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Review Article

HAART in HIV/AIDS Treatments, a Current Limitation

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Abstract

AIDS (acquired immune deficient syndrome) is a deadly human viral infectious disease caused by HIV (human immune-deficient virus) infection. Almost every AIDS patient losses his/her life before mid 1990s. Antiviral drug cocktails-high active anti-retroviral therapy (HAART) has been invented for almost all HIV infection patient treatments. Yet, this type of HIV therapeutics is incurable. HIV/AIDS patients need to take HAART medications regularly and even life-long. In this article, the major progresses and drawbacks of HIV/AIDS chemotherapy (HAART) to HIV/AIDS patients have been discussed.

Keywords: *HIV; AIDS; HAART; Antiviral Therapy; HIV Cure; Drug Delivery System; Medicinal Chemistry; HIV Latency; HIV Reservoirs; Integrase Inhibitors; Pharmacogenomics; Biotherapy*

Historical Backgrounds

AIDS (acquired immune deficient syndrome) is a deadly human disease caused by HIV (human immunodeficiency viruses) infections. Owing to lack effective therapeutics, all AIDS patient loss his/her life before mid 1990s. As a result, HIV/AIDS was once the 1st disease killer in US (1993). HIV/AIDS patients were initially treated with antiviral chemicals or vaccines. But before the invention of high active antiretroviral therapy (HAART, cocktail therapy), the therapeutic responses of HIV/AIDS patients were very limited. Almost every AIDS patient losses his/her life before mid 1990s-all of the AIDS patients died within 2 years after AIDS symptoms occurred. It looks like a capital punishment when a patient infects with HIV.

HAART Invention

HAART was developed approximately 20 years ago, which was to combine utilities of antiviral chemicals of different types or categories and displayed prolonged HIV/AIDS patient survival a great deal (approximately 7 to 10 years survival benefits or even longer) comparing with single antiviral drug utilities. This is a great therapeutic advancement for viral managements in HIV/AIDS patients and a big medical achievement. More HIV infected patients live longer and eventually die of causalities that are unrelated to HIV infection or HIV-induced cancer. Now HAART become a standard of medical care for HIV infection and AIDS symptom control [1-3]. An enormous therapeutic benefit was achieved after this invention in HIV/AIDS patient managements.

Major Protocols Of HAART

Different types of anti-HIV chemotherapeutic agents.

Up-to-date, more than twenty anti-HIV chemicals have been licensed for formal viral therapeutic utilities worldwide, which have been now divided into six classes of therapeutic mechanisms and categories (Table 1).

Drug types	Mechanisms
Fusion inhibitors	Virus penetration through host cell membrane inhibitors
NNRTIs	Bind at position distant from active sites of RT
NRTIs	Competitively inhibit reverse transcriptase
Chemokine receptor antagonists	HIV fusion to host cells (CCR5)
Protease inhibitors	HIV formation
Integrase inhibitors	HIV into host genome

Table 1: *Different types of antiviral drugs for HIV.*

Among these six types or categories of antiviral chemicals, each single antiviral chemical agent fails to exhibit enormous antiviral therapeutic responses and efficacies. HIV-infected patients will generally transit and acquire AIDS symptoms and HIV-induced cancer without HAART. These AIDS patients die for co-infections with other types of active viruses or microbial due to gradually loss of human immunity and self-defensiveness.

Approximately in the mid of 1990s, these anti-HIV chemical agents were combinational utilized. Commonly three different anti-HIV chemotherapeutic agents are utilized in most HIV/AIDS patient treatments. These types of antiviral drug cocktails were then called HAART. A great difference has been found in HIV/AIDS patients by HAART therapeutics.

Initially, HAART therapy commonly combined NRTI and NNRTI agents to inhibit the activity of reverse transcriptase (RT) in HIV viruses as a sole target. Afterwards, more HAART are the combination of NNRTI/NRTI with protease inhibitors-aiming at interfering both HIV virus proliferations and RT activities. More recently, integrase inhibitors have been invented to inhibit HIV virus transportations through host cell and nuclei membrane barriers, and finally penetrations into human genomes. Now new types of antiviral drugs such as integrase inhibitors and fusion inhibitors are frequently selected in HAART treatments and therapeutic tactics based on this idea.

Drawbacks of Present HAART

Incurable characters of present HAART

Apart from these successes of HAART in HIV/AIDS therapeutics, the greatest drawback of present HAART exhibits that those types of HIV therapies are inhibitory rather than eradicative to the disease (cure therapeutics) [1-5]. Though the effective rate of HAART to HIV/AIDS patients is high (> 90%), the patients still carry HIV in their bodies. Once a patient discontinues his therapy or obvious drug-resistance to HIV occurs, the HIV in those patients will flourish again. To conclude, it means there is no cure for HAART in HIV patient until now. So, the HIV/AIDS patients usually need to adherence HAART lifelong. Thus, it is very inconvenient to HIV/AIDS patients and as the biggest drawback of HAART nowadays. It looks simple but difficult to realize.

Toxicity of HAART and cost-effective

The toxicities of HAART are generally modest or even severe. Patients suffer a great deal, such as diarrhea, getting thin in parts of their bodies, lipodystrophy, cardiovascular complications, mitochondrial toxicity, peripheral neuropathy, osteoporosis and so on [2,3]. Otherwise, patients need unwieldy pill burdens, complex dosing schedules and high costs.

Discontinuation of HAART

Owing to obvious antiviral drug toxicities and inconvenience of drug intake, certain amount of patients withdraws the therapy in amidst of formal HAART therapy regimen. In these patients, the risk of drug-resistance to HIV will increase enormously and viral-load in patients will rise again [6]. Due to this drawback, possible HAART updating needs to be promoted.

Possibilities of HAART Updating

New drug developments

Currently, great parts of licensed anti-HIV agents or drugs are synthetic chemical agents. Generally speaking, synthetic chemicals have lower therapeutic index comparing with natural chemotherapeutic drugs owing to high levels or rates of drug toxicities and/or undesired side-effects [7]. Many licensed anti-HIV drugs, especially nucleoside reverse transcriptase inhibitors are too toxic to be tolerated in humans for long-term. This setback of HIV inhibitors prevent us to use enough levels of HIV inhibitor utility that is desperately needed for HIV clearance from human bodies forever.

Since the characters of synthetic chemical agents are inhibitory rather than disease cure for HIV infected patients, other therapeutic options such as biotherapies or natural chemotherapeutic agent discovery or developments are dispensable [7-10]. Across the history, synthetic chemical drugs rarely make magic contributions and improvement therapeutic outcomes for many deadly diseases. Developments or licensed natural chemical agents [7] may be a good solution for HIV infection patient cures. This scientific avenue should be along with other new initiatives in the field of HIV/AIDS studies-including HAART.

Good example can be referred to resistant TB therapy. Recently, it was found that drug combinations of new drug categories can cure many resistant TB patients [11]. This is a good lesson to teach us in the field of HIV/AIDS therapy. Thus, developments of new antiviral drugs or vaccines in HIV/AIDS therapeutics are very useful.

Early intervention vs late intervention

There are some longstanding debating and unresolved questions at present-whether the HAART should be used immediately after HIV virus is diagnosed or HAART should be used after AIDS symptoms occurrence or the cell number counts of CD4 lymphocytes is below 200 - 250 per cubic milliliter in patients.

Generally speaking, clinical treatment paradigm for most diseases should be treated as early as possible. By referring this treatment logic and paradigm, most people and doctors believe HAART should be given immediately after HIV infection diagnostics. Recent years, Cohen et al reported a decrease of HIV-1 infectivity with early antiretroviral therapy interventions comparing with those with later antiretroviral therapy interventions in married serodiscordant couples [12-14]. It was once regarded as one of the foremost discoveries in the world [14]. From this therapeutic overview, early intervention of HIV with HAART seems logic and is a feasible procedure for future medical practices.

However, serious side effects of HAART as well as complicated drug intake procedures are big burdens for long-term antiviral cocktail treatments in HIV/AIDS patients. So many patients cannot adhere to HAART treatment very long and discontinue HAART therapy right after the symptoms and virus-loads have been ameliorated. As a result, drug-resistance to HIV virus might speed up in infectious patients with antiviral therapeutic discontinuation. In practical way, shortening drug treatment term and duration might not always be a bad thing based on the fact that no cure or eradicate HIV can be achieved nowadays. Despite these high-profile papers reporting, it still needs cautious in early HAART intervention and considers the types of HIV treatments according to different clinical situations of HIV/AIDS patients [15].

Since no mortality rate difference was found between early intervention group and late intervention group in previous report [12], whether antiviral therapy should be provided early or later in clinical HIV/AIDS treatments is an indispensable topic for future. In our personal opinions, each option has its own weakness and advantage. Systematic experimental and clinical study in future may solve this controversy and finalize antiviral drug intervention strategies consistently. Good therapeutic modalities may be possible after a few steps of creative and revolutionary scientific investigations in this respect.

Pharmaceutical Innovations

One of the greatest arguments today is that HIV viruses are hided in the deepest parts of human bodies (HIV reservoirs) [16,17]. Thus, therapeutic drugs are commonly unable to kill all of HIV viruses from human tissue hindrance/protections. As a result, nano-particle of therapeutic drugs are proposed to reach these HIV viruses and finally kill them at large. But it is easier said than done. This solution did not work until now. Debates are heating up. Some of researchers have found that normal chemical drugs have similar abilities to penetrate into human cells comparing with nano-states of drugs [18]. If so, this issue remains to be solved. If we can use new delivery systems, may HAART therapeutic outcomes be improved? This open question deserves future scientific investigations. Updating drug delivery systems into HIV-enrich organs (HIV reservoirs) must be developed for improving HAART therapeutics-even for fully HIV clearance from human bodies.

Targeting latency HIV viruses with HAART

The latency state of HIV viruses is the possible way of incompletely killing of HIV by present forms of therapeutics-including HAART [19]. For this reason, developments of agents to specifically target latency states of HIV in updating recipes of HAART might be a new way of HIV/AIDS therapeutics. It includes a strategy of "flourish-and-kill". However, it has not been succeeded yet [20].

Personalized medicine for different choices of drug combinations against individualized HIV/AIDS patients

Owing to the diversity of genetic/molecular backgrounds and changes in different HIV infected patients, personalized medicine is an important future trend [20]. In today's pharmacologic study, it is lack of therapeutic outcome prediction information against different HIV infection individuals. The therapeutic outcome prediction information needs to be based on modern technically supportive diagnostics.

The problem of drug combinations is a complicated issue in clinic therapeutic study [21]. Despite therapeutic efficacy gains, drug toxicity might also increase in many clinical situations. Thus, this topic has much room to improve. It needs that drug toxicity in clinics must be reported as early as possible [22]. The medical or pharmaceutical regulatory bodies play key roles on this matter. Like cancer treatments, thorough drug combinations need enormous experimental and clinical drug sensitivity testing in lab and clinics [23-25]. The more new drugs have been developed, the more complicated drug combination options will be evaluated. According to current drug licensing, the number of drug combination options can be as high as approximately 2,600 options [23,24];

The number of drug combination options = $26\times25\times24/1\times2\times3$ = 2,600 choice

But, current drug sensitivity testing methods are unable to find any differences of drug combinational solutions in clinical HIV treatment studies of these potentialities. Pharmacogenomics are only workable solutions in present clinical study.

Present personalized medicines are commonly dealt with pharmacogenomics. So is the personalized HIV therapeutics. Yet, personalized HIV therapeutic limitations are present [20];

1. Only a few of gene markers has been studied in pharmacogenomics of HIV treatment study.
2. Since the core of HIV therapeutics is drug combinations, it is difficult to be utilized for pharmacogenetics of drug combinations.

These two limitations make this study difficulty. As only small number of SNPs have been determined for therapeutic prediction, it is useless to determine great diversity of pharmacogenomic system in real clinical circumstances. The clinical pharmacogenomic routines for drug therapeutic decision-makings must be established after large-scale, multiple genetic/genomic diagnostics and therapeutic prediction studies. Without accumulations of enough complex genetic diagnostic/therapeutic data, no obviously therapeutic response improvements can be realized no matter how complex genetic/genomic diagnostics has been utilized in clinics. Thus, basic scientific study on this issue is indispensable.

Future Trends

Today, HAART is the only workable means for HIV/AIDS therapeutics. But we must not satisfy with previous achievement. New attempts must be sought after from this therapeutic achievement (Table 2).

Drug categories and disciplines	Drug targets and types	References
Biotherapeutic means	HIV clearance Host cell defensive bio-molecules Genomic editing HIV vaccine developments Vaccine challenge schedules	26-30
Other viral inhibitors	Avian flu Seasonal flu Ebola	31-32
Free radical	Antioxidant NO interference	8
Immune promotions	Polysaccharide	27
Epigenetic agents	HIV latency activations	19
Medicinal chemistry	Drug therapeutic index gains	27
Pharmacology	Choice of optimal drug combinations in different clinical occasions and settings	23-25
Pharmaceutical	Nano-particle drug developments HIV reservoirs penetrations	33

Table 2: *Possible drug targets different from current HAART for HIV/AIDS treatments.*

After scientific investigations, some curable therapeutic options for updating HAART may be underway or found out! (Figure 1).

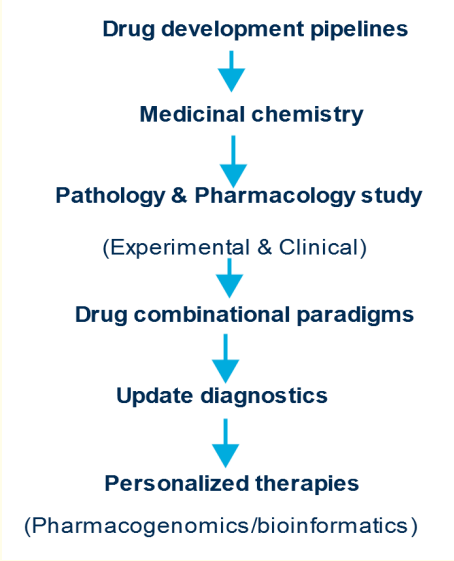

Figure 1: *Outlook of future HIV/AIDS therapeutic studies.*

Conclusion

HAART, though widely utilities in clinics, has its own shortcomings-incurable for HIV infection. In order to overcome this drawback, a great number of efforts and updating therapeutics-including viral pathogenesis [34], new generations of drug developments, updating HIV vaccines, new types of HAART, clinical optimizing or even personalized HIV/AIDS therapeutics (both pharmacogenomics and bioinformatics) must be undergone. We look forward to some excellent breakthroughs in future.

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Competing Interesting

Authors have declared that no competing interests exist.

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