OPTIMISM FOR ACHIEVING A CURE FOR HIV INFECTION

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SOURCE

Valentin Le Douce, Andrea Janossy Houda Hallay, Sultan Ali, Raphael Riclet1, Olivier Rohrand Christian Schwartz 'Achieving a cure for HIV infection: do we have reasons to be optimistic' The Journal of Antimicrobial Chemotherapy, Volume 67 Issue 5 May 20121063–1074. Published online 2012 January 31. doi: 10.1093/jac/dkr599 also available at http://jac.oxfordjournals.org/content/67/5/1063.full.pdf+html

INTRODUCTION

This review will assess the article titled 'Achieving a cure for HIV infection: do we have reasons to be optimistic' written by *Valentin Le Douce,* et al published in 'The Journal of Antimicrobial Chemotherapy'.

In the process of portrayal -- its purpose will be defined, the structure of the article be examined in terms of serenity with which any reader can have access to this piece of information. The article will be dissected based upon its authority, accuracy, currency, relevance, objectivity and stability in that order.

The review will also delve into the article's accessibility and credibility. Upon over all appraisal the article has been found to be well penned -- clear and pertinent.

REVIEW OF LITERATURE

A cure for HIV has always been the holy grail of AIDS researchers and naturally we have plenty of literature available on the various aspects of cure from HIV—like the quest for cure, cracking a consensus about it, need for cure, barriers to cure, sources of residual virus, latent and activated CD 4 cells, viral latency, different reservoirs, different approaches to cure and torch bearers of cure and to many of them find a mention over here though to have accommodated all of them was itself a difficult task.

AIDS is a disease of staggering numbers, of tragically recursive desolation. Since the first diagnosis 32 years ago by Dr Michel Gotleib (reported in Morbidity and Mortality Weekly Report 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 condition. In late nineties the two events have 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.

Dr Robert Siliciano and his team at Johns Hopkins who conducted 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 (Mississippi baby') 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.

In 1997 Tae-Wook Chun and Anthony Fauci from the National Institutes of Allergy and Infectious Diseases (NIAID) recorded that they could still find integrated HIV DNA in resting CD4 cells from a small group of patients who started treatment early and had suppressed plasma viral load after a year on combination anti-retro viral therapy. Ten years down, based on the half-life of latently infected T-cells, Chun's group approximated that early treatment might wipe out all virus in these cells in about 7.7 years.

In the 5th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention 2007, the consensus around the ineffectiveness of a cure was starting to crack and with the approval of two novel classes of antiretroviral drugs—integrase inhibitors and CCR5

antagonists—there came in hand some armory for the first time in years the ability to target HIV at more stages of its life cycle.

The prospect of a cure came into its existence in 2010. At the XVIII International AIDS Conference in Vienna, Sharon Lewin from Monash University said "We should not and cannot continue to accept that HIV is a chronic illness that commits patients to lifelong treatment, In the absence of an effective vaccine, we must seriously pursue the possibility of cure."

The International AIDS Society patronized a workshop titled "Towards a Cure: HIV Reservoirs and Strategies to Control Them," which ushered together 200 researchers and advocates to discuss the latest advances in the field.

At the 18th Conference on Retroviruses and Opportunistic Infections (CROI 2011), researchers presented the first data from a human trial of an experimental gene therapy approach that deletes CCR5 receptors from T-cells in an attempt to halt HIV entry.

In the April 2010 issue of *Nature Medicine,* Maria Buzónsetal from Spain declared that adding the integrase inhibitor 'raltegravir (Isentress) to a suppressive ART regimen led to accumulation of bits of viral DNA known as 2-LTR circles, suggesting that HIV is still copying its genetic material but cannot insert it into host cell chromosomes. Using novel assays, UnaO Doherty's group at the University of Pennsylvania also detected un-integrated HIV DNA, suggesting continued viral replication.

In the April 2010 issue of *Nature Medicine,* Christoph Carteretal from the University of Michigan at Ann Arbor recorded that latent HIV can camouflage in CD34 hematopoietic stem cells, which give rise to all types of blood cells. When these stem cells were forced to differentiate in the laboratory, proviral DNA was activated and began producing new virus. According to Fauci, starting ART even within the first several months after infection can help keep viral reservoirs low, improving prospects for a functional cure.

Overall, intensification studies have not produced impressive results. Some researchers have found that raltegravir and the CCR5 antagonist maraviroc may reduce immune activation and inflammation. But so far there is no conclusive evidence that any combination of current antiretroviral drugs can eradicate HIV, Siliciano has to here to state, "We have reached the theoretical limit of antiretroviral therapy." But researchers have not yet given up on treatment intensification. The German New Era Study (by Dr Hans Jaeger) is looking at treatment-experienced patients with viral load suppressed for three years who add both maraviroc and raltegravir to their existing boosted protease inhibitor regimen. The EraMune trials are evaluating whether an intensified ART regimen with either interleukin 7 or a therapeutic vaccine can eliminate HIV from the body.

In 2004, Ronald Mitsuyasu etal at the University of California at Los Angeles (UCLA) announced that a ribozyme or "molecular scissors" that disrupts the HIV *Tat* gene was

successfully inserted into human hematopoietic stem cells. A follow-up study with 74 HIV positive patients who interrupted ART showed that while the altered stem cells did not significantly reduce viral load, recipients had higher CD4 cell counts over two years. There have been two revolutionary stories about two patients–have changed the scenario for pessimism to hope and anticipation in the arena of cure from HIV (both named as Berlin patients, but we shall call them Berlin 1 and Berlin 2 for our convenience) 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 no 1 was the first individual known to have achieved "remission" of HIV 'ala' cancer model, and the case made headlines around the world, including a reporting 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, this Berlin Patient had been left 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 to measure such. Although his HIV was not wiped out the man's immune system managed to control the virus, showing that a functional cure is within the reach of possibility. The second Berlin Patient came to the world's notice some ten year later.

One American man living in Germany, took treatment for acute myeloid leukemia (AML) at Berlin's Charité Medical University in 2006. At that time, he had been HIV positive for more than a decade and on c- ART for four years, and had undetectable viral load, having a history of high viral load and disease progression, excluding himself from being a natural elite controller. After initial chemotherapy failed, the next step was a bone marrow transplant. The man received a bone marrow transplant containing hematopoietic stem cell after taking strong chemotherapy and the donated stem cells essentially built a new immune system.

The man's doctor, Gero Hütte had learnt that individuals with the CCR5- delta-32 genetic variation were protected against HIV infection. He could find 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. This Berlin Patient no 2 stopped ART one day before his first bone marrow transplant in 2007 and afterward got 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.

A year later, the man had a recurrence of AML and the patient received a second transplant after chemotherapy and whole-body radiation from same donor. The man kept off from ART, two months after the first procedure maintained undetectable plasma HIV RNA and undetectable proviral DNA in resting CD4 T-cells. Dr Hütter presented this Berlin case study at CROI 2008 and in the February 12, 2009, *New England Journal of Medicine.* The case generated interest from both HIV researchers and the public at large after an in-depth article by Schools in the *Wall Street Journal.*

In an update at the IAS Reservoirs workshop and in the March 10, 2011, issue of *Blood,* Hütter's team reported that four years after the first transplant and still off ART, the man remains in remission from AML and demonstrates no signs of HIV. Using the best available technology, 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 count has increased to a normal level. This Berlin Patient revealed his identity as Timothy Brown, now in overall good health and living in San Francisco. Zinc finger gene therapy technology developed by Sangamo BioSciences is furthest along in development. This technique uses a zinc finger nuclease (ZFN), a synthetic protein carried by an adenovirus vector that can cut DNA strands at a specific location.

The nuclease causes a double-strand DNA break in the CCR5 gene, and the ensuing repair process permanently disrupts the gene, passing along to daughter cells. At CROI 2011, Jay Lalezari from Quest Clinical Research and Carl June presented findings from the first pilot studies of the Sangamo zinc finger technique in HIV positive people, assessing whether autologous (self-donated) CD4 T-cells with deleted CCR5 (dubbed SB-728-T) would proliferate, persist, and behave like normal T-cells in the body. At CROI, Craig Wilen from the University of Pennsylvania presented the first data on gene therapy to interfere with CXCR4 expression. Laboratory studies found that the zinc finger procedure did not impair CD4 T-cell proliferation.

Altered cells exposed to HIV were protected from infection and showed a significant survival advantage. In mice with a humanized immune system, altered CD4 cells were protected from infection by CXCR4-tropic HIV. In the August 2010 issue of *Nature Biotechnology,* Nathalia Holt and Paula Cannon from the University of Southern California and colleagues recorded that the Sangamo zinc finger technique can disrupt the CCR5 gene in CD34 hematopoietic stem cells from humanized mice. Since these stem cells give rise to all types of blood cells, the resulting CD4 T-cells lacked the CCR5 coreceptor and therefore were protected against HIV infection. Researchers are studying various methods of activating quiescent cells in order to awaken hidden proviral DNA, with the goal of purging or flushing out the viral reservoir And as per David Margolis, this may be done either by directly activating resting cells and their resident HIV, or by disabling mechanisms that keep them inactive—that is, by "giving them a push" or "taking the brakes off."

Sandrina Da Fonseca et al from VGTI showed that CD4 T-cells containing proviral DNA express more of a surface antigen known as programmed death 1, or PD-1. Interactions between PD-1 and its receptor, PD-L1, help maintain these cells in a resting state and keep integrated virus latent, they reported at CROI 2011. Conversely, agents that block this interaction can stimulate HIV reactivation and release.

A class of agents known as protein kinase C activators activates transcription of latent HIV without prompting activation of uninfected cells. Frank Wolschendorf et al stated the dubbed HIV-1-reactivating protein factor, which stimulates a brief pulse of NF-kB that activates Tat and sets off viral production—portrayed as "hit and run stimulation"

The way to "take the brakes off" is chromatin remodeling, or changing how HIV DNA binds to histones in host cell chromosomes, a chemical reaction called acetylation which keeps DNA accessible, while a complementary reaction, methylation, has the opposite effect. Histone deacetylase enzymes keep DNA tightly bound and unusable; HDAC inhibitors and methylation inhibitors release DNA so it can be used to direct virus production. In the June 19, 2008, issue of *AIDS*, Margolis et al reported from a larger follow-up study using Valproic acid. Here, 11 HIV positive people with stable viral suppression added 1,000 mg valproic acid to their standard ART regimen. Four participants (36%) showed a reduction in latently infected CD4 cells, including three who also experienced further reductions in viral load; the rest, however, had no significant change.

These studies indicate that valproic acid is not potent enough—or perhaps does not target the right forms of HDAC—to appreciably reduce the size of the latent HIV reservoir; they offer proof of concept that this approach may have some benefit.

Sophie Reuse et al (Belgium) reported at the IAS Reservoirs workshop that a combination of clinically available HDAC inhibitors plus prostratin synergistically activated the HIV promoter element, leading to enhanced viral gene expression.

In the June 2009 issue of *Retrovirology*, Savarino's group reported a "shock and kill" approach using Class I HDAC inhibitors plus the pro-oxidant agent buthionine sulfoximine (BSO). The HDAC inhibitors activated latent HIV in cell cultures, but only at toxic doses; adding BSO enabled the HDAC inhibitors to work at lower, more tolerable doses.

In the April 5, 2011, issue of *PLoS ONE*, Michael Kovochicheta l (UCLA) mentioned an approach using nanotechnology to deliver drugs more precisely to desired targets. A nanoparticle with the protein kinase C activator bryostatin-2 activated resting T-cells and stimulated latent virus production *in vitro* and in humanized mice. Adding the HDAC inhibitor sodium butyrate enhanced activation, and the particles could also be loaded with the antiretroviral drug nelfinavir to simultaneously activate latent virus and inhibit its replication.

The resting cell activation approach aims to purge latent HIV from reservoirs, but the opposite strategy—keeping integrated viral DNA permanently silenced—could also be another way to achieve a functional cure.

In the April 15, 2010, *Journal of Infectious Diseases, Siliciano's group* recorded that minocycline selectively interrupts signaling pathways critical for T-cell activation.

In 1999, Cynthia McCoigetal from the University of Texas disclosed that genetically engineered immune toxins targeting the CD45RO marker on memory CD4 T-cells killed HIV-containing memory cells while sparing naive CD4 T-cells and certain other memory cells with different marker configurations.

Abraham Loyteretalat Hebrew University expressed that a combination of peptides plus saquinavir (Invirase) increased integration of HIV DNA into host cells to such an extent that they underwent apoptosis, or cellular suicide. They further stated that in a laboratory study this lethal mix led to death of infected T-cells and "total extermination" of the virus, but it did not appear to have an effect on uninfected cells.

Other research aims to boost the immune system's response to HIV. Dozens of therapeutic vaccine candidates have been tested, but despite some promising activity in laboratory and animal studies, none have been shown to consistently and significantly decrease—much less eliminate —HIV over the long term in clinical trials.

Researchers have also tied to find many other immune-based therapies, including gene therapy to make CD8 T-cells respond more strongly to the virus, but with every method tested so far HIV comes back after ART is stopped.

Finally, reducing the harm caused by HIV could be another way to implement a functional cure. A growing school of thought evidences that persistent immune activation and inflammation are responsible for much of the damage related to chronic HIV infection. If investigators could find a way to abandon this response, the virus might be rendered harmless, in the same way some monkey species harbor persistent replicating SIV without disease progression.

ARTICLE SUMMARY

'Cure does 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 and after the arrival of the combination medicines against this virus, called Anti retroviral therapy (ART) in 1996 (now known as 'highly active antiretroviral therapy - HAART). The advent of HAART has almost reversed a scenario -- a disease equated with death warrant -- to a chronic and manageable illness with a dramatic decrease in mortality and morbidity of AIDS-related symptoms in infected patients. But HAART has not been able to find the cure of HIV infection, There are hurdles to HIV eradication--- the main being the existence

of dormant or quiescent reservoirs. Several other problems have been found with HAART (such as side effects, adherence to medication, emergence of resistance and cost of treatment), and these inspire the search for new ways to treat these patients. 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 seronegative (called Elite Controllers and Slow/Non-progressors) offer a great opportunity to study the mechanisms of resistance to HIV infection and disease. Recent advances hold promise for the ultimate cure of HIV infection. Besides these new strategies aiming to eliminate the virus, efforts must be made to upgrade the current HAART. The medical scientists believe that the cure of HIV infection is not going to be achieved in short term and that a HAART strategy based on purging the reservoirs has to be done aggressively. Till 'Cure' is not achieved we will have to remain steadfast in working towards it. This article fulfills its objectives of sending messages to the readers about the optimism of HAART and its prospective abilities to achieve a cure for HIV, albeit with a question mark.

ARTICLE STRUCTURE

The article commences with an abstract that overtures - an effective overview of the article by establishing the background to the issue of achieving a cure from HIV and relevant points. The article itself is very qualitative in nature and is twelve pages long. It is accessible online as a PDF/html document and the contact details for the authors are adequately provided. There is a logical ordering of points and both the paragraphs and the sentences are just instructive making the availability of the information, its reading and understanding - all that effortless. The conclusion is a straightforward summary of the points made There are more than adequate references, provided in a reference section (in fact a huge list follows --186-One hundred eighty six - in total,) but can be considered taking into the account relevance of the topic. Overall the abstract is concise and terse. The structure of the article makes it easier to interpret and understand.

ARTICLE CRITIQUE

AUTHORITY

The article has been featured in an extremely illustrious ***source 'The Journal of Antimicrobial Chemotherapy'*** This is a peer-reviewed medical journal which covers laboratory aspects and clinical use of antimicrobial agents and is published by Oxford University Press on behalf of the British Society for Antimicrobial Chemotherapy, The Journal of Antimicrobial Chemotherapy is among the foremost international journals in antimicrobial research and its readership includes representatives of academia, industry and health services, and includes those who are influential in formulary decisions. This journal is abstracted and indexed in Biological Abstracts, BIOSIS Previews, CAB International, Chemical Abstracts Service, Current Contents, EMBASE, MEDLINE/Index Medicus, ProQuest Medical Library, *and the* Science Citation Index *and as per* the Journal Citation Reports, this journal received a 2012 impact factor of 5.338, ranking it 7th out of 69 journals in the category *Infectious Diseases*, which makes it more plausible.

The article has been equally contributed by all of the authors as has been suggested in the article and their affiliations to Institute of Parasitology University of Strasbourg, Strasbourg, France speaks their class as the University of Strasbourg in Strasbourg, Alsace, France, is the second largest university in France (after Aix-Marseille University), with about 43,000 students and over 4,000 researchers. All of this information indicates that the article is highly credible and persuasive

ACCURACY

Being published as a 'review article in a distinguished medical journal of the stature of '*The Journal of Antimicrobial Chemotherapy* proves its correctness and exactitude. The article has more than enough (186) references of articles written by some of world famous HIV Experts connotes its great accuracy and credibility.

CURRENCY

The Journal of Antimicrobial Chemotherapy with this article was published in May 2012 in print and went online on January 31 2012. Its references date from 1998 to 2010. The recent publication of the article and the recent references indicate that the article is very topical and contemporary, as does the content of the article which deals with the current advancements in the field AIDS cure.

RELEVANCE

It has been written to furnish information to an educated sector (Medical doctors) and published in a reputable journal (The Journal of Antimicrobial Chemotherapy) and it is relevant to its main intended audience–the HIV health care providers. The topic (HIV Cure) covered too is a

significant one in the context of HIV, which has been long cherished dream. In the conclusions of the article authors asks the question-Are there reasons to be optimistic that a cure for HIV infection may be achieved and themselves answer with guarded affirmation as the cure from HIV will not be achieved in the short term. They discuss the exciting advances offering new opportunities to achieve a cure, using gene therapy to confer HIV resistance (including the CCR5 gene therapy) which is a valuable approach compared with chemotherapy, but fraught with several drawbacks, including toxicities, development of resistance and cost. They surmise that the 'holy grail' for scientists is to achieve a sterilizing cure with total eradication of the virus from the body, although we have got functional cure, with few patients who control HIV-1 infection (the elite controllers). The 'shock and kill' strategy has too emerged as an exciting potential way to eliminate the virus. The German case is the only example where a we have a possible sterilizing cure, incidentally indicating a weakness of HIV. The authors compare these strategies with a war and declare that the war against this virus is far from over and will need much more work. They equate the current therapeutic strategies that could lead in the long term to a cure as the first front line but, to win a war usually a second front line is needed to open which they analogize with the development of an HIV vaccine. They believe that even if in practice this approach (vaccine research) is not yet yielding –(ongoing vaccine trials) not very optimistic results, efforts in this direction must be continued, but the scientists might require new avenues in HIV immunology research They feel that research aiming at a therapeutic cure will benefit from research aiming to develop a vaccine, and vice versa. Finally they cite reasons to be optimistic coming from the intensive efforts made in different fields of research, that of a multidisciplinary approach, including immunologists, virologists, molecular biologists, clinicians, pharmacologists, chemists, physicists and mathematicians, who they feel, have already initiated new ways and amplified new concepts for therapies that are currently being tested in clinical trials. These are global issues (HIV, Cure research) and undoubtedly relate to the global community.

OBJECTIVITY

The information in the article was derived from team of authors' extensive experience working at higher centres of excellence in HIV field – the Institute of Parasitology University of Strasbourg, Strasbourg, France, with over 4,000 researchers. All of this information indicates that the article is highly plausible and trustworthy.

The article shows research decisions, and contains both facts and evidences, opinions have been presented, on the both sides of the argument (availability of strategies of cure vs obstacles in achieving it) are adequately elucidated. The article raises question itself in achieving a cure. The majority of the claims and arguments made have been supported, in the articles and References. The article serves its purpose as an objective presentation of achieving a cure from HIV to the medical community in general and HIV Care providers in particular.

STABILITY

The article has been published in a reputed medical journal and available in both print and electronic forms. The article and all 186 references have been duly been cited by other articles in PMC (The PMC -**PubMed Central** is a free digital database of full-text scientific literature in biomedical and life sciences which has grown from the online Entrez PubMed biomedical literature search system and developed by the U.S. National Library of Medicine (NLM) as an online archive of biomedical journal articles. The full text of all PubMed Central articles is free to read, with varying provisions for reuse. Some participating publishers delay the release of their articles on PubMed Central for a set time after paper publication (often six months). The archive contains approximately 2.6 million items, including articles, editorials and letters. For these reasons, the article is stable as a resource and being accessible through a credible and reliable academic database like PMC.

ANALYSIS OF GRAPH

Not applicable

RECENT ADVANCES RELATED TO THE TOPIC

The Berlin Patient, the VISCONTI cohort and the "cured" baby in Mississippi provide tantalizing hope that a "functional cure" may be possible. A "functional cure" essentially means that people can remain HIV free without the need for antiretroviral therapy. While HIV treatments are effective at controlling the active virus, HIV also persists in the body by hiding in long-lived cells (resting CD4+ memory T cells). In this state, HIV resides in a latent reservoir undetectable by the immune system and unaffected by antiretroviral treatments. Flushing latent HIV from these hiding places has been proposed as a key step towards a cure.

On March 14th, 2013 results from the Visconti trial conducted in France (the name is a contraction of "***Virological and immunological studies in controllers after treatment interruption***") were published, It has made the possibility of using antiretroviral drugs to produce something akin to a cure.

The Visconti trial, which was reported in the Public Library of Science's journal *PLoS Pathogens* by Christine Rouzioux et al of Paris Descartes University has followed the fates of 14 people treated with antiretroviral drugs shortly after they were infected with HIV, and for several years thereafter, who then (under medical supervision) had their drug treatments withdrawn. As the trial's investigators reported to the International AIDS Conference in Washington, in July 2012, this procedure has turned these people into what are known as "elite controllers"—(they still have detectable levels of HIV in their bodies years after infection, but even in the absence of drug treatment those levels do not rise significantly, and certainly not to a point where they are causing symptoms)

Elite controllers do occur naturally, but such people are unusual. Fewer than one person in 100 seems to have the potential to develop natural elite control. What causes natural elite control remains mysterious, but certain versions of what are known as HLA genes (which regulate cell-surface proteins in some immune-system cells) are rarely found in natural elite controllers.

The crucial feature shared by people in the Visconti study is that they were put on drugs within ten weeks of infection, a point where the virus is still establishing itself in the body. This hypothesis is akin what has been used in the "Mississippi baby" case, reported in March 2013, in which an infant girl, infected by being born to an HIV+ mother, was given antiretroviral treatment within a few hours of birth. Her doctors, however, lost touch with the child for five months when she was 18 months old, interrupting the treatment. When the mother came to health facility with the baby, researchers found her infection had regressed to the point of *undetectability*, even though she was no longer on ART. This observation, combined with the Visconti trial, leads to the question of how frequent the phenomenon of elite control following early treatment actually is.

Dr Rouzioux et al tried to estimate this frequency of 'elite controllers' from a database of French AIDS cases, and came to conclusion that about 15% of those who are infected and treated early turn into elite controllers—though with a limitation -- the database in question, the French Hospital Database on HIV, allowed them to draw this conclusion for only the first two years after the end of treatment.

It is all, extremely encouraging and if the common factor between so-called post-treatment controllers can be identified, it will allow experts to offer treatment withdrawal to those likely to benefit from it.

A scientific strategy—consisting of seven major research priorities—has been launched by an International AIDS Society working group, according to a report released July 19 and discussed in detail in a two-day symposium taking place July 21 and 22 ahead of the XIX International AIDS Conference (AIDS 2012) in Washington, DC. As per Françoise Barré-Sinoussi the strategy, baptized as "Towards an HIV Cure,--is the result of a collaborative effort which has produced a roadmap that will constructively move HIV cure research forward." Barré-Sinoussi, the co-discoverer of HIV, a Nobel laureate and researcher at the Institute Pasteur, is co-chair of the group—along with Steven Deeks, MD, of the University of California, San Francisco—consisting of 34 leading HIV scientists and clinicians.

The molecular biology regarding how HIV's DNA becomes integrated in the chromosomes of human cells is the focus of intense research. This work has already led to a number of possible interventions, some of which are being tested in clinical trials.

Recently, in a small study involving people living with HIV, David Margolis, MD, of the University of North Carolina et al demonstrated that a dose of a drug that inhibits an enzyme involved in HIV silencing leads to rapid production of HIV RNA in the patient's latently

infected cells. This could make such previously unreachable viral reservoirs susceptible to curative strategies. For example, in combination with treatments that enhance host immune defense—therapeutic vaccines are an example—unmasking latent virus might allow clearance of infection. Barré-Sinoussi, Deeks and their colleagues note that substantial resources will be required to address these priorities.

A number of clinical trials are planned, or currently underway, to study the safe elimination of latent infection in people living with HIV receiving antiretroviral therapy. These include:

Study	**Intervention**	**Reference (clinicaltrials.gov)**	**Status**
Optiprim ANRS 147	3 vs 5 ARVs during acute infection	NCT01033760	Closed, ongoing
IntensVIH	Isentress + Selzentry intensification	NCT00935480	Closed, ongoing
Eramune 01	IL-7 +intensifcation	NCT01019551	Closed, ongoing
Eramune 02	Vaccination +intensification	NCT00976404	Closed, ongoing
Deeks	Disulfiram	NCT01286259	Closed, ongoing
Margolis	Vorinostat (SAHA)	NCT01319383	Recruiting
Lewin	Vorinostat (SAHA)	NCT01365065	Recruiting
Lalezari	Zinc finger nuclease (ZFN)	NCT01252641	Closed, ongoing
Tebas	Zinc finger nuclease (ZFN)	NCT00842634	Closed, ongoing
Krishnan	Gene therapy/stem cell transplants in	NCT00569985	Recruiting

	HIV lymphoma patients		
Moreno	Bryostatin	N/A	Starting soon
Hatano	Anti-PD1 antibody	N/A	Starting soon
Woolfrey	Autologous HIV-resistant cells	N/A	Starting soon

NEW ERA STUDY

This study ties perhaps first time 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 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 latest reports indicate that here has been decrease in proviral DNA and no patients has stopped medicines due to toxicities, with no unexpected serious adverse events (SAE) --only 2 SAEs (kidney stones), 8 laboratory AEs (Adverse effects) (grade 3), and 32 clinical AEs (grade 1 and 2, i.e. diarrhea, fatigue) have been reported, but therapy has not been interrupted which has been 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'

CONCLUSION

The review analyzes critically the article ***Achieving a cure for HIV infection: do we have reasons to be optimistic'*** written by *Valentin Le Douce*, et al The content, structure, strengths and limitations of the article were construed and dissected. The article has shared to a better understanding amongst the HIV guild, of the pros and cons of a possibility of achieving a HIV cure. It is an accessible, easier to read well researched and highly credible. One familiar axiom

'*to 'Cure occasionally, relieve often, console always* '—coming from the ancient French aphorism ***'Guirerquelquefois, soulagersouvent, consoler toujours'***, 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, though a 'cure' is still elusive) thereby meaning that no body 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.

'Cure' -comes from Latin word 'cura' meaning –care, concern, attention'. The current use of wordseemingly sprang from the belief that proper and sufficient 'care' was tantamount to 'cure'. Would that this were so !

Both these words 'care' and 'cure' are legitimately appropriate in the ambience of HIV/AIDS, more so in present scenarios. And hence this article is being recommended for medical experts especially, the HIV care providers

REFERENCES

1. AIDS Turning Point: 'A Cure Is Possible http://www.spiegel.de/international/europe/aids-cure-new-science-suggests-breakthrough-ways-of-eradicating-hiv-a-920562.html accessed on 24th. Sept, 2013

2. Allers, K. and others. Evidence for the cure of HIV infection by CCR5-delta-32/delta-32 stem cell transplantation. Blood 117(10):2791–99. March 10, 2011.

3. Bob Roehr, The slow and unknown route to a cure for AIDS BMJ 2012; 345 doi: http://dx.doi.org/10.1136/bmj.e5265 (Published 10 August 2012)

4. Deeks, S. and McCune, J. Can HIV be cured with stem cell therapy? Nature Biotechnology 28(8):807–10. August 2010

5. Gero Hütter and others : Long-Term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell Transplantation N Engl J Med 2009; 360:692-69 8February 12, 2009

6. http://online.wsj.com/article/SB10001424127887324539404578338300521959748.html A version of this article appeared March 4, 2013, on page A3 in the U.S. edition of The Wall Street Journal, with the headline: Baby Cured of HIV for the First Time, Researchers Say.' : accessed on 20th. Sept March 2013

7. http://clinicaltrials.gov/show/NCT00908544 New Era Study: Treatment With Multi Drug Class (MDC) HAART in HIV Infected Patients (NewEra) accessed on 21st. Sept, 2013

8. International AIDS Society "Towards an HIV Cure": Global Scientific Strategy http://www.iasociety.org/Default.aspx?pageId=349, accessed on 21st. Sept, 2013

9. 'In Medical First, a Baby With H.I.V. Is Deemed Cured' http://www.nytimes.com/2013/03/04/health/for-first-time-baby-cured-of-hiv-doctors-say.html?pagewanted=all&_r=0 accessed on 21st. Sept, 2013

10. Khan Matin Ahmad 'Cure in the context of HIV /AIDS' accepted for publication in JIMA (Journal Of Indian Medical Association, Sept, 2013

11. Khan, Matin Ahmad 'Has a time to talk about cure of AIDS arrived? International Journal of Collaborative Research on Internal Medicine & Public Health Vol4 No 6 2012:.981-1000 (ISSN I986-5872) June 2012

12. Kent, Stephen J and others The search for an HIV cure: tackling latent infection The Lancet Infectious Diseases, Early Online Publication, 5 March 2013

13. Lisziewicz, J. and others. Control of HIV despite the discontinuation of antiretroviral therapy. New England Journal of Medicine 340(21):1683–84. May 27, 1999

14. Presentation 'Is Cure for HIV Infection possible? ASICON-2010, Hyderabad, India October 31st. 2010 Hans Jaeger, MD from Munich, Germany

15. Tae-Wook Chun and Anthony S. Fauci :HIV reservoirs: pathogenesis and obstacles to viral eradication and cure'www.projectinform.org/pdf/AIDS_0312.pdf, accessed on 21st. Sept, 2013