

## THE ERA OF HIV CURE RESEARCH

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## SUMMARY

**Timothy Ray Brown is widely referred to as the first HIV patient to be cured of the disease. He received a CCR5 deficient bone marrow transplant as a treatment for Acute Myeloid Leukemia, with HAART controlled HIV-1 infection at the background. Seven years after the transplant, and discontinuation of HAART, he has been free of the virus. Several tests conducted to detect elements of the virus have turned up negative. This has suggest renewed and more determined interest in finding a lasting cure for HIV-AIDS and has given birth to the era of HIV cure research.**

## INTRODUCTION

The Human Immunodeficiency Virus (HIV) has earned an indelible place in the history of man. First discovered and described in 1981<sup>1,2</sup> It is rapidly becoming the most significance pandemic in history of diseases of man. The only other pandemic that caused more deaths than HIV-AIDS to date is *Yersinia pestis*, the Black Death which led to over 70 million deaths<sup>3</sup>. Next to cancer, HIV is currently the most feared disease in modern times, affecting over 30 million people worldwide<sup>4</sup>. Sub-saharan Africa bears the largest burden of the pandemic, with South-Africa and Nigeria being the worst affected countries in the world<sup>4</sup>. The disease is presently incurable despite the huge sums of money that has been devoted to rigorous and cutting edge research. The virus, which infects every age group, causes an acute – chronic and eventually fatal illness. Factors complicating efforts towards controlling the disease include the huge stigma associated with the illness. Stigma results in many infected individuals hiding their status by rejecting voluntary screening and delaying or even rejecting treatment. This continues to promote the spread of the virus.

The advent of Highly Active Antiretroviral Therapy (HAART) has significantly transformed the natural history of the disease. Today millions are living normal lives with complete suppression of the virus by powerful combination therapies known by the abbreviation HAART. Highly Active Antiretroviral Therapy (HAART) has been shown to effectively reverse the effects of the disease and reduce the viral load to undetectable levels<sup>5-8</sup>. Well coordinated efforts are ongoing to further expand the drug options for HAART and reduce the side-effects of the drugs. There are also promising efforts towards finding easier drug regimens and cheaper options to enable more people living with the virus have access to the drugs and be

able to adhere to therapy. However, the ultimate goal remains developing a cure for the disease.

Hope for a cure was very low and the focus for a long time was, and still is, optimizing HAART regimens; then a totally unforeseen phenomenon occurred. This phenomenon was a European patient who today is known as the Berlin patient.

**Timothy Ray Brown, the Berlin Patient**

Functional cure for HIV AIDS has been achieved in patients who received experimental therapies that left them free of the virus for many years without Anti-retroviral drugs. Two such patients have been mentioned in the history HIV cure research. Similar cases of cure have come to be colloquially known as “Berlin patient.” In 1998 the first Berlin patient was described but the identity of the patient was not revealed in the report and since then not much has been said or known about him<sup>9</sup>. In 2008, the well known case of Timothy Brown was reported in the New England Journal of Medicine<sup>10</sup>.

Timothy Ray Brown had acute myeloid leukemia and HIV for over ten years before he underwent the miracle procedure. He was on HAART (600mg of efavirenz, 200mg of emtricitabine, and 300mg of tenofovir daily) with adequate HIV-1 control. When he suffered a relapse in his leukemia, his doctor and managing team decided to give him a bone marrow transplant. In 2002 he received an allogenic bone marrow transplant from a patient who was homozygous for a 32bp deletion in the CCR5 allele known to result in resistance to HIV invasion of CD4 cells<sup>10</sup>. Since the transplant he has remained free of HIV-1 despite not being on HAART for over seven



**Fig. 1:** Timothy Ray Brown, *Photo credit: Washington Blade's Michael Key;*

<http://www.washingtonblade.com/2012/07/25/berlin-patient-announces-foundation-to-seek-aids-cure/> (website accessed on 08-05-2014)

years. He is currently considered as the first case of HIV-1 to be cured of the disease. The transplant cured his leukemia and eliminated the HIV.

### HIV Cure

The case of Timothy Ray brown has generated new hope in finding a lasting cure for the disease. This hope has resulted in workshops, conferences, and seminars on research with potential for cure of HIV, an idea that was once considered impossible or too distant for any serious consideration. Now the possibility of curing the disease is before us and there are some immediate challenges. There is the need to start putting in place the required terminologies in this emerging era of HIV cure research.

New definitions are already being considered and proposed, some of which include:

**Stage 0 HIV:** a new case definition of the disease that considers the presence of viral elements before immunologic seroconversion, usually within weeks to six months of primary infection<sup>11</sup>. This case definition may become very relevant based on emerging evidence indicating that one of the factors associated with cure or prolonged viral control is early commencement of antiretroviral therapy.

**HIV suppression therapy:** patient who is on effective HAART and meeting the criteria for viral control, below detectable limits. This is currently a major objective of HIV therapy.

**Post Treatment Controllers (PTCs):** Subjects who are initiated on HAART within 10 weeks of a primary HIV infection and are able to achieve a steady state of therapy with a viral load below 400 RNA copies/ml over a period of at least 24 months. They were first reported by Hocqueloux *et al* in 2010 as a special population of patients<sup>12</sup>.

**Functional cure:** HAART treated Patient who remains controlled after discontinuing therapy for prolonged periods, usually over 6 months of being HAART free. This is the lack of detectable viremia in the absence of HAART despite presence of replication-competent virus and normal or near normal immune functions<sup>13</sup>.

**Sterilizing cure:** HAART treated patient without any detectable element of the virus in his or her cells after 10 years of discontinuing therapy. This is as a result of the eradication of all replication-competent viruses<sup>13</sup>.

These are some of the evolving terminologies that will need further refinements in this new era of HIV cure research; they come along with a lot of excitement and hope. What is certain today is that HIV research has moved closer to finding a cure like never imagined in recent years. It is also becoming clearer that early initiation of HAART within 10 weeks of primary HIV infection may be the foundation for achieving functional cure, the 'Hit fast, Hit hard' principle<sup>14</sup>. The challenge of getting infected subjects early enough for commencement of therapy will require a lot of effort by HIV researchers if the goal of early commencement of therapy is to be attained.



**Fig. 2:** Prof Richard D'Aquila; *Northwestern University Profile photo:*

### HIV Cure Researchers

The foremost name here is Gero Hütter (born December 18, 1968), a German hematologist whose medical team managed Timothy Ray Brown. In 2009,

Hütter, Eckhard Thiel and others from the Charité Hospital in Berlin, Germany, published their report in the New England Journal of Medicine(10). This feat earned Hütter the recognition of being the first doctor to functionally cure the disease. This achievement has led to an increasing number of workers searching for methods of curing HIV infection. Workshops pulling together workers in the field of HIV Cure Research are increasingly being held worldwide.

The number of HIV Cure Researchers is rapidly increasing. A search of PUBMED (search terms: HIV Cure Research, unstructured search) done on the 5<sup>th</sup> of May 2014, clearly showed a rapid increase in numbers of Publications reporting HIV Cure Research. The search yielded 16 publications spanning 1989 – 2010 (22 year period), and 67 publications spanning 2011- 2013 (4 year period), table 1. The first publication was by Franchini in 1989<sup>16</sup> while the latest report was in December 2013 by Watters<sup>17</sup>. While an unstructured

**Table 1:** A selection of review articles on HIV Cure Research

Year	Publication Title (citation)
2014	Early treatment during primary infection holds the key to a functional cure for HIV <sup>19</sup>
2013	Child cured of HIV: can this be repeated? <sup>20</sup>
2013	A cure for AIDS: a matter of timing? <sup>14</sup>
2013	Development of hematopoietic stem cell based gene therapy for HIV-1 infection: considerations for proof of concept studies and translation to standard medical practice <sup>21</sup>
2013	Will it be possible to live without antiretroviral therapy? <sup>22</sup>

On Thursday April 24, 2014, Prof Richard D'Aquila of the Feinberg School of Medicine, Northwestern University, Chicago (whose work on HIV Cure is at the cutting edge of research<sup>15</sup>) coordinated such a workshop to develop feasible HIV cure research strategies that synergize with HIV prevention efforts. This workshop had international presenters with research focus on understanding how anti-retroviral therapy started very early, after HIV infection, may lead to sustained remission when therapy stops and research to determine specific immune defenses that makes this response possible. The high point of the workshop was an address by Timothy Ray Brown who is currently free of the virus and is off HIV medications.

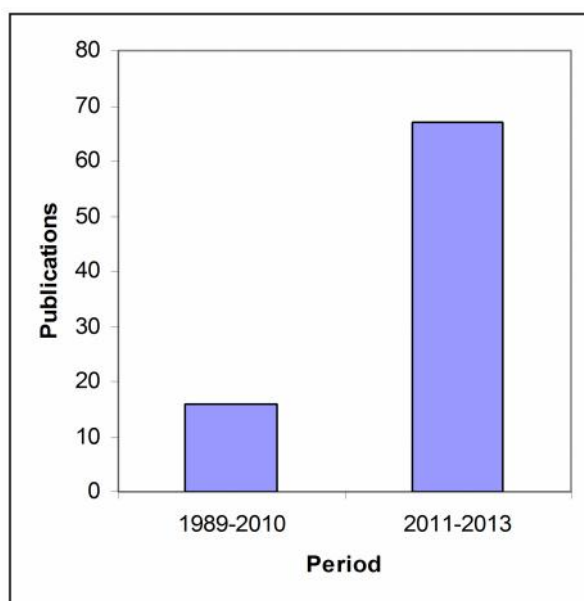
PUBMED search has limitations, the trend of this new era is clear; HIV Cure Research will witness exponential increase in interest and publications in the coming years. Table 1 is a brief compilation of some excellent review articles in this new focus of HIV research. The much anticipated cure for HIV is at the Horizon; a new era has begun and indications show that this is an era that will end in success.

### CONCLUSIONS

HIV is a global pandemic that has affected every ethnic group in the world. The disease has remained incurable but the focus of research into therapeutic approaches is changing. The goal of therapy is evolving from control to functional and hopefully sterilizing cure. A new era has begun. People living with the virus are eagerly awaiting the announcement of an effective, affordable, side-effect free, cure. This will bring an end to the stigma associated with the infection. The disease has led to development of international linkages and novel methods in biomedical research. It is a pandemic that places a demand for action on every medical scientist in every country of the world. The bigger picture is that every step towards finding a cure for HIV is also a step closer to finding a cure for other incurable diseases, especially cancer<sup>18</sup>. This Hope must be kept alive, vigorously pursued, and adequately funded by sitting governments and wealthy individuals in every nation of the world.

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**Fig. 3:** PUBMED Publications with themes on HIV Cure Research

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