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HIV/AIDS treatment, therapeutic strategy break throughs

Abstract

HIV/AIDS is currently an incurable viral infectious disease characterized with life-long drug utility. To overcome this therapeutic setback, fatal pathological processes and different therapeutic mechanisms must be explored in broader-range and greater dimension. In this Article, the major types of global HIV/AIDS therapeutic strategies (pharmaceutical modification, herbal medicine, novel drug targets, drug combination modality, animal models, palliative medicine, immune-stimulate for HIV latency as well as HIV clearance by biological-based therapy) are especially highlighted. After novel pathologic identifications and therapeutic evolution, HIV/AIDS therapeutic curability will be translated from animal model unto larger human population. In this biomedical scenario, major breakthroughs are looked forward.

Keywords: HIV infection, HIV vaccination, virus latency, human genome, herbal medicine, human immunity, drug target

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Introduction

Backgrounds

HIV (human immunodeficiency virus) and AIDS (acquired immune deficient syndrome) is currently an incurable viral infectious disease characterized with life-long drug utility. High active anti-retroviral therapy (HAART, a drug combination strategy) saves the life of millions of HIV infect patients in the clinic now.[1–6] To complete eliminate virus from patients, different features and spectra of HIV-induced pathogenesis that associate with pathologic and therapeutic variations need to be especially classified,[1–6] Unlike other deadly viruses, prophylactic/therapeutic vaccines for HIV,[7–11] are not equipped until now. Facing this therapeutic setback for HIV, different therapeutic mechanism and modality needs to be eventually developed. Following sectors show certain patterns and spectra of HIV-induced pathogenesis and relevant therapeutics in the clinic.

Medical knowledge

Endocytotic pathways and networks of HIV infection

An association between HIV-induced pathogeneses and therapeutic variation is largely unknown at present; Endocytric mechanisms and pathways are focal-points for selectively molecular disruption against HIV proliferation, binding and integration with cellular components in hostal lymphatic cells.[12] A sequence of such invasive mechanism is informed.

i. Cell adhesion for viruses (Heparin sulfate proteoglycans HSPG)
ii. Cell-surface receptor binding (Sialic acids on glycoprotein and glycolipids; CCR-5)
iii. Intracellular receptors and biological molecules (Niemann Pick C-1, NPC-1, lysosome proteins)
iv. Internalization (Fusion proteins)
v. Genetic and genomic involvement (HIV Pol-encoded reverse transcriptase)
vi. These infective pathways are very important for drug designing and targeting.

Anti-HIV/AIDS drugs

Generally, anti-HIV chemotherapeutic agents (approximately 30licensed chemical agents) may be utilized to elongate or even save the life of most HIV/AIDS patients by drug combinations. (Table 1) These antiviral drug cocktails were usually termed as HAART. A great difference of life-saving has been made in HIV/AIDS patients by different drug combinations.[4–6] This needs clinical experience for drug selections and therapeutic changes after the sign of therapeutic failure.[2]

Table 1 Current antiviral drugs for HIV/AIDS cocktail treatment

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

NNRTIs, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors

With the global efforts of four decades, the body of HIV/AIDS knowledge expanded greatly. This series of drug categories (6classes) is the prototypes of anti-HIV drugs. Yet there is no boundary to specific pathways or chemical structure in the future. There is a big space for anti-HIV drug developments in the future because a lot of new infectious and immune-related pathways can be targeted. They contain a great number of different possibilities. Yet, these efforts meet with complicate situations in reality. This is why there is no remarkable progress of anti-HIV drug development in the past decade. Big challenge is still facing.

Current challenges

A slow progress of pathological knowledge enrichment leads to shortage of excellent ways of experimental and clinical therapeutic validations. Important causalities leading to therapeutic incurability are proposed in Table 2.

Table 2 Major factors for HIV therapeutic incurability nowadays

Pathologic routes	Pharmacological limitations	References
HIV prevention	Lack effective vaccines	11-Jun
HIV latency	Need high concentration of drug to kill	13
HIV reservoirs	Barriers for drug entering	9-Aug
HIV integration to human genomes	No effective medication until now	14-16

Owing to the shortage of HIV pathological knowledge, the number of HIV/AIDS patients continues to expand.[17] As a result, scientific approaches for HIV pathology and pharmacology are urgently needed. HIV preventive and treatment strategies will be discussed.

Preventive & treatment strategies

Pathology *versus* therapy

The key elements and processes of HIV-induced pathogenesis (lymphatic cell number declining and dysfunction) and human mortality (co-infection, cancer and drug resistance) are proposed. Avenues are given to fight against different pathological pathways and network in a curable manner.[4–6] To attain these goals, the relationships between HIV pathogeneses and therapeutic outcomes must be closer associated (Table 3).

Table 3 The relationship between pathogenesis and therapeutics

Pathologic processes	Affected components	Therapeutic targets
Viral attachments	Membrane ligands and so on	Cell signal inhibitors/ promoters
		HIV vaccines
		Fusion inhibitors
		CCR5 antagonists
		Proteasome inhibitors
Viral cell entry	Membrane receptors Membrane channel	Fusion inhibitors
		CCR5 antagonists
		Nucleotide antagonists
Transcription/viral replica	Reverse transcriptase	NNRTIs
		Reverse transcriptase inhibitors
Human HIV reservoirs	Tissue & cell membrane	Nano-particle HIV inhibitors
		Combine antibody
HIV latency	Histone deacetylase NF-kB Bromodomain-containing protein Protein kinase C (PKC)	Anti-body + activators HAART + activate or inhibitors
DNA integration	Host cell genome	Integrase inhibitors
		Nucleases
Viral egress	Host defensive mechanisms	Cytokine
		Interferon
Cell lysis and apoptosis	Host defensive systems	Cytokine
		Interferon
		HIV vaccines
Physiological abnormality	Fever, wasting, metabolic illness	Traditional Chinese medicine
Human immune dysfunction	No of active lymphocytes	HAART
		Traditional Chinese medicine
AIDS	Co-infections or cancer	HAART
Human mortality	Loss of physiological functions	Too late

Evaluative protocols and models

All categories of drug and therapeutic study need high quality evaluative models. As a result, wider ranges of therapeutic drugs and options can be successfully found out. For smart HIV targets, we must develop animal models of clinical relevance. However, current HIV evaluative models are used by parameters of biochemical assay, viral-load inhibition in vitro or in mice. Among these HIV target models, immune-functions and molecules are especially compared in completely eliminative mechanisms. Until now, these evaluative models are not well established because there is a difference in HIV species between humans and non-human-primates. To overcome this setback, there is long-way to go through.

Therapeutic agents

HIV vaccine and antibody

In viral vaccine evaluation, both efficacy and toxicity of vaccines should be overall considered. However, the formulae of HIV vaccines and development technology must be well balanced.[7–9] More detailed immune knowledge and modern technology as we argued will be noticed and investigated.

HIV is diverse and complex in molecular forms. Different spectra of biological molecules (genetic/transcript factors, polysaccharides, glycol-proteins, lipids and so on) require different forms of HIV vaccines.[11] Accordingly, no defined HIV antigen can be 100%

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reliable because other forms of HIV components may evade this form of vaccine in the clinic. Certain types of incomplete HIV debris may survive and reproduce in human bodies after single formulae vaccination. Thus, diverse and sequence of HIV vaccines may be developed into clinical paradigms.

Since HIV is not stable in genome integrity, heterogeneity of wild-type HIV genome makes it difficult for targeting by genetic-based vaccine manufacture (uniformity in vaccine samples).[3] It is so big an obstacle that makes genetic HIV vaccine development in dilemma. To keep up the quality of genetic-based vaccines, multi-epitome vaccines and multivalent antibody are provided yet still not 100% effective in clinical trials.[11]

Genetic study

No modern medical disciplinary can be complete without genetic/epigenetic study nowadays. Systemic genome-wide associate study (GWAS) for biomedical problems of HIV-risky/mortality prevention and reduction is an important area for HIV/AIDS pathology and treatment study (a mystery and complex frontier and projects).[14–16] These researches are not only a question of biology or pathology, but also a technique of ever-changing. Given the next generation sequencing (NGS) maturity, the enigmatic question of HIV integration into human genomes are easier to be known about and targeted with. As a result, different therapeutic strategies may treat different pathologic stages and individual genomic backgrounds of an individual patient.[17–22] Different therapeutic agents (chemical, biological and immune-stimulators) may be separately developed in the future. With the breakthrough of genetic/epigenetic study, HIV curability may be achieved by targeting HIV-human genomic interaction and integration (latest such arguments and reports).[22]

Biotherapy

It has been well recognized that host (human) cells have their own defensive systems (a body of diverse and spectra of biological molecules) that can perform a lot of physiological functions in different human cells, tissues and organs. [2,3] If we further study these systems of diverse bio-molecules, may we translate underlying mechanisms and modality of host cell defensive actions against HIV proliferation, latency and immune deleterious action in the clinic?,[23,24] As usual, these types of therapeutics are remarkable efficacy and quite expensive in most clinical occasions. In addition, they may be more promising for therapeutic curability while biotherapy can combine with HAART (new forms of therapeutic trinity).[6] To benefit more patients, bio-similar agents may replace licensed bioagents in patients who are not able to pay high-costs of licensed biological agents for diseases treatment.[25]

The potential anti-HIV bioagents in this area are interferon and micro-RNA. Interferon used for other viral infections has been developed more than three decades. If we stay focusing on interferon development against HIV, something difference may be made. It needs to get licensing, industrialized and finally hospitalized as quick as possible.

Pharmaceutical modification

HIV-latency (a pathological pathway) is difficult to be targeted completely by normal forms and blood concentration of anti-HIV agents. Pharmaceutical modification and renovation may help a lot for that. Long drug releasing prodrugs (fatty acid modified prodrugs or nanodrugs) make drug utility easier, safer and long-lasting in the clinic.[26] These long releasing drugs can maintain a long course of effective drug concentration in HIV infectious patients and kill HIV in relative lower toxic concentrations.

Herbal medicine

Herbal medicine is a less cost therapeutic system to treat patients with chronic diseases. It is an original form of disease treatments (ancient and legendary medicine divided between different countries worldwide).[27–34] A lot of countries loss this tradition now. Generally, each country has its own system and tradition of herbal medicine-such as allopathic in ancient Greece, Ayurveda in India and traditional Chinese medicine (TCM) in China.[27] A lot of attempts have been intensively explored—including herbal ingredients and herbal formulae worldwide.[28–30]

Cordyceps (one type of therapeutic fungal) having a strong immune stimulate activity and function was reported in Chinese medical books.[35,36] May it be useful for HIV infection and AIDS episode, such as cancer and co-infections. It is an open question for further investigations.

Herbal medicine has been replaced by modern medicine now. However, there is still therapeutic usefulness for herbal medicine worldwide, especially in natural chemical drug developments and preventive measures after new virus outcomes (no useful drugs available).

Treatment strategy

Current therapeutic modality designed for HIV curability

In the past therapeutics, HIV treatments are incurable.[5] Key therapeutic barriers and associated therapeutic breakthroughs are outlined in Table 4.

Table 4 Proposed therapeutics for key pathological targeting

Pathology	Pathways for breakthroughs	References
HIV-latency	Long-acting slow effective releasing	26-35
	Herbal medicine	
	Drug combination	
HIV reservoirs	Cell/tissue penetrable agents	23-24
	Immune stimulation	
Genetic integration	DNA binding	17-22
	HIV insertion reversal	
	Integrate enzymes	
	Genomic editing	

Therapeutic combination with new twists

HAART (anti-HIV chemical drug cocktail) is a strategy of combining several antiviral chemicals in the clinic—generally licensed anti-HIV drugs.[1–6] In the past, new forms of therapeutic trinity and combination—chemical drugs combined with biotherapies and immune-stimulators are argued for possibly HIV therapeutic curability,[6] (Figure 1) However, it needs a series of robust scientific investigation and clinical validity because previous drug combination

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(HAART) reports and contains some unfavorable side-effects in the clinics (cardiovascular and metabolism).[37,38] As a result, therapeutic side-effects need to be reduced as complete as possible.[39] More recently, therapeutic cure in animal models has been reported by combining chemical drugs (long acting slow releasing antiviral drug) with biotherapy (genomic editing) in humanized mice.[40] This is a piece of exciting news that may interact with past knowledge and therapeutics. Ground-breaking discovery may follow up from similar therapeutic modality and theory.

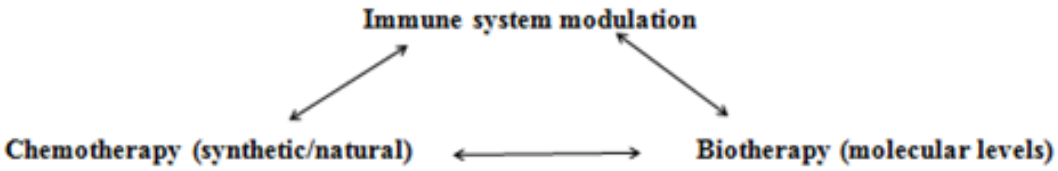

Figure 1 New forms of therapeutic trinity for HIV/AIDS.

Therapeutic comparisons with other viral infections

Different from HIV-infection, deadly virus infections, such as avian flu and Ebola can cause quick human deaths and dreadful epidemics events worldwide.[41–44] Yet HIV-induced human mortality may last at least one year. These pathologic and therapeutic variations between different viral infections are still unclear yet interesting. Drug development and clinical paradigm discovery should also come from these pathological comparisons, therapeutic protocol analysis and personalized medicine in different individuals.

Computational analysis and assistance

As usual drug pharmacological study, compounds are evaluated by *in vitro* or *in vivo* pharmacological methodology. More recently, compounds can be evaluated and analyzed by computers (*in silico* methodology) and artificial intelligence systems.[45–47] This kind of evaluative work is very cheap (electric bills).

Unanswered questions

Theoretic basis and establishment for HIV treatments

The HAART is a term of drug combination strategy for HIV infection. Yet, this is a general terminology that can be translated into different medical meaning and scientific theory. How to optimize and highlight these paradigms are still an emerging frontiers and future biomedical challenge. Several major topics are suggested as;

i. What is the timing and drug choice optimizing? (providing more pathological detail and information)

ii. Can other types of drugs (beyond above six drug categories) be combined with to improve clinical therapeutic outcomes—high therapeutic-index/beneficial and less serious side-effects?

iii. Is there any therapeutic difference (choice of drugs and administrative route) between various pathological stages of HIV/AIDS patients?

iv. Can substantial therapeutic cost-down and long-acting drugs by new techniques, drug categories, delivery systems and herbal medicine become reality?

v. Is there any new diagnostic technology leading to improve and assist HIV/AIDS therapeutic selections and personalized?

Therapeutic strategy across the history

HIV infection treatment is evolving constantly (Table 5) (Figure 2) provide general information of latest discoveries on HIV pathology and therapeutics.[47–52]

Table 5 Therapeutic strategy evolution

Therapeutic strategy	Therapeutic outcomes	References
Single vaccine or drug	No therapeutic benefits in the clinic	8-Jul
Chemical drug combination	Dramatic survival benefits yet no cure	6-Jan
Different therapeutic combinations	Therapeutic cure in animals	6, 40
Future direction	Complete HIV elimination in the clinic	48

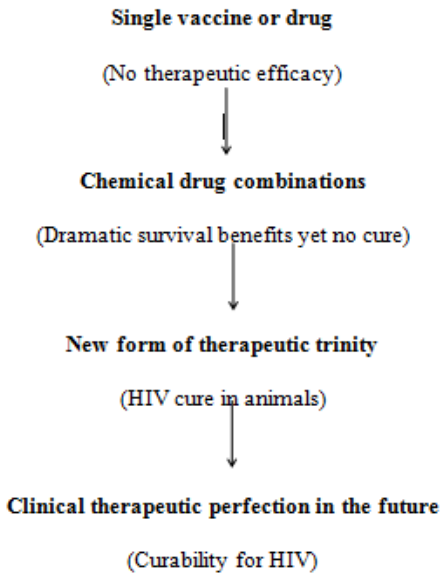

Figure 2 The roadmap of HIV treatment evolution and breakthroughs.

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Future direction

Four distinct categories of scientific approaches may bring promotion of medical care and service for HIV/AIDS; they are

1) New vaccines and drugs of high therapeutic index
2) Deeper understanding therapeutic failures from HIV origin and pathological studies
3) Integration of therapeutic drugs, vaccines, strategies and paradigms
4) Multi-functional and cutting-edge diagnostic techniques and animal models

The greatest part of biotherapies is under investigations yet incomplete until now. Owing to growing understanding about HIV-induced immune-dysfunction, we certainly believe that ground-breaking HIV therapy will be developed. Since future directions about HIV therapeutics could be multi-routes and different networks, cooperation between academia, pharmaceutical companies and governmental funding/regulatory bodies may facilitate biomedical breakthroughs and therapeutic curability worldwide—including new patent and drug licensing and clinical applications.[44–54]

Conclusion

HIV curability is an ultimate goal for fighting against HIV/AIDS.[5] In search for highly effective and low risk HIV vaccines and drugs of both chemical and biological formula, medical achievements will be made based on the clearly understanding the pathological knowledge between diagnosis and treatments. After all, both new ideas and vaccine/drug will be developed. We sincerely wish that a new generation of therapeutics for deadly virus infections such as HIV can be effectively controlled at the times of any virus outbreak. We look forward to more powerful therapeutic arsenals and strategies against HIV epidemics.

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Conflicts of interest

The authors declare no conflict of interest.

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