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Review Article

Advances and shortcoming of HIV/AIDS therapy

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Abstract

Increasing incidence of resistance of anti-tubercular drugs worldwide and the beginning of multi drug resistant in tuberculosis raise the need of new drugs for the treatment of tuberculosis and to understand the advances. AIDS (acquired immune deficient syndrome) can now be controlled by antiviral drug cocktails—high active anti-retroviral therapy (HAART). However, it turns out to be a chronic disease. In order to counteract all possibilities of incomplete HIV/AIDS therapy, many obstacles must be hurdled. In this review, many important weakness and drawbacks of HIV/AIDS therapies have been addressed and highlighted.

Keywords: HIV, AIDS, HAART, antiviral therapy, vaccine, HIV infection, viral pathology, virus therapy, traditional Chinese medicine

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1. Introduction

AIDS (acquired immune deficient syndrome), first discovered in West countries in 1981, is a human viral infectious disease. AIDS patients, if untreated, commonly suffer a gradual loss of human immuno-defensive cells and finally die of whole-body infections or immune-deficient-induced cancer within 2 years after AIDS symptoms occurrence in patients [1-3].

AIDS patients are caused by infection of HIV (human immune-deficiency virus) by sexual transmission, blood donation transmission, drug abuse with contaminated syringes, mother-to-child transmission and so on. The HIV viruses can be transported into human bodies and remain non-pathogenic for certain amount of times, sometimes even as long as ten years. These humans are called HIV infectious. After HIV infection, HIV viruses gradually inactivate human immune functions, especially for CD4 lymphocytes. Until the symptoms of immune deficient occur, these patients are then called AIDS patients.

Methods

Evolutions of HIV/AIDS treatments

AIDS patients now can be treated with anti-viral drug cocktails to decrease the virus-load (part of infectious patients), stabilize the number of effective lymphocytes in AIDS patients and eventually slow the pace of occurrence AIDS and ameliorate the symptoms of immune deficient and overall prolong the life-spans and living qualities of HIV/AIDS patients.

Less HIV/AIDS patients die of HIV/AIDS related pathogenesis now. A large number of AIDS patients or HIV infectious can live much longer span (approximately more than 7 years survival benefits in HIV/AIDS patients). If they are properly treated, sometimes even achieve normal life-spans [1-3].

Despite antiviral chemical and vaccine treatments, HIV/AIDS patients response to therapy slightly and are unable to markedly enhance HIV/AIDS patients' survivals in the initial stages of HIV/AIDS discovery. Before the invention of high active antiretroviral therapy (HAART, cocktail therapy), the therapeutic outcomes of AIDS patients were nullified. The AIDS patients usually died within 2 years after AIDS symptoms occurred before the mid-1990 to 2000 [1-3].

High active anti-retroviral therapy (HAART) was developed approximately 20 years ago, which was to combine use of antiviral chemicals of different mechanistic types and categories and could dramatically prolong the HIV/AIDS patients survivals. It is a great feast and medical miracle. HIV infected patients can live much longer and eventually die of causations unrelated to HIV infection. Now HAART becomes the standard of heath cares for HIV infection [1-3].

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) [2-4].

Table1. Different types of antiviral drugs for HIV

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

NNRTIs: non-nucleoside reverses transcriptase inhibitors; NRTIs: nucleosides reverse transcriptase inhibitors [2, 4]

Initially, HAART therapy is to combine utilize NRTI and NNRTI to inhibit the reverse transcriptase. Afterwards, more HAART are the combination of NNRTI or NRTI with protease inhibitors—aiming at interfering HIV virus proliferations. Now more types of antiviral drugs can be combined and some new types of drugs other than licensed targets have been studied for wider disease control [5].

Toxicity of HAART

The toxicities of HAART are generally modest and sometimes even severe for long-term HAART utilizations. Patients commonly suffer a few of toxicities, such as diarrhea, getting thin, lipodystrophy, mitochondrial toxicity, peripheral neuropathy, osteoporosis [2-3, 6-7]. Unwieldy pill intakes, complex dosing schedules and high costs of HAART therapies are burdens to patients [2-3].

Shortcomings of current HIV/AIDS therapy

General features of HARRT and other current therapeutic options

The realistic HIV therapies are supposed to be safe, effective, and eradicative if possible. Despite the great advancements, no safe and eradicative HIV therapy has been invented yet.

Discontinuation of HAART

Owing to antiviral drug toxicities and inconvenience of drug intake, certain amounts of HIV/AIDS patients withdraw the therapy after a series of HAART therapy regimen. In these therapeutic withdrawn HIV/AIDS patients, the risk of drug-resistance to HIV increases greatly [8]. This phenomenon not only harms for HIV/AIDS patients, but also threatens the world for fast accumulations of vast drug-resistant HIV viruses. If we could not overcome this drawback of HIV/AIDS therapy, the re-outbreak of HIV/AIDS epidemics worldwide might be possible.

Early intervention or late intervention

There are longstanding heated debates and unresolved questions at present—whether the HAART should be used immediately after HIV diagnoses or other options?

Clinical treatment paradigm for most diseases should be treated as early as possible. By referring this custom, most people and doctors believe HAART should be given as early as possible. Recent years, Cohen et al reported the decrease of HIV-1 infectivity with early antiretroviral interventions than those with later antiretroviral interventions in married serodiscordant couples [9-10]. It was once regarded as one of the foremost discoveries in the world [11].

However, serious side effects of HAART medication are big burdens for long-term antiviral cocktail treatments in HIV/AIDS patients. So many patients cannot adhere to HAART treatment after the symptoms and virus-loads amelioration. Drug-resistance to HIV virus might speed up in patients with therapy discontinuation or long-term exposure to drugs. It still needs heed for possible early HAART intervention and considers optimizing HIV treatments according to clinical situations of patients [12]. In our personal opinions, each option has its weakness and advantage. This controversy needs systematic experimental and clinical study in future.

Not curable for HIV/AIDS patients in spite of using HAART

The greatest shortcoming of present HAART are that these therapies are inhibitory rather than eradicative to the disease [2-3, 13-14]. Though the effective rate of HAART to HIV/AIDS patients can be high (>90%), the patients still carry HIV in their bodies. The HIV infections are currently life-long no matter what kinds of therapies are utilized [13-14]. Once the patients discontinue their therapy or drug-resistance to HIV occurs, the HIV in those patients' body will proliferate again rapidly [8]. Patients have to change the recipe of drugs and use some unused drugs. Since no patient has been cured by the treatment of HAART, the HIV/AIDS patients need adhering HAART therapies lifelong.

Future directions :

Emphasize in vivo experiments in HIV treatment study

Since most in-depth preliminary HIV therapeutic and strategic study cannot be first undergone in human bodies because it is too risky. Current renovations aiming at eradication of chronic status of HIV in patients must be first testified *in vivo* animal models and late undergo clinical treatment investigations [13-15]. Currently, *in vitro* HIV/AIDS treatment studies are too simple to be well understood the complexity of HIV infections and AIDS progressions. In current understanding, some factors linking with long-term infections, such as HIV-reservoir in human bodies have to be further explored in animals. Furthermore, many key pathogenesis progression steps and related biological molecule involvements, such as different infection mode, disease silence mechanisms and outbreak of AIDS epidemics must undertake into animal studies first. Whether many genetic modified mice (GMM) [16-17] can be used to improve the quality of animal HIV/AIDS therapy study?

Developing drugs of higher active, low toxicities and penetrate to HIV-infected human cells and tissues

Continue to develop anti-HIV drugs of higher active, lower toxicities and penetrating to HIV-infected human tissues are still future trends. High therapeutic dosage ranges without obvious toxicities is the ultimate goal of HIV/AIDS treatments and antiviral drug developments and manufactures. In many clinical circumstances, drugs inhibit diseases in intermediate concentrations or dosages. However, drugs kill pathogens and cure many diseases in relatively high concentrations and dosages. Pathogens often create mutation or drug-resistance in relatively low drug concentrations or dosages. Next generations of anti-HIV drugs are proposed to effectively penetrate infected human cells and kill or eliminate latent HIV virus in infected patients [13-14].

Using antibody combination strategies

It has long been a paradigm to use vaccine [18-22] or antibodies [22-24] against viral infection and progressions in humans. Again, human's antibodies against HIV have therapeutic effects and used in treatment of AIDS [2-3, 23]. Despite antibodies as therapeutic options for long period of times, it is seldom very successful to deadest viruses across the history. There are some shortcomings in antibody-based therapy (ABT) [24]. Firstly, current antibodies commonly utilize homogeneous antibody. However, a lot of diseases, such as cancer and HIV are characterized as heterogeneous. Thus, a homogeneous antibody can only neutralize small proportion of HIV virus (at most 30% of virus in one human body) in clinical trials. Homogeneous antibody even facilitates the productions of resistant virus strains in patients. So it is possible that some antibody cocktail could be used in HIV infected patients. Antibody combination strategies, if possible, can improve therapeutic efficacy? [22-24].

Studying the treatment benefits of HIV-AIDS by traditional Chinese medicine (TCM) and other ancient medicines

TCM exhibits all the characteristics of curing HIV infected patients for clinical trials. The reasons are given by following arguments.

1. It is a combinative recipe. Large number of natural ingredients contain in a single herb that is parallel and agreed with current theme of HIV treatment (cocktail approach).
2. TCM aims at modulating and recovering human cells or organs from the scope of whole body considerations. This is a unique medical strategy different from core of Western-based medicines in many ways, such as generally targeting pathogens alone by active drugs.
3. A lot of viral or microbial infection diseases, such as malaria, seasonal or bird flu, can be cured by TCM for long history in China [23, 26-31].

To facilitate these studies, setting proper models for HIV-infection and therapy are currently heating topics in China. Many TCM doctors are now discussing the possible models of disease categorizations or testified recipe of TCM for treatment considerations [30-31]. There is a large room for future TCM studies in the world. Some breakthroughs might be expected in this area.

Intensively study the HIV-integration to the genomes of different animal models, human cells or tissues or HIV-infected patients

The most harmful HIV pathogenesis might be virus-penetration into human genomes of infected cells or tissues [33-34]. Despite future roadmap of genomic study being proposed [35], this hypothesis has been less systematically studied and widely recognized. No marked breakthrough in this respect has been reported. If it is true, almost all chemical drugs will be useless when human genome in infected cells are integrated with HIV. Studying the HIV-integrating to the genomes of different animal or human cells/tissues in HIV-infected patients might be a paramount task in current HIV-treatment study. Yet this study is still not overwhelmed in this era.

Systemic genome-wide study for understanding the relationship between human genomic makeup and virus-penetration is unavoidable avenue for in-depth HIV/AIDS therapeutic study. These researches are not only on biology or pathology, but also on technical improvements and innovations [2-3]. Drafting human genomes is much easier now owing to the advent of next generation sequencing (NGS) [36-38]. This dramatic technical improvement might finally impact the HIV/AIDS study circle by unprecedented speed of genome sequencing and least amount of money (less than ten thousand USD). In future, the heavyweight of genomic sequencing forces might be transformed from biomedical major students into mathematics or physics major students or scholars because the laboratory protocols for computation or alignments of different DNA pieces into a whole genome will take longer times than handling genetic sequencing devises and machines [39]. For computational work, the mathematics or physics major students might be more smart and advantageous over biomedical major students [40].

Creating high effective and safe vaccines

Creating high effective and safe vaccines are always the priority interests for majority virologists. One possible final solution of cure HIV/AIDS is by employing effective HIV vaccines.[18-23] This strategy must also be proved and fulfilled by animal models first. Deadest virus infections such as Ebola etc can cause widespread human death and dreadful catastrophe worldwide [41]. Until now, the exact etiological pathways and mechanisms of action for drug interventions are still unknown. Thus, vaccines especially many raw inactivated viruses or chicken egg modified viruses to treat the healthy and sick humans are often the first option of many doctors and virologists. We know that 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 at least one hundred thousand USD. Present tight budget of biomedical researches cannot support all these studies [42]. Moreover, it seems unlikely to clear up HIV by vaccine alone [2-3]. Furthermore, whether further promotions of combining vaccine with HAART are useful? If these approaches

complements with each other, satisfactory outcomes may be expected [2-3].

Is vaccine always useful? From our understandings, two important steps that the viruses possibly encounter may hinder the effectiveness of vaccines; (i) viruses penetrate into living cells from the blood [43]; (ii) viruses if exist further penetrate into human genome [33-34]. We have many reasons to believe these virus-entries may prevent or at least slow down antibodies or activated lymphocytes in sera from binding and clearing of viruses within the living cells. So it is highly skeptical whether vaccine-induced antibodies or activated lymphocytes can penetrate into the membranes of the infected cells to clear up all HIV viruses. We therefore think this is the exact reason of why there are frequent failures of currently available vaccines in human applications, not yet the widely-accepted reason of virus-mutations as a main contribution of vaccine failures [2-3].

Activate or manipulate cellular or host defensive systems

It has been long discovered that host (human) cells have their own defensive systems that are outside of antigen-antibody system [23]. If we further study these systems, may we learn the underlying mechanisms of host cell defensive actions against viruses and well manipulate them into good therapeutic options (Table 2).

Table 2. Potential biological therapeutic options for HIV/AIDS [2-3]

Methods	Mechanism of action	Ref
Antibodies	Virus binding and clear up	24
siRNA or other	Host cell defensive systems	44-45
Therapeutic vaccines	Human immune systems	18-23
Cytokines or interleukin	Cell defensive systems	46
Interferon	Virus infected cells	47
Exogenous DNA	Infected DNA	48

Combination of chemical agents with biological means of therapy

Since we have succeeded in combination of chemical agents of different mechanisms of action (HAART), may we further suggest that combination of chemical agents with biological means of therapy might expect more? This strategy may be useful for realizing our ultimate goal of eradication of virus from patients' bodies [2-3, 13-14].

New paradigms of deciphering relationship between genotyping and potential relevant therapeutic targets

Until now, we still do not know whether HAART should be given early or later because our understanding of the genetic pathogenesis of HIV in patients is lacking and incomplete. We do not know why patients are killed by HIV. Previous hypotheses and studies suggested that penetration of HIV virus into human genome is possible. This needs further experimental work to support. Figure 1 and figure 2 represent the blueprint of next generation of genomic study on HIV/AIDS infectivity and deaths. If we can understand the cause of AIDS patient, we can decide whether HAART should be given early or later [9-12].

Table 3. Different levels of genomic study for HIV infection, pathogenesis and therapy

Methods	Possible evaluation	Ref
Biophysically monitor the interactions between pure host DNA or genome and HIV	Integrase inhibitors	33
In vitro pathogenesis and bioinformatics study of HIV in infected animal and human cells	Biotherapy and other therapy	33, 35
In vivo genomic or bioinformatics study of HIV and its relationship between viral vaccine/drugs and animal disease progressions and survivals	Different evaluations of vaccines and antiviral drugs	15
Building relationship between HIV and human genome changes for susceptible and infected patients	Pathogenesis and therapeutic studies	34

Different levels of genetic study of HIV's genomic integrations might trigger different levels of HIV infectivity and pathogenesis knowledge. For example, it was found that HIV was very easily to integrate into pure DNA in vitro [33]. These data, nonetheless, cannot be directly transformed into clinical applications. Only after genetic studies in animals, especially in HIV-infected patients, many experimental or clinical therapeutic methods or outcomes can then be repeated in HIV infected patients. Likelihood, genetic or genomic studies in humans must be more relevant than that in animals [49].

Figure 1. Possible avenues for genomic study and comparisons of HIV infectivity and pathogenesis among normal human cells, HIV-infected, AIDS and died patients.

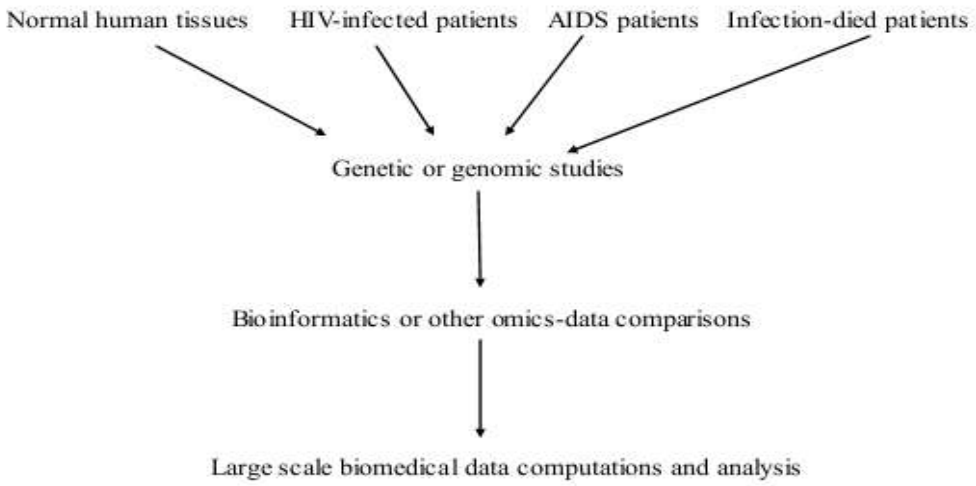
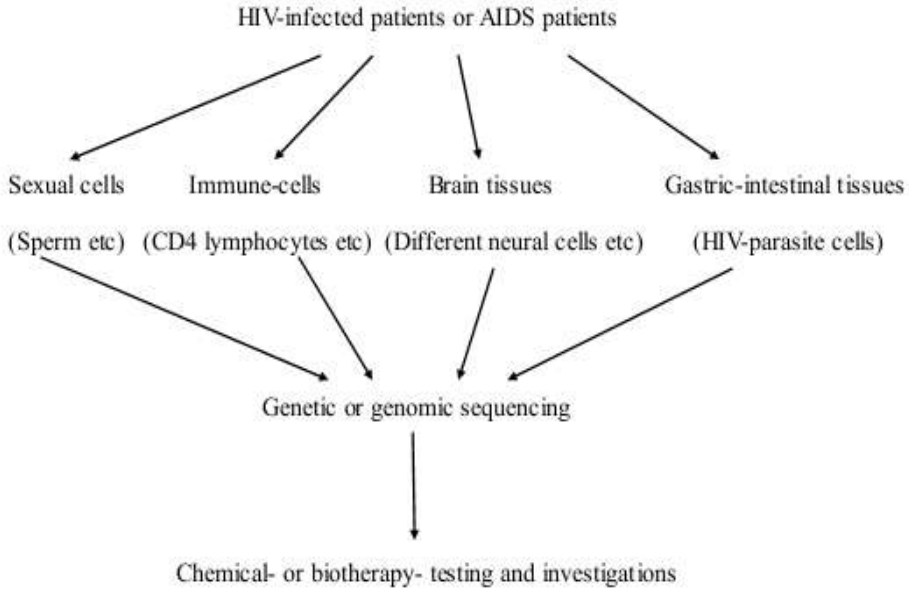


Figure 2. Possible tissues and therapeutic options can be tested by genomic studies.



Treatments of HIV-induced complications and others

Treatments of HIV-induced complications can reduce the discomfort and painful complications by disease-progressions in HIV/AIDS patients [50]. Eradicative neutralizations and elimination of HIV from HIV-infected patients is an unresolved question and is the priority ultimate goal of future HIV/AIDS treatment studies. More efforts such as medicinal chemistry, pharmacogenomics [51-52] or others are needed to testify each possible mechanism or pathway relating to the role of HIV persistence in infected patients. Possible roadmaps and new alternatives are outlined in Table 4 (Table 4).

Table 4. Future directions and roadmaps of HIV/AIDS therapeutic studies

Possible mechanisms of action and pathways for targeting and interventions
• New anti-HIV drugs targeting resistant HIV strain, reduce toxicity of drugs or even eradicate or completely neutralize HIV viruses from infected patients • Boosting the study of therapeutic vaccines, especially to deeper understand of the disease and new vaccine production systems. • Optimizing and promoting revolutionary antibody treatment systems for HIV/AIDS, such as antibody combinations. • Genetic or molecular study of HIV/AIDS pathogenesis and mechanisms of actions by drugs or vaccines • To decide which is better between early drug interventions and late drug interventions in HIV/AIDS patients? Or there is a more effective systems • Create excellent animal models for in-depth therapeutic study and comparisons between different treatment strategies, such as genetic engineering mice (GEM) • Optimizing experimental and clinical therapeutics for reducing drug toxicities and resistance by medicinal chemistry or pharmacogenomics studies • Seeking new forms of therapeutic strategy, such as traditional Chinese medicine (TCM) and other longstanding medical options (such as Indian and middle-east medicines) etc • Genetic or genomic studies of HIV and AIDS in animals and in humans by in vitro or in vivo experimental models and HIV infected patients for deeper understanding the pathogenesis and therapeutics of HIV/AIDS. • Cooperation between pharmaceutical companies, academics and government funding systems for strong support of groundbreaking discoveries and different therapeutic options.

Conclusion

The HIV/AIDS epidemic worldwide is stable now. After persistent efforts, more effective therapeutic options can be used in clinics. Since these new therapeutic initiatives might help to shrink HIV/AIDS epidemics worldwide, it's the time for embracing new generations of therapeutics for HIV and AIDS treatments.

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Competing interesting

Authors have declared that no competing interests exist

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