



High Active Anti-retroviral Therapy for HIV/AIDS, Progresses and Drawback

Da-Yong Lu^{1*} and Ting-Ren Lu²

¹School of Life Sciences, Shanghai University, Shanghai 200444, PR China

²College of Science, Shanghai University, Shanghai 200444, PR China

Abstract

AIDS (acquired immune deficient syndrome) is a human infectious disease. AIDS patients, if not be treated, commonly suffer a gradual loss of human immune-defensive functions and finally die of infectious complications within 2 years after AIDS symptoms occur in patients. AIDS patients can be treated with a series of anti-viral drugs to decrease the virus-load and slow the pace of occurrence AIDS and ameliorate the symptoms of immune deficient and prolong the life-spans of patients by high active anti-retroviral therapy (HAART). Even though HAART is very effective, HIV/AIDS patients cannot be cured by HAART. And there are a lot of precautions for this therapy. There are a plethora of reasons behind these phenomena. In this review, we will detail address this problem and try to give new directions.

Keywords: HIV; AIDS; HAART; Antiviral therapy; Human genome; Drug toxicity; Vaccine

AIDS (acquired immune deficient syndrome), first discovered in West countries in 1981, is a human infectious disease. AIDS patients, if not be treated, commonly suffer a gradual loss of human immune-defensive functions and finally die of infectious complications within 2 years after AIDS symptoms occur in patients.

In the pathogenesis mechanism, AIDS patients are caused by infecting with HIV (human immune-deficiency virus) by sexual transmission, blood donor transmission, drug abuse with contaminate syringes and mother-to-child transmission and so on. The HIV viruses can parasite in human bodies and remain non-pathogenic for certain amount of times, even as long as ten years sometimes. These humans are called HIV infectious. Gradually, HIV viruses inactivate the functions of human immune-system, especially for CD4 lymphocytes. Until the symptoms of immune deficient occur, these patients are then called AIDS patients.

AIDS patients can be treated with a series of anti-viral drugs to decrease the virus-load and slow the pace of occurrence AIDS and ameliorate the symptoms of immune deficient and prolong the life-spans of patients.

Now, a large number of AIDS patients or HIV infectious can live much longer life (approximately 10 year after first AIDS symptoms occur in patients) if they are properly treated, even achieve normal life-spans.

HIV/AIDS patients can be treated and ameliorated with antiviral chemicals. But before the invention of high active antiretroviral therapy (HAART, cocktail therapy), the therapeutic outcomes of AIDS patients were unsatisfactory. The AIDS patients generally died within 2 years after AIDS symptoms occurred.

HAART was developed approximately 15 years ago, which was to combine use of antiviral chemicals of different mechanistic types and categories and could prolong the AIDS patients survival to approximately 10 years. This was a great achievement. More infected patients live longer and eventually die of causes that are unrelated to HIV infection. Now HAART become the standard of care for HIV infection [1].

More than twenty anti-HIV chemicals have been licensed for formal utilizations worldwide, which are now divided into 6 mechanistic types and categories (Table 1).

NNRTIs—non-nucleoside reverse transcriptase inhibitors

NRTIs—nucleoside reverse transcriptase inhibitors

The initial HAART therapy is to combine utilize NRTI and NNRTI. Late, more HAART are the combination of NNRTI or NRTI with protease inhibitors. Now more types of antiviral drugs can be combined and some new types of drugs have been hypothesized and studied [2].

Toxicity of HAART

The toxicities of HAART are generally modest or even severe. Patients will suffer a great deal, such as diarrhea, getting thin in parts of their bodies, lipodystrophy, mitochondrial toxicity, peripheral neuropathy, osteoporosis [3,4]. Patients need unwieldy pill burdens, complex dosing schedules and high costs. The most obvious HAART toxicity is metabolic complications. These toxicities are included as abnormality of human metabolism, induce some complications such

Drug types	Mechanisms
Fusion inhibitors	Virus penetration inhibitors
NNRTIs	Bind at position distant from active sites of RT
NRTIs	Competitively inhibit reverse transcriptase
Chemokine receptor antagonists	HIV fusion to host cells
Protease inhibitors	HIV formation
Integrase inhibitors	HIV into host genome

Table 1: Different types of antiviral drugs for HIV.

*Corresponding author: Da-Yong Lu, School of Life Sciences, Shanghai University, Shanghai 200444, PR China, E-mail: ludayong@sh163.net; ludayong@shu.edu.cn

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as diabetes, cardiovascular disorders. These symptoms are also very harmful to patients.

Discontinuation of HAART

Owing to antiviral drug toxicities and inconvenience of drug intake, certain amount of patients withdraw the therapy in the mid of formal HAART therapy regimen. In these patients, the risk of drug-resistance to HIV will increase greatly [5].

Early Intervention or Late Intervention

However, there is a longstanding debate—whether the HAART should be used immediately after HIV virus is diagnosed or HAART should be used after AIDS symptoms occur or the cell counts of CD4 lymphocytes in patients is below 200-250 per cubic millimeter. We may reflect that almost all diseases should be treated as early as possible by conventional logic. So most people believe HAART should be given as early as possible. Last year, Cohen et al. reported the prevention of HIV-1 infection with early antiretroviral therapy than later antiretroviral therapy in married serodiscordant couples [6,7]. It was regarded as the first important discovery of all science worldwide in 2011 by *Science* [8]. So early intervention of HIV with HAART seems logical.

However, HAART has serious side effects, including medication-induced diarrhea, getting thin in parts of their bodies, lipodystrophy, mitochondrial toxicity, peripheral neuropathy, osteoporosis. Patients need unwieldy pill burdens, complex dosing schedules and high costs. So many patients can not adhere to HAART and discontinuation of therapy after the symptoms have been ameliorated. Also, viral drug-resistance might occur in patients with therapy discontinuation or long-term exposure to drugs. It means to shorten drug treatment term and duration might make HIV virus less easily producing drug-resistance in patients with HAART. In the other hands, since some of drugs in HAART have high toxicities, drug-induced deaths are also possible. We argue herein that we still need cautious in early HAART intervention [9]. The most important drawback is no mortality rate difference is found between early intervention group and late intervention group [6].

Drawback of Present HAART

The greatest drawback of present HAART lies that these therapies are inhibitory rather than eradicated to the disease. Though the effective rate of HAART to AIDS patients is high (>90%). But the patients still carry HIV in their bodies. Once the patients discontinue their therapy or drug-resistance to HIV occurs, the HIV in those patients will grow again. Patients have to change the recipe of drugs and use some unused drugs. However, drug resistance is not common if a patient adhere to HAART. But there is no cure patient no matter how long you treat with HAART. So the patients need to adherence HAART lifelong. Thus it is very inconvenient to patients.

New Perspectives

The paramount task of future HAART should focus on eradicating HIV virus from infected patients. This might be a long way, or it might be so near to us. It all depends on our new perspectives and efforts to this matter. The present answers can be following:

By manipulating and strengthening human immune systems

To let human immune systems to complete clear up the virus. Therapeutic vaccines are aimed to reach this ultimate goal [10]. But it has not been succeeded at present. We have contributed this phenomenon to the following reasons. It is the penetration of virus

to host cells or even to host cell genome that make the antibodies or activated lymphocytes cannot bind and clear up these viruses [11]. If this is true, it faces a great challenge for therapeutic vaccines and needs new ideas and more effective antigens. Or we can combine use of HAART and therapeutic vaccines. Let these two therapeutic options assist one another or any other ideas.

Activate or manipulate host cell defensive systems and other biotherapy

More recently, it has been discovered that host (human) cells have their own defensive systems that are differed from antigen-antibody system [12-15]. If we extensively study these systems, may we learn the underlying mechanisms of host cell defensive actions against viruses and well manipulate then into therapeutic purposes.

Also, human's antibodies against HIV might have therapeutic effects and used in treatment of AIDS [16].

Combination of chemical agents with biological means of therapy

We have succeeded in combination of chemical agents of different mechanisms in treatment of HIV/AIDS and extended survival of AIDS patients from less than 2 years into 7-10 years, may we further suggest that combination of chemical agents with biological means of therapy. This strategy may reach our ultimate goal of eradication of virus from patients' bodies. However this hypothesis must base on thorough understanding of HIV in AIDS patients—what is the main cause of AIDS patients' death (Table 2).

Genetic Study of HIV/AIDS Pathology

Until now, we still cannot be sure whether HAART should be given early or later. It is because our understanding of the genetic pathogenesis of HIV in patients is lacking. We do not know why patients are killed by HIV. Our previous hypotheses suggested that penetration of HIV virus into human genome is the cause of human death and we designed experimental processes to solve them [17,18]. This needs further experimental work to support. If we can understand the cause of AIDS patient, we can decide whether HAART should be given early or later.

Is Vaccine always Useful?

Deadest virus infections can cause widespread human death and dreadful catastrophe worldwide. Until now, people are still unknown the exact pathways and mechanisms these deadest viruses kill the human beings, so we eager to rely on producing effective vaccines to treat the healthy and sick humans. For our understandings and retrospectives, important facts resulting in lag behind of vaccine manufacture are lack of funds to implement phase III clinical trials to so many types of potential vaccines. We know there are more than one hundred types of vaccines have been proposed, one type of vaccines of phase II or phase III clinical trial needs more than 1 million USD. Present tight budget of medical research cannot support all these studies. And it seems unlikely to clear up HIV by vaccine alone [10,11,19]. May we further consider and seek to combine vaccine with HAART? If these approaches complements with each other, satisfactory outcomes may be expected. It is always dependent on the effectiveness of a vaccine [20].

Methods	Mechanism of action
Antibodies	Virus binding and clear up
siRNA or other	Host cell defensive systems
Therapeutic vaccines	Human immune systems

Table 2: Potential biological therapeutic options for HIV/AIDS.

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