Bioactive Materials 1 (2016) 109–121

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: http://www.keaipublishing.com/en/journals/bioactive-materials/

Development of peptide inhibitors of HIV transmission

Siyu Shi [a], Peter K. Nguyen [d, e], Henry J. Cabral [d, e], Ramon Diez-Barroso [b], Paul J. Derry [a], Satoko M. Kanahara [c, **], Vivek A. Kumar [d, e, *]

[a] Department of Chemistry, Rice University, Houston, TX 77030, USA
[b] Baylor College of Medicine, Houston, TX 77030, USA
[c] Community Healthcare Network, New York, NY 10010, USA
[d] Department of Biomedical Engineering, New Jersey Institute of Technology, University Heights, Newark, NJ 07102, USA
[e] Department of Chemical, Biological and Pharmaceutical Engineering, New Jersey Institute of Technology, University Heights, Newark, NJ 07102, USA

ARTICLE INFO

Article history:
Received 30 June 2016
Received in revised form
18 August 2016
Accepted 7 September 2016
Available online 16 September 2016

Keywords:
HIV
HIV treatment
Drug development
Peptide therapeutic
Peptide inhibitor

ABSTRACT

Treatment of HIV has long faced the challenge of high mutation rates leading to rapid development of resistance, with ongoing need to develop new methods to effectively fight the infection. Traditionally, early HIV medications were designed to inhibit RNA replication and protein production through small molecular drugs. Peptide based therapeutics are a versatile, promising field in HIV therapy, which continues to develop as we expand our understanding of key protein-protein interactions that occur in HIV replication and infection. This review begins with an introduction to HIV, followed by the biological basis of disease, current clinical management of the disease, therapeutics on the market, and finally potential avenues for improved drug development.

1. Introduction

The human immunodeficiency virus (HIV) is one of the hardest to control, medically manage, and lethal infectious diseases. HIV is a major public health problem globally and domestically. The World Health Organization estimates 37 million people living with HIV or acquired immunodeficiency syndrome (AIDS) worldwide in 2014 with Sub-Saharan Africa accounting for almost 70% of new global HIV infections [1]. About 44,000 people become infected with HIV each year in the United States [2], 350,000 in Asia, 25,000 in the Middle East & North Africa, 94,000 in Latin America, 88,000 in West and Central Europe and North America, 110,000 in Eastern Europe and Central Asia, and 12,000 in the Caribbean [3]. The CDC estimates about 1.2 million people in the United States were living with HIV at the end of 2012 [4]. Of those people, about 12.8% do not know they are infected [5]. The number of new infections continues to rise, particularly in women. HIV treatment is costly. Estimated cost per patient per year in 2010 was $13,251 [6] in the United States, impeding HIV treatment in low-resource settings [7]. Therefore, HIV is still one of the hottest topics in basic science, clinical, and public health research.

Given the magnitude of this pandemic, numerous global efforts have been gathered to fund research needed for HIV prevention and treatment. Over $15 billion has been devoted from 2000 to 2014 [8]. The cumulative HIV/AIDS treatment costs from 1996 to 2010 are estimated to be $242 billion. FY2016 US funding for domestic HIV research is $2.8 billion [9]. North America provides the vast majority of HIV prevention R&D investment (90.9%) [8].

Peptide therapeutics are composed of short amino acid sequences that target protein-protein interactions, such as the critical interaction between the host cell receptors and HIV glycoproteins required for viral entry into host cells. Peptide based therapies offer

Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; CDC, Centers for Disease Control and Prevention; FY, fiscal year; R&D, research and development; FDA, US Food and Drug Administration; HCV, hepatitis C Virus; ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; NRTI, Nucleoside/Nucleotide Reverse Transcriptase Inhibitors; NNRTI, Non-nucleoside reverse transcriptase inhibitors; INSTI, Integrase strand transfer inhibitors; RT, reverse transcriptase; LEDGF, lens epithelium-derived growth factor.

* Corresponding author. Department of Biomedical Engineering Department of Chemical, Biological and Pharmaceutical Engineering, New Jersey Institute of Technology, University Heights, Newark, NJ 07102, USA.
** Corresponding author. Bronx Health Center, 975 Westchester Ave, Bronx, NY 10459, USA.
E-mail address: vak@njit.edu (V.A. Kumar).

Peer review under responsibility of KeAi Communications Co., Ltd.

http://dx.doi.org/10.1016/j.bioactmat.2016.09.004

several advantages over small molecule based therapies, including versatility, high potency, and lower side effects [10]. Peptide/Protein based therapeutics can bind a domain more specifically and effectively than small molecule drugs, as it has larger surface area and stronger interaction between the target domain and the drug [11]. It also has fewer medication interactions and toxicity, as it has more specific binding to target domains and is metabolized into nontoxic amino acids [12]. Peptide therapeutics are less likely to encounter drug resistance, as it requires much more drastic changes in the viral structure for the virus to develop resistance against a peptide. However, peptide based therapeutics face challenges, such as poor in vivo stability and difficulty of forming oral formulations [13]. Currently, two peptide based therapeutics are being used for HIV treatment: Enfuvirtide, a fusion inhibitor that binds and blocks conformational change in gp41 [14], and Maraviroc, an entry inhibitor which blocks binding of gp120 to CCR5 [15], with others under investigation for FDA approval.

Treatment of HIV has advanced significantly over the past 3 decades. This review will briefly discuss the etiology of HIV [16], medical management [17], and approved drugs commonly used [18]. An interesting avenue that has gained much traction for HIV treatment is the development of HIV virion inhibitor peptides. The subsequent focus of this review will be to discuss the fundamental facets of peptide based therapeutics, specifically those currently in research. Finally, we provide insight into how these and other novel therapeutics may change the way we treat HIV. Overall, to be an *effective* drug in the treatment of HIV the following are required: 1) Cost-effective synthesis, 2) high potency with minimal side effects, 3) easy administration to enhance patient compliance, and 4) educational outreach for disease management and prevention.

2. The biological basis of HIV

2.1. Basics of HIV

The origin of HIV has not been clearly understood [19], with wide speculation that includes its evolution from the simian immunodeficiency virus [20]. HIV is the virus that can lead to AIDS. HIV infects and destroys CD4 cells (T cells), and undermines the human immune system in AIDS. In general, HIV cannot be cured at present and therefore requires life-long treatment. When not treated, undermined immunity surrenders to co-infections, such as HCV (hepatitis C Virus) [21], tuberculosis [22], other sexually transmitted infections [23], cytomegalovirus [24], and papillomavirus [25]. It can also result in age associated morbidities, such as myocardial infection and cancer [26], and eventually leading to significant patient mortality.

HIV is highly heterogeneous, mutates quickly, and can be latent for over 10 years, increasing the difficulty in prevention and treatment [27]. Although uncommon, there has been at least one report of a long-term control for HIV reported using CCR5 Delta32/Delta32 stem cell transplantation that is resistant to HIV-1 [28,29]. A number of research efforts are ongoing to find a cure for HIV [30,31]. Efforts have focused on finding treatment and prevention methods through vaccine and other methods of prophylaxis, including anti-retroviral drugs like Tenofovir in topical applications such as vagina gel and ring [32–34], in oral pre-exposure prophylaxis [35], and in implants [36]. Oral pre-exposure prophylaxis has shown effective protection for men who have sex with men by reducing HIV incidence by 44% [37], but not for heterosexual women, potentially due to low pill adherence or low drug concentrations at the genital tract [38]. Preclinical studies have also shown significant reduction of HIV infection by topical pre-exposure prophylaxis [39].

2.2. Clinical treatment and procedures

Antiretroviral therapy (ART) is the treatment for HIV infection. Multidrug regimens are used to reduce the progression of disease to AIDS, occurrence of opportunistic infections, hospitalizations, and death. There are currently more than 25 antiretroviral medications available in 5 drug categories (discussed below). Although a small portion of these are recommended for initial therapy, continuous assessment of the patient for adverse effects and toxicities as well as adherence guides medication choice. Multiple comparative clinical trials have shown that combination therapy consisting of 2 nucleoside reverse transcriptase inhibitors and a third agent from another class is the most effective treatment. The other classes used in initial treatment are non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and integrase strand transfer inhibitors [40].

2.3. Clinical presentation of HIV

HIV infection can present early as a mononucleosis-like illness; however, many affected individuals are asymptomatic. Estimates for those who are asymptomatic with HIV are between 10 and 60%, but it is hard to estimate because most diagnoses are made after a symptom has led to a work up. Those who have an acute infection, also known as acute retrovirus syndrome, develop symptoms two to four weeks after infection. However, incubation of up to 10 months has been reported [41]. Symptoms of acute HIV infection include fever, lymphadenopathy, sore throat, rash, myalgia, arthralgia, and headache. None of these symptoms are specific, but the presence of these features for an extended duration or with associated mucocutaneous ulcers is suggestive. Many patients experience nausea, diarrhea, anorexia, and weight loss. Patients can present with aseptic meningitis and rarely self-limited encephalopathy. The peripheral nervous system can also be affected. Opportunistic infections (OIs) usually occur in the later course of the infection and rarely occur during early infection with the transient lymphopenia [42]. Oral and esophageal candidiases are the most commonly occurring OIs. Other OIs in early HIV include cytomegalovirus (CMV) colitis, proctitis, hepatitis, pneumocystis jiroveci pneumonia, and cryptosporidiosis.

The chronic period of HIV infection is the time from acute infection to a CD4 count of <200, and it usually lasts 8–10 years. AIDS is diagnosed when CD4 reaches <200 cells/μL or with the presence of an AIDS defining illness, which includes OIs, recurrent infections, lymphoma of brain, and invasive cervical cancer [43]. Mucocutaneous candidiasis, oral hairy leukoplakia, seborrheic dermatitis, and herpetic infections occur with greater frequency when the CD4 cell count is < 200 cells/μL. Eosinophilic folliculitis, xerosis, prurigo nodularis, molluscum contagiosum, bacillary angiomatosis, exacerbation of psoriasis, and severe scabies are associated with AIDS. Anemia, leukopenia, lymphopenia, or thrombocytopenia is present in 40% of those with CD4 < 200 cells/μL. Polyclonal hyperglobulinemia is another hematologic aberration.

2.4. Severity of HIV and associated diseases

OIs usually occur at CD4 levels <200 cells/μL and less often at levels above that, with approximately 10% of patients developing an AIDS-defining diagnosis with a CD4 count ≥200 cells/μL [44]. Disseminated M. avium infection and CMV infections occur predominantly with a CD4 cell count <50 cells/μL. In the absence of antiretroviral therapy (ART), the median time to an AIDS-defining condition in someone with a CD4 cell count < 200 cells/μL is estimated at 12–18 months [45].

In the absence of ART, the average survival of patients with a CD4 < 50 cells/μL is 12–18 months. Most patients who die of AIDS-related complications have CD4 < 50 cells/μL [46]. Above CD4 of 50 cells/μL there is an average of one HIV-related death per 96.7 patient-years of observation as compared with one death per 2.5 patient-years of observation after the CD4 count had fallen below this level ($P < 0.0001$) [47].

2.5. Clinical management of HIV

ART is initiated in nearly all HIV infected patients and is usually started immediately after the initial assessment. Most patients benefit from the effects of ART regardless of CD4 count. However, there is a small subset of patients known as "HIV controllers" who maintain very low HIV RNA levels without ART therapy in which no clear benefit has been demonstrated. The urgency of initiating ART depends on CD4 count as well as the presence of opportunistic infections. Patients with CD4 counts in normal ranges, >500 cells/μL may elect to defer therapy, but they should be counseled as to the benefits of ART regardless of CD4 count. Starting ART at CD4 counts of <350 cells/μL and especially <200 cells/μL has significant reduction in mortality and morbidity. The higher the CD4 count at time of initiation the higher the long term CD4 count will be, which is associated with better long term outcomes [48].

2.6. Morbidity and mortality rates of patients

One study showed a 50% reduction in morbidity and mortality in those who initiated ART versus those who did not [40]. The overall outcome however depended on the level of immunodeficiency, as indicated by CD4 count at the time of treatment initiation. The hazard ratio for mortality for treated versus untreated are: 0.29 for CD4 < 100 cells/μL, 0.33 for 100–199 cells/μL, 0.38 for 200–349 cells/μL, 0.55 for 350–599 cells/μL, and 0.77 for >/ = 500 cells/μL. Another study showed that after 5 years of ART, the mortality of patients who initiated ART with low CD4 levels and begins to converge with those with intermediate to high CD4 levels. When opportunistic infections are present, early initiation of ART within 14 days leads to a 50% reduction in morbidity and mortality as compared to late initiation of ART after 14 days.

3. Therapeutic treatments of HIV

3.1. Approved therapeutics on market

More than 25 antiretroviral drugs from 5 therapeutic classes are available for the management of HIV with over 30 FDA approved in single and multi-class combination agents [49–51]. Therapeutics currently on the market aim to suppress the virus replication below the level of detection (<50 RNA copies/ml) and to reconstitute immunity by increasing $CD4^+$ T cells [52]. These therapeutics can be classified into 5 categories based on their mechanisms [53,54]. 1) Entry inhibitors and 2) integrase inhibitors are two new categories of anti-retroviral therapeutics [14,55,56]. 3) Nucleoside/nucleotide reverse transcriptase inhibitors, 4) non-nucleoside reverse transcriptase inhibitors, and 5) protease inhibitors were the targets of first generation HIV therapeutics. These are summarized schematically in Fig. 1.

3.2. Entry/fusion inhibitor

The entry and fusion process of HIV into the host cell is a complicated process involving several protein-protein interactions that can be drug targets. Entry of HIV into host cells involves several viral and host proteins [57], which are reviewed in detail elsewhere [58]. Briefly, the first step of HIV entry is attachment – HIV surface protein gp120 or host proteins integrated in the HIV membrane typically bind to target cell membranes of $CD4^+$ T cells [59]. The CD4 transmembrane glycoprotein domain on target T cells attaches to the CD4 binding site on gp120. This induces a conformational change in gp120, exposing its co-receptor binding sites [60]. The co-receptors include but are not limited to CCR5 and CXCR4 on target T cells, which bind to their respective binding sites on gp120 that are now exposed [61]. Fusion of the viral and host membranes begins as co-receptor binding induces the second conformational change in the HIV-1 envelope. As a result, gp41 is exposed and inserts into the host cell membrane [62]. As mechanisms of entry and fusion are being elucidated, inhibitors have been discovered that target different steps in the process.

Entry inhibitors prevent HIV from entering host cells. These differ from integrase inhibitors, which prevent viral DNA from integrating into host genome as detailed below [63]. A variety of compounds including small molecules and antibody-based inhibitors have been tested against gp120 and CD4 binding [64–66]. However, this approach has been shown to be ineffective with HIV isolates [67]. Development of entry inhibitors face this challenge due to the variability of the viral *env* gene that codes for gp120 and gp41 and the variability of co-receptors. With respect to blocking binding of co-receptors, an FDA approved entry inhibitor, Maraviroc (approved in 2007), targets CCR5. It is an inverse agonist of CCR5, which allosterically binds the CCR5 receptor and stabilizes the inactive conformation of CCR5 [68]. Maraviroc blocks binding of viral envelope protein gp120 to its CCR5 co-receptor in order to prevent further steps of membrane fusion necessary for viral entry [15]. Another prime example of an entry/fusion inhibitor is Enfuvirtide, a 36 amino acid peptide (approved in 2003) [69–71]. Enfuvirtide binds to a region of the HIV-1 envelope protein gp41 involved in the fusion of viral membrane and host cell membrane [14].

Although two drugs have been approved by the FDA in this category, they face challenges and still need to be improved upon. Maraviroc is only effective for HIV strains that utilize CCR5 for infection, but not CXCR4-tropic or CXC4/CCR5 bitropic (dualtropic) HIV strains [72,73]. Inhibition of the CCR-5 co-receptor may interfere with the normal function of CCR5 as a chemokine receptor, which is required in inflammatory responses to infections [73,74]. Enfuvirtide has a very limited window of action when gp41 is exposed after a conformational change in HIV envelope structure during the entry/fusion process. As a result, a high concentration of Enfuvirtide must be maintained in the patient [73]. To maintain this concentration, Enfuvirtide requires dosing at 90 mg subcutaneously twice daily, which is very difficult to achieve in resource-limited settings or with good patient compliance. Notwithstanding, skin sensitivity and side effects commonly associated with high dosages limit utility. Viral mutation leads to limitations of Maraviroc and Enfuvirtide due to the nature of their targets. Therefore, new compounds in development potentially target other proteins in the entry/fusion process and avoid limitations associated with CCR5 and gp41 [75–78].

3.3. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) [79]

NRTIs were the first antiretroviral drugs that appeared on the market [80]. NRTIs are analogs of native nucleoside substrates that target reverse transcriptase. Reverse transcriptase (RT) is a viral enzyme that catalyzes the transcription of viral genomic RNA into double-stranded proviral DNA [81]. The heterodimer of RT is important for incorporation of the viral genome into the host's genome. RT has two catalytic activities: DNA polymerase activity,

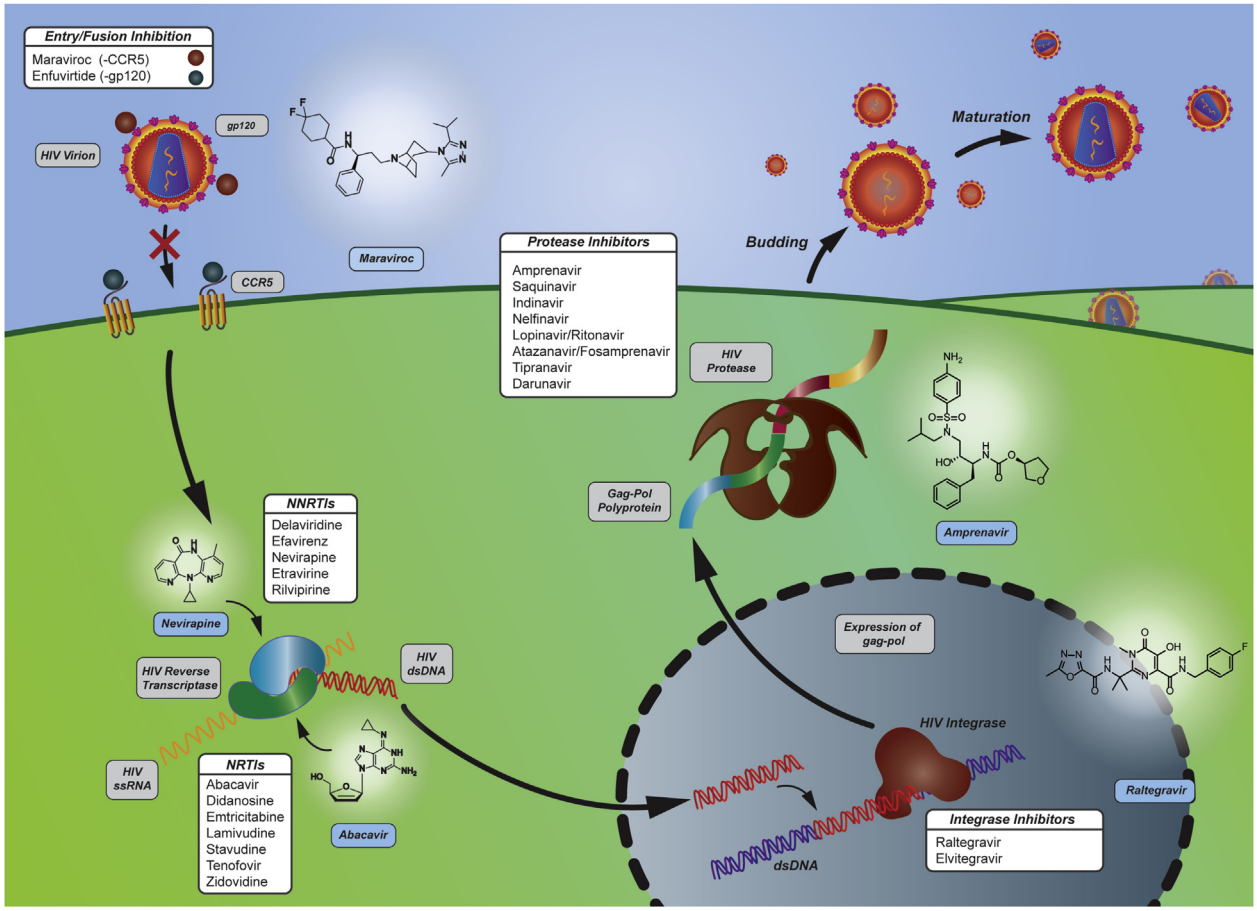

Fig. 1. HIV proliferation targets and their anti-retroviral drugs. Targets for anti-retroviral drugs include entry inhibition, reverse transcription, genome integration, and protease inhibition. Contemporary HIV treatments consist of administering multiple drugs (cocktails) to inhibit multiple phases of the HIV life-cycle.

which synthesizes DNA from RNA, and DNA and ribonuclease H activity that cleaves the RNA strand in the DNA-RNA duplex formed after DNA polymerase activity [82]. Seven approved NRTIs are on the market: Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Tenofovir, and Zidovudine [83]. After being phosphorylated by host cellular kinases, NRTIs compete with the natural substrate - endogenous deoxyguanosine triphosphate [84]. NRTIs add to and cap the growing viral DNA chain. NRTIs not only target reverse transcriptase in RNA-dependent DNA synthesis but also inhibit DNA-dependent DNA synthesis, preventing production of both (−) and (+) strands of viral DNA. Significant toxicity is a major challenge faced by NRTIs, which compromises treatment effectiveness [85]. For example, Stavudine was once part of first-line anti-viral regimens, but then its recommended dosage was reduced [86] until the use of Stavudine was limited due to its well-recognized toxicities [87]. Mitochondrial toxicity results from NRTI inhibition of mitochondrial DNA polymerase and manifests as myopathy, neuropathy, hepatic failure, and lactic acidosis [88,89]. Current management of side effects is through symptomatic treatment and reducing dosage regimens [90]. Consequently, drugs in this pipeline specifically require mitochondrial toxicity testing in preclinical phases of development [91].

3.4. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) [92]

NNRTIs are the most popular first-line HIV treatment regimens both in the United States and world-wide [93,94]. Some FDA approved NNRTIs include Delavirdine, Efavirenz, Nevirapine, Etravirine, and Rilvipirine. NNRTIs also target reverse transcriptase but are allosteric inhibitors. Allosteric binding of NNRTIs to HIV-1 RT [95] induces conformational changes in substrate binding site of reverse transcriptase, reducing its activity [96]. Challenges to NNRTIs are a low genetic barrier to drug resistance and cross-resistance even from a single mutation [97]. Drug resistance is another major challenge faced by first-generation NRTIs, causing most virologic failures of first-line regimens. As a result, NNRTIs are not recommended for second-line regimens in order to avoid the risk of resistance [98–100]. Such problems have been partially improved upon by second-generation NRTIs whose conformational flexibly allows them to interact with new residues in the binding pocket or with the main chain residues, which are less likely to mutate by single side chain residues [101,102]. Consequently, second-generation NNRTIs can act on first-generation NNRTI resistant HIV strains. In fact, the second-generation NNRTIs, Rilpivirine and Etravirine, are second-line drugs in resource-limited countries. They are indicated in patients for whom Efavirenz or Nevirapine fail due to their different resistance profiles (low cross-resistance) and suggested high genetic barrier brought on by their different structures [98,103]. Increasing resistance to both NRTIs and NNRTIs that decrease drug-RT binding has been observed in low-income and middle-income countries. Therefore, new drugs are urgently needed for emerging drug resistant HIV strains [104]; drugs that do not come with major side effects including skin rash, liver toxicity, and gastrointestinal disturbance [105]. Development of new NNRTIs is currently in multiple stages, aiming to target resistant HIV strains and reduce side effects [98].

3.5. Protease inhibitors

Protease inhibitors are a central part of highly active antiretroviral therapy (HAART), accounting for 10 out of 26 FDA approved anti-HIV therapeutics. Protease inhibitors target the viral encoded aspartyl protease, which is essential for viral maturation and infectivity [106]. Proteases are important enzymes in many biological processes and catalyze the hydrolysis of peptide bonds with high selectivity through activated water molecules or activated thioesters. HIV Protease in particular is an aspartic protease that cleaves gag-pol (polypeptide precursors) and gag-polyprotein precursors into smaller proteins (e.g. reverse transcriptase, RNase H and integrase) that are modified and assembled into new viruses [106,107]. Gag-pol and gag polyprotein precursors are translated from the viral pol and gag gene [108]. These genes are important for the formation of gag-pol and gag, which are important precursors for enzymes synthesis. FDA approved protease inhibitors are competitive inhibitors to viral proteases. Some FDA approved therapies include Saquinavir, Indinavir, Nelfinavir, Amprenavir, Lopinavir/Ritonavir, Atazanavir and Fosamprenavir, Tipranavir, and Darunavir. Saquinavir was the first FDA approved drug for the treatment of AIDS, and it mimics the tetrahedral intermediate of the proteolytic reaction catalyzed by viral protease [109]. Next generation protease inhibitors have been developed by modifying the structure of previous protease inhibitors. Most protease inhibitors share similar mechanisms of action by mimicking the substrate transition state in the proteolytic reaction [106]. They are competitive inhibitors and all but one (Nelfinavir) are peptidomimetics of the polyprotein cleavage site of the viral protease [110]. The disadvantage of protease inhibitors include the necessity for costly life-long treatment, off-target side effects, toxicity, and adherence [111]. First-generation protease inhibitors were described as highly peptidic and thus suffer from high instability and poor bioavailability [112]. Second-generation inhibitors were designed to address pharmacokinetic stability, side effects, and drug resistance of first-generation protease inhibitors [112]. Side effects to first-generation protease inhibitors include gastrointestinal distress, nausea, diarrhea, abdominal pain, and most commonly lipodystrophy caused by altering adipocyte metabolism [110,113]. A significant disadvantage is the extensive drug-drug interactions of protease inhibitors with other drugs, making protease inhibitors undesirable for patients on other drug regimens [98].

3.6. Integrase inhibitors [105]

Integrase inhibitors target the integration process of HIV viral DNA into host DNA. This is a two-step process mediated by the retroviral enzyme integrase: 1) cut viral DNA and 2) join viral DNA into host DNA, termed DNA strand transfer [114,115]. Integration is an essential step in establishing irreversible and chronic infection [116]. Integrase strand transfer inhibitors (INSTIs) are competitive inhibitors to integrase that bind to the host DNA binding site and inhibit DNA strand transfer activity [117,118]. Current integrase inhibitors target the strand transfer step of the integration process by binding to the enzyme active site and disengaging it from the viral DNA [119]. The first-generation INSTIs, Raltegravir and Elvitegravir [120] were derived from modification of the monoketo acid motif of quinolone antibiotics with chelating ability [121,122]. The development of the first INSTI Raltegravir started with the discovery of a β diketo acid moiety with selective inhibitory activity against DNA strand transfer reactions [123]. Raltegravir had the disadvantage of a low genetic barrier to mutation and frequent dosing (twice daily) [98]. Research efforts have been focused on optimizing interactions between INSTIs and integrase, and it has resulted in the development of small molecules similar to Raltegravir. For example, Elvitegravir only requires once per day dosing. However, as Raltegravir-resistant HIV mutations emerge, integrase inhibitors with mechanisms similar to first-generation INSTIs are likely to fall victim to the mutational competence of HIV [120]. The second-generation INSTI Dolutegravir was developed as drug resistant mutations emerged towards first-generation INSTIs [55]. Compared to the first-generation INSTIs, Dolutegravir improves binding with viral DNA through its more flexible linker region [119], and has shown fewer drug-drug interactions and side effects [124]. Most frequently reported adverse effects are headache (around 2%) and insomnia (around 3%) [124] (see Tables 1 and 2).

3.7. Disadvantages of current therapeutics [125]

Drug resistance is a major problem with current HIV therapeutics for patients failing therapy and therapy-naive patients due to the genetic diversity of HIV. 1 to 10 mutations may be generated every viral replication cycle [54]. Therefore the constant evolution of HIV demands constant evolution of HIV therapeutics. The prevalence of HIV-1 mutated strains that are resistant to one or more antiretroviral inhibitors or drug classes remains one of the leading causes of treatment failure among patients with HIV/AIDS [105,126,127]. NNRTIs are particularly susceptible to small mutations because single nucleotide changes can result in high-level resistance with only a slight loss of replicative fitness [54]. Resistance to therapeutics undermines the efficacy of HAART as multidrug resistant strains evolve. Currently available therapeutics used in HAART also need to be improved because of serious side effects. NRTI and NNRTIs have been reported to induce a variety of adverse effects: neuropathy, lactic acidosis, pruritus, fatigue, nausea, and myalgia [107,125,128]. Abacavir, for example, causes an immune-mediated hypersensitivity reaction in 5% of the patients [129]. Injection site reactions are the most common adverse events associated with Enfuvirtide [130], which requires twice daily subcutaneous administration due to the high concentration that needs to be maintained in the body (discussed above in 3.2.). Protease inhibitors have shown unbearable toxicity [106]: metabolic syndrome, dyslipidemia, insulin-resistance, lipodystrophy/lipoatrophy, and cardiovascular and cerebrovascular toxicity [131–134]. Additionally, they have shown poor oral bioavailability and poor penetration across the blood brain barrier [52]. Lowering toxicity of new HIV drugs has been predicted to improve life expectancy and compliance for many patient groups [135]. Inability of drugs currently employed in HAART to reach latent viral reservoirs leads to the necessity for life-long, consistent treatment [136], and the rapid relapse after any non-compliance [137]. Current drugs have poor targeting ability and short residence time, contributing to the latent viral reservoirs [138]. Thus, prolonged and consistent treatment also contributes to the build-up of toxicity and emergence of resistant HIV strains. Nanotechnologies have been proposed to solve this problem [138]. Nanotechnologies have been employed to improve drug oral or i.v. formulation for better bioavailability [139–143], targeted release [144–146], or long-term action through sustained release [147]. Among the three nanotechnology applications in HIV treatment, peptides have been mostly studied for cell targeting [148–150] and cell penetration [114,151] in delivery of small molecules and/or biologics for treatment and prevention of HIV. The synthetic and chemical approach to HIV treatment has left much to be desired in the ways a technology can overcome current drug resistances, reduce toxic effects, and improve ease of administration for wider acceptance, compliance, and application in global settings, especially in resource-limited areas [18,152,153]. Short peptides/proteins are a new field that may hold promise for the treatment of HIV, especially for inhibiting

Table 1
Antiretroviral medications.

Medication	Target	Type	Usage	Toxicity
Enfuvirtide	gp41	Fusion inhibitor	Binds & blocks conformational change in gp41	Significant
Maraviroc	gp120	Entry inhibitor	Blocks binding of gp120 to CCR5	hepatotoxic
Abacavir	RT	NRTI	Inhibit DNA-dependent synthesis	+
Didanosine	RT	NRTI	Inhibit DNA-dependent synthesis	++++
Emtricitabine	RT	NRTI	inhibit DNA-dependent synthesis	+
Lamivudine	RT	NRTI	Inhibit DNA-dependent synthesis	+
Stavudine	RT	NRTI	Inhibit DNA-dependent synthesis	++++
Tenofovir	RT	NRTI	Inhibit DNA-dependent synthesis	+
Zidovudine	RT	NRTI	Inhibit DNA-dependent synthesis	++
Zalcitabine	RT	NRTI	inhibit DNA-dependent synthesis	++++
Raltegravir	Enzyme active site	Integrase inhibitor	Inhibit DNA strand transfer activity	Adverse effects
Elvitegravir	Enzyme active site	Integrase inhibitor	Inhibit DNA strand transfer activity	Adverse effects
Dolutegravir	Enzyme active site	Integrase inhibitor	Inhibit DNA strand transfer activity	Adverse effects
Efavirenz	RT	NRTI & NtRTI	Induce conformational change of RT	Toxic effects to CNS
Saquinavir	Aspartyl protease	Protease inhibitor	Viral protease inhibitor	GI toxicity
Ritonavir	Aspartyl protease	Protease inhibitor	Viral protease inhibitor	GI toxicity
Darunavir	Aspartyl protease	Protease inhibitor	Viral protease inhibitor	GI toxicity
Indinavir	Aspartyl protease	Protease inhibitor	Viral protease inhibitor	GI toxicity
Tipranavir	Aspartyl protease	Protease inhibitor	Viral protease inhibitor	GI toxicity
Fosamprenair	Aspartyl protease	Protease inhibitor	Viral protease inhibitor	GI toxicity
Nelfinavir	Aspartyl protease	Protease inhibitor	Viral protease inhibitor	GI toxicity
Atazanavir	Aspartyl protease	Protease inhibitor	Viral protease inhibitor	GI toxicity
Lopinavir	Aspartyl protease	Protease inhibitor	Viral protease inhibitor	GI toxicity
Amprenavir	Aspartyl protease	Protease inhibitor	Viral protease inhibitor	GI toxicity

++++ Strongest association with mitochondrial toxicity, +weakest association with mitochondrial toxicity; Enfuvirtide has common adverse events which include pain, erythema, pruritus, and induration. Central nervous system (CNS) toxicity involves abnormal mood, delusions, and insomnia; Gastrointestinal toxicity (GI) includes abdominal pain, nausea, emesis, diarrhea; Adverse effects: nausea, dizziness, headache, insomnia, and fatigue [271,272].

Table 2
Peptide inhibitors.

Peptide	Amino acid sequence	Type	Target	Reference
Anti-gp120	DGGNSNNESEIFRPGGGDMRDN	Entry inhibitor	HIV-1/gp120	[162]
Anti-CCR5	YQVSSPIYDINYYTSEPCQKINVKQIAA	Entry inhibitor	Co-receptor CCR5	[163]
PIE12-trimer	HPXXCDYPEWQWLCXXELGK	Entry inhibitor	HIV gp41 N-trimer pocket	[159]
P_{AW}	GTKWLTEWIPLTAEAEC	RT inhibitor	HIV-1 RT	[179]
G12	GI-p-benzoylphenylalanine-FVSL	Protease inhibitor	ε-amino group of Lys 14 of HIV protease	[205]
E1P47	WILEYLWKVPFDFWRGV	Entry inhibitor	HIV-1 Fusion Peptide	[168]
p7	KETWETWWTE	RT inhibitor	Dimerization of RT	[182]
Apam (2)-Tyr-Glu-T (4)-OH		RT inhibitor	HIV-1 protease dimer interface	[180]
Vpr 57-71	VEAIIRILQQLLFIH	RT inhibitor	HIV-1 IN & RT	[183]
Vpr 61-75	IRILQQLLFIHFRIG	RT inhibitor	HIV-1 IN & RT	[183]
NYAD-1	HITFEDLLDYYGP-NH2	Gag inhibitor	HIV-1 Gag polyprotein	[245]
Vif peptide	LITPKKIKPPLPSVT	Vif inhibitor	HIV-1 Vif	[234]
p27	PQITLRKKRRQRRRPPQVSFNFCTLNF	Protease inhibitor	WT & PI resistant HIV-1 protease	[190,207]
Tetrameric peptide 10	$((ILPWKWPWWPWPP)_2K)_2K\text{-}NH_2$	Integrase inhibitor	HIV-1 integrase	[270]
Tetrameric RIN-25	$((ILPWKWPWWPWPP)_2K)_2K$	Integrase inhibitor	HIV-1 integrase	[209]

newly discovered protein-protein interaction targets due to its greater affinity than small molecules to these weak binding pockets.

4. Targets of peptide inhibitors [154–156]

4.1. Peptide inhibitors

Peptide inhibitors share similar targets to currently approved therapeutics and have also been applied to other targets. The targets that have been investigated include entry/fusion, reverse transcriptase, protease and integrase. HIV therapeutics are now generally discovered through 1) high-throughput compound screening with virus-specific assays, 2) optimization of lead compounds, and 3) rational drug design based on the structure of viral proteins [54]. Peptide inhibitors are usually designed based on 1) viral or host protein targets and protein-protein interactions and 2) screening of peptide libraries. Structures are then subject to virus specific assays. Peptide/protein inhibitors hold great promise to improving upon the drug-resistance of small molecular antiviral therapeutics because resistance to macromolecules like peptides and proteins requires evolutionary mutations or co-receptor changes that are a lot less likely than single nucleotide changes in NNRTI-resistant mutations [111,125,157–159]. Thanks to Qureshi et al., a database of HIV inhibiting peptides has been developed and is constantly updated [160]. Peptides in development, summarized in previous reviews and databases [156,160], are summarized below according to their targets.

4.2. Entry and virus cell fusion [125]

Peptide inhibitors that target the entry process inhibit one or more key proteins including gp41, gp120, coreceptors (CCR5, CXCR4, APJ), and CD4 [77,111,125]. Currently as the biological understanding of the entry process increases, a number of design and modification schemes have been presented, and a large number of prospective fusion peptides have emerged [161]. The most promising peptides and proteins that inhibit the entry and fusion process

function as antibodies that neutralize the virus or as direct inhibitors by binding viral or host proteins. Antibodies include anti-gp120 monoclonal antibodies and smaller derivatives [162,163], anti-CD4 antibodies, and anti-CCR5 monoclonal antibodies. Direct inhibitors include soluble gp120 receptors as gp120 inhibitors, synthetic and natural gp41 inhibitors [159,164–166], synthetic anti-CCR5 peptides [167], CXCR4 inhibitors, and multi-functional inhibitors (lectins and defensins) [125]. Another class of peptide inhibitors targeting the entry/fusion process mimics the E2 envelope glycoprotein and the NS5A phosphoprotein from GB virus C (GBV-C), which has been shown to inhibit HIV entry [168]. Molecules under investigation share similar limitations to the peptide fusion inhibitor Enfuvirtide - poor bioavailability [169,170] and high cost of production [171,172]. Some protease inhibitors show adverse side effects, such as an inflammatory response induced by anti-CCR5 peptides [125,172]. High dosage is needed for current anti-gp120 antibodies [173]. Due to such limitations, microbicides were used as an alternative to oral administration or injection for several promising peptide entry inhibitors (T20 (Enfuvirtide) [174], T1249 [175], L′644 [176] and Sifuvirtide [177]).

4.3. Reverse transcriptase (RT)

Peptide mimics of reverse transcriptase subunits have been found to inhibit heterodimerization and conformational changes during the formation of reverse transcriptase [81,178–181]. Examples include residues 395–404 of RT [182] and Paw [179]. Peptide mimics of other RT binding viral proteins, such as a Vpr protein-derived peptide, also hold promise as peptide inhibitors [183]. Other peptide inhibitors for RT include peptides derived from ribonuclease [184,185], polyarginine transporter molecules [186], N-methylated peptides that bind RNA [187], protein targeting RTC [188], and anti-fungal peptides [189]. Similarly to protease and integrase peptide inhibitors, RT peptide inhibitors also face the problem of low potency (high IC50 values) and thus have not advanced to in vivo evaluation or clinical studies. There are much fewer publications on RT peptide inhibitors than on entry peptide inhibitors, integrase peptide inhibitors, and protease peptide inhibitors, which is partially due to the success of small molecules in inhibiting RT.

4.4. Protease inhibitors

Peptide inhibitors have also been shown to inhibit protease dimerization. The dimerization interface of protease is created by the conserved active site triad, Asp-Thr-Gly, and four antiparallel beta sheets of the C-terminus and N-terminus of each monomer [190–192]. Short peptides were synthesized according to the N and C terminus of the protease, which prevents the protease monomer from associating with another monomer. As dimerization is necessary for proteolytic activity, prevention of dimerization effectively inhibits protease activity [178,193]. To improve upon the weak inhibitory potency of C-terminus and N-terminus mimics [194–196], flexible linkers and rigid scaffolds have been used, as well as side chain tethering (intercalating “molecular tongs”) [113,197–200] and terminal modification with lipophilic groups and alkyl chains [201–204]. Interfacial peptides can also serve as irreversible inhibitors by covalently associating with protease [205,206]. Another type of peptide inhibitor that targets dimerization is the fusion of N-terminal HIV-1 protease peptide with cell permeable domain of the HIV-1 Tat protein, which is the transactivator of the virus [190,207]. Peptide-based protease inhibitors require modulation to overcome the weak binding potency of inhibitors with the protein-protein interaction interface, which increases the complexity of drug design involving optimization of covalent modifications of peptide chains [198]. Prevalence of and similarities between families of proteases in the human body increases the standard for protease inhibitors in recognizing and inhibiting viral proteases and penetrating cell membrane [208]. Meanwhile, peptides show great promise as protease inhibitors because of their versatility in targeting parts of proteases and protease-binding proteins other than the catalytic domain and binding sites that are similar between human and viral proteases.

4.5. Integrase inhibitors

Protein-protein interactions involving integrase, including integrase dimerization and integrase-substrate and allosteric cofactor interactions have been investigated for peptide inhibitor designs [81,105,209]. The first group of peptides was derived from the dimer surface of integrase inhibitors with the intent to disrupt integrase inhibitors' dimerization or to inhibit their enzymatic activity [178,209–215]. Lead peptides were then improved in design with D-amino acids to prevent degradation. Advancement in the understanding of protein-protein interactions involving integrase has enabled more targeted drug designs. The second group of peptides were derived from integrase inhibitor-binding proteins in order to inhibit integrase inhibitor interaction with host proteins (cofactors such as LEDGF/p75 [216–219]) [220] or viral proteins [221–223], such as viral reverse transcriptase [224], Vpr protein [183], and Rev protein. Besides designing inhibitory peptides from integrase inhibitors and integrase inhibitor-binding proteins, inhibitory peptides have been found through screening of phage display libraries or with yeast two-hybrid systems. Antimicrobial peptides showing integrase inhibitory activities include Indolicidin, a host cell defense tridecapeptide [225]. Protein-protein interaction inhibitors, including dimerization inhibitors, have been shown to be relatively week inhibitors with IC50 in the range of 1–250 μM [209]. The advantage of macromolecules, such as peptides and proteins, over small molecule drugs is that they can potentially be optimized in designing shallow binding pockets, such as protein-protein interactions. Since current lead peptide inhibitors are only tested in vitro assays, potency needs to be optimized before in vivo assays and clinical studies. Peptide interface inhibitors of protease and integrase have been studied since the last century [193,196] from biochemical standpoints but have yet to come close to testing in animals. As interface inhibitors need to bind the target protein tightly enough to outcompete its natural binding partner, it is challenging to design peptides that mimic the binding partner yet have significantly higher binding affinity to achieve clinically meaningful potency [226]. Alternatively, next generation designs of small molecule drugs have been proposed using peptides as starting points [209,222,223].

4.6. Others

Other HIV inhibitors include those designed based on other specific targets [227–229] and through screening of existing peptide libraries [230–233]. Target-based design of HIV inhibitors have involved targeting: 1) interactions between viral Tat protein and host TAR protein [227,228], 2) polyproline interfaces of viral infectivity factor for the multimerization of viron infectivity factor proteins [234], 3) the budding of HIV after replication in host cells [235,236], 4) viral gene expression [237], 5) viron maturation (gag-derived peptides [229], inhibiting gag processing), 6) multi-stage infectivity (CD4 antigen-based anti-receptor peptides [238]), 7) unidentified GBV-C E2 protein [239,240], 8) syncytium formation [241,242], 9) viral Vpr and rev proteins [243,244], 10) viral assembly [245–247], and 11) alpha-glucosidase [248]. Antimicrobial peptides have been derived from a variety of species, such as amphibians, or

through antimicrobial databases screened for anti-HIV activity [230]. They have been shown to inhibit HIV infections of T cells and disrupt HIV envelope and viral core proteins [230–233]. A prime example is caerin antimicrobial peptides [230]. Anti-HIV antimicrobial peptides have been developed in vitro thus far, and more research is needed to evaluate the suppressing or enhancing effects, as well as chemotactic effects of antimicrobial peptides on the native immune system [249]. Physiological toxicity is a major drawback antimicrobial peptides [250].

4.7. Promising strategies in development

As drug resistance continues to emerge, new drug classes (integrase and virus entry inhibitors) and new drugs in old classes (NRTI and NNRTIs) that are active against drug-resistant HIV strains are needed to combat drug-resistant HIV strains [251,252]. Because of viral resistance to integrase strand transfer inhibitors targeting the catalytic site, new generations of HIV inhibitors not based on the catalytic triad, such as allosteric integrase inhibitors (ALLINIs), can target INSTI-resistant viruses [105].

Peptide inhibitor design starts from designing peptides according to certain regions of viral or host proteins, screening in peptide libraries for anti-HIV activities, and screening of the entire span of viral proteins and protein-protein interactions that can generate lead peptides needed to be refined [183]. For integrase inhibitors, it is easier to design peptide inhibitors than small molecule inhibitors for preventing protein-protein interactions because it is easier to use peptides to mimic existing binding sites [209]. Limitations faced by peptide inhibitors before clinical trials include bioavailability, instability, and high cost of production [111]. Peptides are polar compounds, and cell penetration is necessary for most targets except for entry/fusion inhibitors, which requires lipophilicity [11]. The inability to penetrate cell membranes has halted development of many peptide based therapeutics [245]. Cell penetration can be aided by nanotechnologies discussed earlier in the review, including conjugating peptides with a cell penetrating peptide derived from HIV Tat protein [253]. Peptide/protein drugs are very prone to degradation in vivo and therefore generally are susceptible to GI first pass metabolism [11]. This instability of peptide/protein drugs and poor oral bioavailability necessitates subcutaneous, intramuscular, or intravenous delivery. Using peptides as a starting point, small molecule drugs can be designed for systemic administration [254]. Alternatively, peptide/protein inhibitors can be used in topical applications, such as peptide/protein based microbicides [125]. Unlike other small molecules, peptide fusion inhibitors may be adsorbed slowly and could extend their half-life at mucosal sites [168]. The high cost of production due to costly expression systems in bacteria, yeast, or mammalian systems has been one of the major limitations for several promising peptide inhibitors [125].

5. Discussion

HIV therapeutics have developed significantly over the past few decades. Clinically, decreasing the spread of HIV begins with education. Rationale approaches given the socioeconomic and societal considerations of the patient population encourage the use of preventative approaches such as pre exposure prophylaxis (PrEP). Once infection is established, the current standard of care is combination of ART initiation with two nucleoside reverse transcriptase inhibitors and a third agent from a different drug category. This is followed by monitoring for any adverse events, toxicity, adherence issues, or drug resistance and making appropriate changes in medication.

The primary deficiencies of current HIV therapeutics in development are administration difficulties, adverse effects, and emerging resistance. Peptide and protein drugs are an exciting new field in medicinal chemistry, as evident by more than 1000 peptide-based drugs that have reached the market [255]. The development of peptide based inhibitors of HIV infection have the benefit of higher potency, higher selectivity, lower toxicity, fewer side effects than small molecules, predictable metabolism, shorter time to market, lower attrition rates, standard synthetic protocols, targeted designs to a broad range of targets, lower accumulation in tissues, higher chemical and biological diversity, and lower chances of developing drug resistance [11,256].

An interesting approach to improve target cell interaction is to increase the epitope presentation of peptide based drugs [257]. In a recent study based on angiogenesis for the treatment of peripheral artery disease, a novel self-assembling peptide therapeutic, termed SLanc, has shown the potential for improved angiogenesis [258]. The potential mechanism of action is increased peptide epitope presentation that enhances angiogenic receptor activation and signaling [258]. Similarly, the potential for self-assembling peptides to present inhibitory signals at high epitope density on the surface of T cells or virons, may allow for smaller dosing regimens and higher efficacy [259]. One useful application for self-assembling peptides is in vaginal microbicide for prevention of HIV [260]. Using a self-assembling peptide hydrogel to present inhibitory signals reduces dosing and costs, which are significant challenges to be solved in HIV microbicide development [261]. Another strategy is conjugating self-assembling peptides with mimetic peptides derived from the viral envelope proteins or receptors that neutralize HIV particles [262,263]. Self-assembling peptides conjugated with mimetic peptides in vivo can potentially bind and aggregate HIV particles. The third potential of conjugation of a self-assembling peptide with HIV peptide inhibitors involves using self-assembling peptide to improve bioavailability and stability, as shown in PEGylation of peptide inhibitors [49,264]. Such conjugation may protect peptide inhibitors from rapid degradation and clearance from the circulation by self-assembly. Conjugation of small molecule and peptide drugs to polymers may allow slow and constant release of drugs and avoid spikes in the blood plasma [265]. Slow, steady release can be further tuned by the length and self-assembling properties of peptide scaffolds and results in decreased dosage and improved patient compliance [266–269]. Overall, conjugation of self-assembling peptides presents an opportunity to significantly improve major limitations of peptide-based drugs, including unsatisfactory pharmacokinetic properties, rapid metabolism, poor solubility, and poor bioavailability.

6. Conclusion

HIV is a difficult disease to manage with high rates of morbidity and mortality. There are 37 million infected individuals worldwide and 12.8% of them do not know they are infected. Given the magnitude of this pandemic numerous research efforts looking for prevention and treatment of HIV are made with $15 billion being devoted from 2000 to 2004. We aimed to discuss HIV viron inhibitor peptides as a potential effective therapeutic. HIV requires life-long treatment. ART is the treatment for HIV: 2 nucleoside reverse transcriptase inhibitors and a third agent from another class is the most effective treatment. The other classes used in initial treatment are non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and integrase strand transfer inhibitors. HIV can present as an early mononucleosis-like illness or can be asymptomatic early on. Chronic infection occurs from the time of acute infection to a CD4 count of <200 cells/μL. AIDS is defined as a CD4 count of less than 200 cells/μL or the presence of an AIDS defining illness.

ART is recommended for all patients immediately after initial assessment regardless of CD4 count. More than 25 antiretroviral from six therapeutic classes are available. A variety of compounds have been tested against gp120 and CD4 binding. Development of these compounds faces challenges due to the variety in the *env* gene that codes for gp120 and gp41 and the variety of co-receptors. With regards to co-receptors, CCR5 is blocked by Maraviroc, which blocks binding of gp120 to CCR5. Enfuvirtide binds gp41. These are the two FDA drugs approved as entry/fusion inhibitors and each have their own limitations. Novel agents are looking to target proteins other than CCR5 and gp41. NRTIs were the first antiretroviral drugs available. These agents are complicated by associated toxicity. NNRTIs are the most utilized first line treatment and are faced by the challenge of a low genetic barrier to drug resistance. Protease inhibitors are complicated by being costly and having side effects, as well as drug-drug interactions. Integrase inhibitors block the incorporation of HIV DNA to host DNA. Drug resistance is one of the major challenges to current therapeutics. There are also a variety of toxicities and side effects. They lack good targeting ability and have a short residence time. Short peptides used to inhibit newly discovered protein-protein interaction targets are an area of research that holds promise for novel therapeutics.

Peptide inhibitors share similar targets to currently approved therapeutics as well as other targets. They hold promise on improving drug resistance issues. Many entry and fusion inhibitor models exist for peptides. There are fewer publications on peptide reverse transcriptase inhibition. Peptide inhibitors for integrase inhibition have been investigated. For integrase inhibitors, peptide inhibitors are better than small molecules to target protein-protein interactions. They are limited by bioavailability, instability, and high cost of production.

Competing interests

No authors report competing interests with the current work.

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