two potential strategies for cure. The first is what could be considered an 'infectious diseases model' of cure which would require the elimination of all HIV-infected cells in all compartments and sanctuaries and for patients to have a plasma HIV RNA count of less than 1 copy/ml. This is now commonly referred to as a sterilizing cure. The alternative approach would be to aim for remission or what could be considered a 'cancer model' of cure, in which an individual would have long-term health in the absence of treatment, with

low-level viraemia at less than 50 copies/ml. This is commonly referred to as a functional cure.

Example of Sterilizing cure: Elimination of HIV following a bone marrow transplantation

The recent case report of a German patient with acute myeloid leukaemia, who received a bone marrow transplant from a donor who carried a 32-base pair deletion in the CCR5 gene, is the only current example of a sterilizing cure. Following transplantation, the patient stopped cART and HIV RNA remained at below 1 copy/ml. In more detailed studies, including multiple biopsies of his gastrointestinal tract, analysis of his cerebrospinal fluid (CSF) and bone marrow and even a brain biopsy, neither HIV DNA nor HIV RNA was detected. The patient has now been off cART for over 60 months and HIV is still not detected. Reconstitution of circulating and mucosal CD4+ T cells that did not express CCR5 was observed. CCR5+ macrophages were detected early post transplantation in the gastrointestinal tract but at later time points, all mucosal macrophages expressed the mutant CCR5. In addition, the patient's peripheral blood mononuclear cells (PBMCs) were permissive to CXCR4 using laboratory isolates *ex vivo*, demonstrating that the patients CD4+ T cells were not resistant to HIV. Potential factors leading to the elimination of long-lived reservoirs in this patient could have included the specific chemotherapy administered, total body irradiation or low-grade graft-versus-host disease in addition to eliminating the capacity for any residual replication by removing target cells that express CCR5. Whereas a strategy of using bone marrow transplantation with a CCR5 mutant donor is not a realistic cure for HIV given the toxicity and complexity of the treatment, we need to continue to comprehensively study this patient to fully understand how and why HIV was eliminated.

Example of Functional cure: Elite controllers: Living with the virus

The “functional cure” approach is based on the observation that monkeys can live with the simian version of the virus for many years without getting sick. A small percentage of humans—called “elite controllers”—are capable of doing the same. If researchers could figure out how their immune systems manage to control the virus, then it might be possible to find a way to modify other people’s immune systems to act in the same way.

Elite controllers represent a unique group of patients who are able to achieve a consistent and long-term control of viral replication with HIV RNA of less than 50 copies/ml in the absence of cART. In addition, the reservoir is significantly smaller in elite controllers with low concentration of HIV DNA in different subsets of circulating CD4+ T cells in blood as well as in rectal tissue. There have been multiple studies examining the role of genetics, the virus and the immune response in elite controllers. One of the consistent results from this work is the clear association with HLA class one genes. Recent work has also demonstrated the importance of an effective cytolytic CD8+ T-cell response in blood which has been associated with enhanced activity of the T-box transcription factor t-bet and increased production of IL-2. Strong HIV-specific CD4+ and CD8+ T-cell responses were also identified in mucosal tissue from elite controllers. The innate immune system may also be important with enhanced activity of myeloid dendritic cells. These data provide supportive evidence that inducing an effective immune response, perhaps via vaccination, may be one strategy to achieve a functional cure. As some elite controllers do not bear

the protective alleles HLA B-27 or HLA B-57, mechanisms other than enhanced T-cell immunity have also been explored. Several investigators have demonstrated lower replicative capacity of the virus isolated from elite controllers, and very low level of viral replication soon after infection. There is no evidence currently that activated CD4+ T cells from these patients are resistant to HIV.

Despite apparent 'functional cure' in elite controllers, it is important to remember that low-level viraemia and infected resting CD4+ T-cells are detected. Compared with patients receiving cART, PBMC from elite controllers have similar levels of total DNA, but significantly lower integrated DNA and higher 2-long terminal repeat (2-LTR) levels. Immune activation is higher in elite controllers compared with healthy controls. In contrast to patients on cART with HIV RNA below 50 copies/ml, there is evolution in HIV RNA sequences in elite-controllers and in approximately 7% of elite controllers, CD4+ T cells decline over time. Because of the low total number of infected cells and robust HIV-specific immune responses, elite controllers could potentially be the best candidates to test strategies aimed at achieving a sterilizing cure.

New Era Study

First time efforts have been made to define ‘Cure/ Eradication in the context of HIV/AIDS One interesting trial is going on in Germany since May 2009 under Dr Hans Jaeger, which is a multicenter, open-label, non-randomized trial to evaluate treatment with multi-drug class (MDC) HAART and its impact on the decay rate of latently infected CD4+ T cells. (The author of this article knows Dr Hans Jaeger personally Dr Jaeger has presented a paper on eradication /cure at AIDS Society of India Conference –ASICON on 31st. Oct 2010 Hyderabad, where he tried to define ‘Eradication or Cure from AIDS on certain end points for his study. This is probably the first time that ‘Eradication or Cure’ has been tried to be defined scientifically. Once this study gets completed then we can learn whether Mega- HAART can have really some effect on decay of latently infected CD4+ T Cells, affecting ‘a cure’ at least on programmatic terms.

The purpose of this study is to decrease viral reservoirs in N=40 HIV-infected patients with either primary infection (PHI) or chronic infection (CHI) and successful HAART for at least three years. All patients will be started on a multi-drug HAART including two NRTI, one PI, a CCR5-inhibitor and an integrase inhibitor. Decay of viral reservoirs like latently HIV-infected CD4+ T-cells will be monitored over time.

The primary objective of this study is to reduce proviral DNA (a surrogate marker) in PBMC (peripheral blood mononuclear cells) and achieve HIV eradication. The study design consisted of PHI group N=20 patients with primary HIV-infection and CHR group N=20 patients with chronic HIV-infection and plasma VL < 50 copies/ml for ≥ 3 years on PI-based HAART.

Study endpoints will be (= definition): Eradication /Cure:

Standard VL assay: Plasma VL < 50 copies./ml for ≥ 5 years
And Single-copy assay (SCA): Undetectable plasma VL for ≥ 2 years (VL < 1 copy./ml) And Undetectable proviral DNA in PBMC for ≥ 2 years Patients fulfilling the criteria for eradication and willing to stop HAART will be monitored for proviral DNA for a follow-up period of 12 months.

Virological Failure

For CHI: Confirmed virological rebound in plasma viral load to levels >1000 copies./ml

For PHI: Confirmed plasma viral load (>50 copies./ml) 6 months after HAART initiation
 OR Confirmed virological rebound in plasma viral load to levels >1000 copies./ml
 Study intervention for PHI: 2 NRTI + 1PI + MVC+ RAL
 CHR: 2 NRTI + 1PI...ongoing + add on MVC+ RAL
 (MVC -Maraviroc RAL -Raltegravir NNRI -Non Nucleoside Reverse Transcriptase Inhibitor. PI -Protease Inhibitor)

Treatment time is 7 years or until endpoint (eradication or virological failure) start date: May 2009

Study visits will be CHR: Months -6, -3, Base Line, M1, 3, 6-monthly thereafter

PHI: Screening/Base Line, M1, 3, 6-monthly thereafter
 Other treatments or immunomodulators which may have a potential impact on viral reservoirs will not be discouraged during the course of the study and the treatment regimen can be modified based on current knowledge

Summary of the study: Decrease in proviral DNA. No patients stopped due to toxicity, No unexpected serious adverse events. 2 SAEs (kidney stones) reported but, therapy was not interrupted, 8 laboratory AEs (grade 3), 32 clinical AEs (grade 1 and 2, i.e. diarrhea, fatigue), but therapy was not interrupted and above all so far encouraging. We will have to wait for 2019 for its results, but this will certainly pave the way whether earlier & aggressive treatment will have any bearing on the elimination of reservoirs of HIV leading to a possible 'cure'

Early interventions

Based on the model of 'hit early hit hard' one study suggest that if patients start HAART early enough—within a few weeks of becoming infected—that might help the immune system develop responses that are better able to control the virus. It might also help reduce seeding of the reservoirs, which seems to occur very early in the process, probably during the acute infection stage. This could make the process of eradication easier.

The French Visconti cohort study was a retrospective look at about 700 patients who began treatment during acute HIV infection—a median of 40 days after being exposed to the virus. Some 75 of them continued that therapy for at least a year before stopping, As per Dr Asier Saez-Cirion, the investigator at the Pasteur Institute, fourteen of them have been able to continue off therapy for an average of six years with little or no detectable HIV in their blood. The patients do not have immune system genetic markers associated with HIV elite controllers, they might carry other as yet unidentified genetic variations that protect against the disease. On detailed virologic analysis of these, a small reservoir of latently infected, non-long-lived T cells was hypothesized to be contributing to their viral control, similar to the baby presented at CROI.

Torch bearers of Cure!

Case reports of two men—both dubbed "the Berlin Patient No 1 & 2" and more recently one child ' dubbed as 'Mississippi Baby ' — will be remembered as ' torch bearers ' in the discovery for a cure, which have changed the course of history, particularly with the publication of the Berlin patient No 2 case report (2009) with AML BMT(Bone Marrow Therapy) from a donor who carried a 32 base pair deletion in the CCR5 gene, has infused new hope in researchers for at least a 'functional cure '

The first Berlin Patient was a young German man who in 1996 sought care due to flu-like symptoms about three weeks after

having unprotected sex. His doctor, Heiko Jessen, started him on ART and hydroxyurea, a cancer drug. Hydroxyurea expert Franco Lori described the case at an AIDS conference in Hamburg in 1997. After starting combination therapy, the man rapidly reached an "undetectable" viral load according to an older test with a lower limit of 500 copies/mL. When he stopped his drugs a few months later due to a bout of hepatitis A, his HIV viral load stayed undetectable. About five weeks later, he decided to permanently discontinue therapy and his virus remained suppressed.

This Berlin Patient was the first individual known to have achieved "remission" of HIV, and the case made headlines around the world, including a profile in the New York Times Magazine. Lori's team presented further details at CROI 1999 and in the *May 27, 1999, New England Journal of Medicine*. By that time, Berlin Patient No 1 had been off treatment for about two years, still with no plasma viral rebound. But traces of HIV RNA were detected in his lymph nodes, and replication-competent virus was isolated from a small number of resting CD4 T-cells after Robert Siliciano developed a sensitive test. Although his HIV was not eradicated, the man's immune system managed to control the virus, demonstrating that a functional cure is within the realm of possibility.

The second Berlin Patient came to the world's attention a decade later. An American man living in Germany, he underwent treatment for acute myeloid leukemia at Berlin's Charité Medical University in 2006. At that time, he had been HIV positive for more than ten years and on ART for four years, and had undetectable viral load. But he had a history of high viral load and disease progression, so was not a natural elite controller. After initial chemotherapy failed, the next step was a bone marrow transplant. Strong chemotherapy was used to kill off white blood cells, which eliminates the cancer but leaves the patient without a functioning immune system. The man then received a bone marrow transplant containing hematopoietic stem cells; the donated stem cells essentially build a new immune system.

The man's Physician Dr, Gero Hütter—a hematologist, had read that individuals with the CCR5-delta-32 genetic variation are protected against HIV infection. Against all odds, he found a bone marrow donor who was both a genetic match and carried two copies of the uncommon variation, meaning the donor's cells did not express CCR5 receptors.

Berlin Patient No2 stopped ART the day before his first bone marrow transplant in 2007 and afterward received immunosuppressant drugs to prevent the donor cells from attacking his body. The transplant was successful and, as hypothesized, the newly reconstituted CD4 T-cells lacked CCR5 receptors. But almost a year later, the man had a relapse of leukemia. The same donor was persuaded to part with more bone marrow, and the patient received a second transplant after chemotherapy and whole-body radiation. The man stayed off ART, and since two months after the first procedure has maintained undetectable plasma HIV RNA and undetectable proviral DNA in resting CD4 T-cells. Hütter presented this Berlin success story at CROI 2008 and in the *February 12, 2009, New England Journal of Medicine*. The case has sparked interest from both HIV researchers and the public at large after an in-depth article by Dr Schoofs in the Wall Street Journal. In an update at the IAS Reservoirs workshop and in the March 10, 2011, issue of Blood, Dr Hütter's team reported that four years after the first transplant and still off ART, the man remains in remission from leukemia and shows no signs of HIV. Using the best available technology, Dr Siliciano and

others have found no HIV RNA or DNA in his blood plasma, lymph nodes, rectal mucosa, cerebrospinal fluid, brain tissue, or resting CD4 T-cell samples. What's more, his CD4 T-cell (the donor ones!) count has increased to a normal level. A few months after the Vienna meeting, this Berlin Patient revealed his identity as Timothy Brown, now in overall good health and living in San Francisco. Brown has been found with no remaining HIV anywhere in his body— but whether disappearance of HIV is due to the CCR5-delta-32 stem cell transplant, strong chemotherapy, a graft-vs-host reaction, the anti-inflammatory effect of immunosuppressant drugs, or some other unknown factor—he appears to have achieved a sustained 'functional cure, possibly leading to a 'sterilizing cure', though still he carries some risk of getting his new CD4 T-cells infected, by even a single remaining previous virus if it choose to, through another co-receptor CXCR4, though luckily this appears to not happened in this patient.

There has been worldwide media coverage of a case presented at the CROI meeting in Atlanta in 2013 of a baby born in Mississippi, known as 'Mississippi Baby' who was infected with HIV at birth but was reported to be apparently free of the virus for two years. This 'baby' born to an HIV-infected mother received a full-treatment regimen of antiviral drugs within hours of birth, instead of the customary prophylactic regimen typically used in suspected but unconfirmed newborn infections. The baby's HIV infection was subsequently confirmed. The child was lost to follow-up and went off treatment but later returned to clinic. A series of standard and ultrasensitive tests failed to detect HIV in the child's blood. In total, the child remained free of HIV infection - with undetectable viral loads and free of HIV antibodies - for 27 months despite receiving no treatment. By contrast, most HIV-infected people experience dramatic viral rebound within a few weeks of treatment cessation. Described as the first documented instance of HIV remission in a child, the Mississippi case suggested that very early treatment with antiretroviral drugs quashed the formation of viral reservoirs. The child was followed by a University of Mississippi pediatrician, a University of Massachusetts immunologist and a Johns Hopkins pediatric HIV expert, Deborah Persaud, M.D., whose case report on this baby was published in Nov. 7, 2013, in *The New England Journal of Medicine*.

Though in July 2014 it was reported that HIV had returned in this Mississippi toddler, but such "failures" may be in fact stepping stones to new understanding of what "cure" may look like and new therapies that tame the virus into long-term remission. Clinically, they provide a dramatic illustration of the real barrier to an HIV cure and illuminate important therapeutic strategies. The 27-month off-treatment remission experienced by the Mississippi toddler is, in and of itself, a laudable therapeutic goal, and is what cure of HIV may look like in the foreseeable future. Finding ways to induce long-term remission and to closely monitor its course will be the next frontier in HIV treatment. The ability to put the virus in remission and go off treatment for months or years at a time is an important goal, because it can spare HIV-infected people from a lifetime of daily antiviral regimens, which can be difficult to tolerate and hard to follow. Failure to comply with the strict treatment protocol, which occurs often, can lead to viral mutations that make HIV resistant to drugs.

While both cases are importantly different in their practical meaning and application, both cases highlight a fact that escaped humanity for decades: HIV is not permanent, HIV can be destroyed, and HIV, just like the human body, has

vulnerabilities that can be exploited to kill it. HIV can be treated with antiretroviral drugs, but treatment needs to be life-long, and examples of cure — elimination of the virus from the body— are almost unheard of. *A cure for HIV is the holy grail of HIV research, as described in a Lancet Infectious Diseases review published online on March 5, 2013.*

Two weeks after the revelation in 2013 that a baby has been "cured" of HIV, there have reports suggesting a similar treatment effecting a cure in some adults too. Early treatment seems crucial, but does not guarantee success. Dr Asier Sáez-Cirión of the Pasteur Institute's unit for regulation of retroviral infections in Paris analyzed 70 people with HIV who had been treated with antiretroviral drugs (ARVs) between 35 days and 10 weeks after infection – much sooner than people are normally treated.

All of the participants' drug regimes had been interrupted for one reason or another. For example, some people had made a personal choice to stop taking the drugs, others had been part of a trial of different drug protocols.

Most of the 70 people relapsed when their treatment was interrupted, with the virus rebounding rapidly to pre-treatment levels. But 14 of them – four women and 10 men – were able to stay off of ARVs without relapsing, having taken the drugs for an average of three years. The 14 adults still have traces of HIV in their blood, but at such low levels that their body can naturally keep it in check without drugs.

On average, the 14 adults have been off medication for seven years. One has gone 10-and-a-half years without drugs. It's not eradication, but they can clearly live without pills for a very long period of time, as per the scientist Sáez-Cirión.

As written before, a baby was reported to have been "functionally cured" of HIV after receiving a three-drug regime of ARVs almost immediately after birth. Sáez-Cirión warns that rapid treatment doesn't work for everyone, but the new study reinforces the conclusion that early intervention is important.

"There could be three benefits to early treatment," "It limits the reservoir of HIV that can persist, limits the diversity of the virus and preserves the immune response to the virus that keeps it in check."

Further analysis confirmed that the 14 adults were not "super-controllers" – the 1 per cent of the population that are naturally resistant to HIV – since they lack the necessary protective genes. Also, natural controllers rapidly suppress their infections, whereas these 14 mostly had severe symptoms which led to their early treatment. "Paradoxically, doing badly helped them do better later, "as per the doctor treating them.

Implications of Cure

Transmission of HIV from a pregnant infected mother to her baby is most likely to happen around the time of birth. The usual medical intervention is to give the mother antiretroviral therapy (ART) and the baby a short course of drugs after birth to prevent viral transmission. We call it 'PPTCT' – Prevention of Parent to Child Transmission which is one the success stories in the path of 'Cure'. This approach makes HIV transmission from mother to baby almost entirely preventable. However, in the case of the Mississippi baby, the mother was not known to be infected until the time of birth, and tests done when the baby was 2 days old showed that it was HIV positive. Doctors decided to give the baby a full regimen of ART. By 29 days, no virus was detectable. Treatment continued for 18 months, at which point mother and baby were lost to follow, and the child stopped getting antiretrovirals. Despite the lack of treatment, when the child was next seen by doctors at 2 years old, it remained free of functional HIV. The

child is still off treatment and HIV negative. What seems to have happened is that the early drug hit on the virus stopped it getting to the CD4 cells of the immune system, which act as a reservoir of HIV that drugs are never able to eliminate. We will hopefully know more detail of the case when it has been published in a peer-reviewed journal.

The findings from this report may support the use of a full antiretroviral treatment regimen instead of a prophylactic regimen for infants exposed to HIV during pregnancy or childbirth. It is already recommended that HIV-exposed infants should receive 6 weeks of Zidovudine prophylaxis, with the addition of 3 doses of nevirapine during the first week of life if the mother was not receiving antepartum ART. Expanding this to a triple-therapy regimen and treating for perhaps 18 months to ensure the infant is not infected could be done in any pediatric facility today, even in resource-limited settings in which access to HIV DNA or RNA testing may not be available. A finite course of treatment in infants—perhaps 18 months or so—might eliminate HIV if latent reservoirs are small enough to be adequately reduced with ART.

These findings might also have implications for the treatment of acute HIV infection in adults. A recent observational study and a prospective clinical trial has showed that starting an ART regimen during or soon after primary infection leads to greater initial and more sustained CD4+ cell count increases than starting later.

Although these observations hold out the hope that treatment during acute HIV infection has the potential to transform the outcome of HIV infection in at least some individuals, acute HIV infection is often difficult to detect in adults (who rarely present to care promptly after they were infected) than in an expected child. The recently released fourth-generation HIV antibody/antigen ELISA test that can detect acute HIV infection earlier than the standard HIV antibody ELISA may help identify these patients more efficiently. For infants, we probably should be using 3-drug ART regimens more often than not, and we should not be afraid to continue it for an extended period of time.

The real burden of mother-to-child transmission of HIV is in low-income/developing countries like ours—India (an estimated 430,000 babies infected at birth according to latest available figures), where it is doubted that the case of the Mississippi baby will have much impact. We know how to prevent mother-to-child transmission of HIV in these countries—the problem is ensuring that drugs and healthcare workers are available where when, how and whom --they are needed to treat pregnant women and protect their babies. If the facilities are not available in the developing countries to prevent transmission, it is highly unlikely that babies will get the full course of ART given to the Mississippi baby.

The use of early and aggressive treatment could be a paradigm shift in HIV/AIDS treatment in children in the developing world, where mothers are typically treated during pregnancy to lower the risk of passing the virus on to the child.

Discussion

Relevance of Cure

Despite remarkable advances in antiretroviral treatment (ART) people with HIV still face a lifetime of therapy with its known and unknown long-term toxicities. Lifelong adherence is a challenge for many people, and treatment can eventually fail even in the most conscientious patients due to the very character of the virus. Neither can prevention efforts alone be sufficient to put an end to HIV. Persistent immune activation

and inflammation due to chronic HIV infection can wreak havoc throughout the body, even when plasma viral load (VL) is undetectable. We are now finding that HIV patients have started to come more with cardiovascular/renal complications, cancer, and the appearance of accelerated aging as persistent virus contributes to the elevated risk of these illnesses to them due to their increased longevity following HAART (Highly Active Anti-Retroviral Therapy) Despite considerable progress toward universal access to antiretroviral drugs, providing long-term ART to millions of people worldwide through public and private aid efforts is unlikely to be sustainable. For every two people who start therapy today, it is estimated that three more are newly infected, so we will not be able to ourselves out of the epidemic. So what have we achieved in the past 30 years, HAART has evolved from simply keeping people alive, to maintaining undetectable viral load as long as possible, to dealing with non-AIDS conditions in an aging population and here lies the relevance of finding a ‘Cure of AIDS more than ever before, perhaps !

The word "cure" and the hope it brings have remained in the minds of many, leading to countless questions from many of the more than 30 million people infected with HIV worldwide, as well as friends, families and care providers. For now, their questions are mostly unanswered. To understand what the word "cure" means for HIV, it is helpful to review how people become infected and why a cure has been so hard to develop. People can be exposed to HIV when they have contact with infectious bodily fluids, which can include blood products during donations (an incredibly rare event with today's blood-screening techniques), sexual intercourse or, in the case of newborns, in utero, during birth or breast-feeding.

As we know there has been one prior cure of one infected adult, involving a bone-marrow transplant, a procedure that is too risky and expensive to be a common cure. Today, dozens of researchers and millions of dollars in funding support a mission to locate, activate and kill cells infected by dormant virus without harming patients. In the case of the Mississippi baby, we know, she was exposed to HIV, had HIV in her blood, and that at least some cells in her blood, were found with sleeping virus—though we will likely never know if those cells were from the child or maternal cells that had been transmitted during pregnancy or birth. Now the million dollar question is: was the baby infected with HIV and, thus, cured?

To many of the researchers, the answer may be a "no." It seems more likely that her treatment prevented her, after exposure to HIV, from being infected. The reason we give medicines to both pregnant women and their newborns is precisely to prevent HIV exposures in children from becoming established infections, an intervention that can decrease the rate of transmission from about 30% to less than 1% in optimal conditions. (called ‘PPTCT ‘these are one of few ‘success stories’ in the context of HIV /AIDS along with PEP - Post Exposure Prophylaxis, PrEP -Pre Exposure Prophylaxis) So what does this mean for patients with HIV? We have been providing PPTCT for the thousands of pregnant women who are diagnosed with HIV infection at the time of delivery, as it offers hope for further decreasing the likelihood of passing the virus to their children. The only difference from this case, from PPTCT program is that we give ATZ or NVP to infants for a shorter period (6 weeks) while ‘Mississippi baby’ received the full regimen of ART from the start till she was lost to follow up (18 months) and probably ‘hit hard hit early ‘ approach did not allowed the ‘reservoirs’ to settle down. Of course this could be a hypothesis but it has certainly given

hope to millions of HIV patients and researchers as well.

More so, the way of presentation of the mother of the Mississippi baby' in labor without any prior testing of HIV and her disappearance after 18 months of treatment, is more or less what we expect to get in developing countries like ours and so this model needs to be studied and corroborated by these hypotheses and improve our ability to prevent HIV transmission. It also offers more data to support the notion that very early treatment after HIV exposure can prevent establishment of infection in some populations.

Although these findings hold out the hope that treatment during acute HIV infection (ala –Mississippi baby) has the potential to transform the outcome of HIV infection in at least some individuals, acute HIV infection is often difficult to detect in adults (who rarely present to care promptly after they were infected) than in an expected child. The recently released fourth-generation HIV antibody/antigen ELISA test that can detect acute HIV infection earlier than the standard HIV antibody ELISA may help identify these patients more efficiently. For infants, we probably should be using 3-drug ART regimens more often than not, and we should not be afraid to continue it for an extended period of time.

But for the more than 30 million adults and children currently infected—and for the vast majority of the hundreds of thousands who are newly infected annually—this knowledge represents neither a path toward a cure nor support for discontinuing antiviral medicines. While a cure certainly remains years away, we can now "envision a cure from two different perspectives," either by eradicating the virus from a person's body (sterilizing cure) or coaxing the body to control the virus on its own (functional cure).

Till then those of us in the field of HIV care and research will have to remain steadfast in working toward a cure, a vaccine, better-tolerated therapies, and better access to care and reproductive-health services for those infected and at risk and at times combinations of all.

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