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Progress in Formulation-Based Approaches for Antiretrovirals

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ABSTRACT

The human immunodeficiency virus has infected millions of people and the epidemic continues to grow rapidly in some parts of the world. Antiretroviral (ARV) therapy has provided improved treatment and prolonged the life expectancy of patients. Moreover, there is growing interest in using ARVs to protect against new infections. Hence, ARVs have emerged as our primary strategy in combating the virus. Unfortunately, several challenges limit the optimal performance of these drugs. First, ARVs often require life-long use and complex dosing regimens. This results in low patient adherence and periods of lapsed treatment manifesting in drug resistance. This has prompted the development of alternate dosage forms such as vaginal rings and long-acting injectables that stand to improve patient adherence. Another problem central to therapeutic failure is the inadequate penetration of drugs into infected tissues. This can lead to incomplete treatment, development of resistance, and viral rebound. Several strategies have been developed to improve drug penetration into these drug-free sanctuaries. These include encapsulation of drugs in nanoparticles, use of pharmacokinetic enhancers, and cell-based drug delivery platforms. In this review, we discuss issues surrounding ARV therapy and their impact on drug efficacy. We also describe various drug delivery–based approaches developed to overcome these issues.

Introduction

Despite significant progress in the understanding, treatment, and prevention of the human immunodeficiency virus (HIV), 2 million new cases of HIV infection were recorded in 2014.[1] There were ~36 million people living with HIV infection and ~1.2 million acquired immunodeficiency syndrome (AIDS)-related deaths in 2014.[1] The prevalence of HIV infection is disproportionately high in Africa.[2] There are ~25 million HIV-infected individuals in Africa, accounting for 70% of the HIV-infected population.[3] In the absence of a cure, these numbers are bound to increase, suggesting that we are not past the epidemic yet. However, there are many drugs available for the management of the disease. Optimum use of these drugs will enable control of the epidemic and improve disease-associated morbidity and mortality.

The first report of HIV-AIDS appeared in a morbidity and mortality weekly report in 1981.[4] The 5 patients described in this report were homosexual men living in the Los Angeles area, who presented with *Pneumocystis carinii* pneumonia, and other infections.[4] Similar occurrences, coupled with Kaposi's sarcoma, were later reported in New York as well.[5] However, little was known about the cause of this mysterious disease. In 1983-1984, groundbreaking work from the labs of Montagnier and Gallo showed that it was a retrovirus, later named the HIV-1, which was responsible for this disease.[6-8] Subsequently, the HIV-1 main type (M-type) of the virus was associated with millions of infections around the world. Other types of HIV-1 such as N, O, and P have also been identified.[9] Another virus, which is morphologically similar to HIV-1, also causes AIDS and has been termed the HIV-2. The probability of disease development with HIV-2 is less than that with the HIV-1[10] and the latter is the more predominant virus.[9]

Following the isolation of the virus, research in this area progressed at a swift pace.[11-13] In 1987, zidovudine was the first antiretroviral (ARV) drug approved for the treatment of HIV.[14] After almost 3 decades, today, there are nearly 30 drugs approved for the treatment of HIV infection.[15-17] Interestingly, today, the life expectancy of an HIV-infected individual diagnosed early and having ready access to medical services is comparable to that of a healthy individual.[18] Moreover, HIV drugs can now be used as a preventative measure to protect healthy individuals who are at a high risk of encountering the virus.[19-21] This approach, referred to as pre-exposure prophylaxis (PrEP), promises to have a significant

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impact on the spread of the disease and potentially protect millions of people around the world.

Despite these successes, several challenges remain concerning the management of the disease. We highlight here 2 factors, which we believe, are central to the performance of HIV drugs. The first is that of patient adherence to the therapeutic regimen. Finding alternatives that enhance patient adherence can allow for more effective application of anti-HIV drugs. The second limitation with current ARVs is their poor penetration into several tissues. Improving drug penetration into these tissues may provide an opportunity for the complete elimination of virus, reduced dosing, and/or improved therapeutic efficacy. In this review, we describe drug delivery interventions to address these 2 problems, poor adherence to therapy, and unfavorable biodistribution of drugs.

ARV Drugs for the Treatment and Prevention of HIV Infections

Before the discovery of ARV drugs, patient mortality in the HIV-infected population was high due to the development of AIDS.[22] However, with the discovery of several potent ARV drugs, there is tremendous improvement in patient life expectancy and their quality of life.[22] Moreover, in the absence of a viable HIV vaccine[23] and limited effectiveness of behavioral interventions,[24] ARV drugs have emerged as an important strategy for the prevention of HIV infection as well. Consequently, ARV drugs have been central to our efforts in combating HIV. In this section, we provide an overview of various ARV drugs approved for therapy.

Life Cycle of the HIV

The life cycle of the HIV is integral to the understanding of ARVs. We outline here the various steps of the viral life cycle starting from infection of a host cell to the formation of a new virus.[25]

One of the primary targets of HIV are $CD4^+$ T cells.[26] The viral gp120 protein engages chemokine receptors, mainly the CXC chemokine receptor 4 (CXCR4) or the CC chemokine receptor 5 (CCR5), on the surface of T cells.[27-30] This process triggers a conformational change in the gp120 protein and leads to the exposure of the gp41 protein.[31] This enables the fusion of viral cell membrane with the host cell membrane allowing entry of viral contents (reverse transcriptase complex) into the host cell. Reverse transcriptase converts the viral RNA into double-stranded proviral DNA.[32] The proviral DNA is then transferred into the nucleus and integrated into the host DNA via the enzyme integrase.[33] Using host mechanisms, the viral DNA is transcribed and later translated into precursor polyproteins. The Gag polyprotein brings about the assembly of viral components such as polyproteins and nucleic acids at the host cell membrane. This is followed by the budding of viral particles from the cells and their maturation, enabling them to infect new cells.[34,35]

ARV Drugs

Zidovudine, the first approved ARV, is a competitive inhibitor of reverse transcriptase.[36] Zidovudine is a structural analog of thymidine and upon 3 successive intracellular phosphorylations can be incorporated into the growing cDNA chain.[15] However, due to the lack of a 3'-hydroxyl group, it acts as a chain terminator and prevents the formation of proviral DNA. Following the clinical success of zidovudine, several drugs (such as didanosine, zalcitabine, stavudine, and lamivudine) with a similar mechanism of action were approved. These drugs are termed nucleoside reverse transcriptase inhibitors (NRTIs).[15]

Nucleotide reverse transcriptase inhibitors (NtRTIs) are another class of competitive inhibitors of reverse transcriptase. Their mechanism of action is similar to that of NRTIs. However, these drugs contain an additional phosphate group and require only 2 additional phosphorylations to produce the active drug form. Due to the altered attachment of phosphorus, these drugs are less vulnerable to esterase activity and pyrophosphorolysis than NRTIs.[15,37] Tenofovir, a NtRTI, has now become an integral part of several ARV drug regimens.

Non−nucleoside reverse transcriptase inhibitors (NNRTIs) are allosteric inhibitors of reverse transcriptase.[38] These drugs bind at a site ~10 Å from the catalytic site of the enzyme and effect a conformational change in the enzyme inhibiting its normal catalytic activity. Currently, there are 5 NNRTIs approved for use in HIV treatment, with efavirenz being one of the most commonly prescribed drug. Unfortunately, NNRTIs are prone to rapid development of resistance stemming from mutations in the drug-binding pocket of the enzyme.[39] Newer NNRTIs such as rilpivirine show activity against multiple viral strains and hold immense promise for HIV therapy.[40]

Integrase inhibitors block the integrase-mediated incorporation of proviral DNA into the host genome. Integrase works via a 2-step process to incorporate viral DNA into the host genome. These 2 steps are termed 3'-processing and strand transfer. Integrase inhibitors work predominantly by inhibiting the second step of this process.[41] Raltegravir was the first approved integrase inhibitor, followed by dolutegravir and elvitegravir.[42]

The HIV-1 protease is key to viral multiplication and is distinct from human proteases. Protease inhibitors block the viral protease, which is responsible for the cleavage of viral proteins and maturation of viral particles. Protease inhibitors such as saquinavir, ritonavir, and indinavir contain an amide bond resembling the phenylalanine-proline sequence found in gag-pol proteins of the virus,[15,43] allowing their binding to the viral protease. Newer protease inhibitors such as tipranavir do not contain the peptide-like bond but still efficiently inhibit the viral protease by forming strong hydrogen bonds with the active site of the enzyme.[15,44]

The first step of viral infection is its entry into $CD4^+$ cells. Drugs that block this process are termed entry inhibitors and have been the subject of extensive research.[45] Viral entry is mediated by the binding of viral gp120 to the CCR5 or CXCR4 chemokine receptor on the surface of $CD4^+$ cells. Maraviroc is an allosteric inhibitor of CCR5 and blocks viral entry.[46] Maraviroc is used only in patients infected with the CCR5 tropic virus and is not recommended as a first-line treatment.[47] Inhibition of gp41 protein can also mediate antiviral activity. Enfuvirtide, the first approved viral entry inhibitor, elicits its activity by binding gp41 and altering its folding.[48]

Although the use of a single HIV drug can limit viral replication, emergence of resistance is common. This finding underscored the need for therapeutic regimens that prevented, or at least delayed, the development of resistance. In their seminal work, Gulick et al.[49] showed that the combination of zidovudine, lamivudine, and indinavir controlled viral load better than zidovudine-lamivudine combination or indinavir alone. Following this study, the use of a 3-drug combination therapy (usually containing drugs from 2 different drug classes) has been the backbone of HIV therapy. This 3-drug combination therapy generally consists of 2 NRTIs and a third drug from a different class. This third drug can be either a NtRTI, integrase inhibitor, or a protease inhibitor combined with a pharmacokinetic enhancer.[50] Inhibiting the virus at different stages in its life cycle reduces the development of resistance. Additionally, it is suggested that the use of NNRTIs and protease inhibitors leads to unique form of intermolecular cooperativity resulting in greater activity with the multidrug combination.[51] There are currently 6 recommended ARV combinations, viz. dolutegravir/abacavir/lamivudine, dolutegravir/tenofovir disoproxil fumarate (TDF)/emtricitabine, elvitegravir/cobicistat/tenofovir alafenamide fumarate