Ranjita Shegokar
Yashwant Pathak *Editors*

Viral Drug Delivery Systems

Advances in Treatment of Infectious Diseases

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Editors
Ranjita Shegokar
CapnoPharm GmbH
Tübingen, Germany

Yashwant Pathak
Taneja College of Pharmacy
University of South Florida
Tampa, FL, USA

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Preface

The Washington Post of 2016 stirred an intense discussion between the public, scientific communities, and health authorities. How many diseases are precisely known to humankind? At the moment, scientist estimates the presence of more than 10,000 human diseases and only fewer available treatments that too for major diseases[1].

In 2022, the scenario is not far different considering the deliberate speed of academic/industry research, economic up-downs, tougher regulatory policies, complex clinical trial setups, the impact of the Covid-19 pandemic in slowing processes, businesses, and changing world political dynamics and policies. The same question on "availability of effective treatment" is valid now and maybe even for the next 2–3 decades.

Diseases can be genetic or caused by environmental factors (mainly known as infectious diseases). Human infectious diseases are typically classified according to the source of infection as anthroponoses (human–human transmission), zoonoses (animal–human transmission), and sapronoses (abiotic decaying substrate—human). These infectious diseases contribute to the enormous financial burden on the country's economy. By 2001, around 1415 species of organisms had been recorded known to be pathogenic to humans, mainly comprised of bacteria, viruses/prions, fungi, protozoa, and helminths.

This book is a trivial attempt to compile all possible and available information on etiology, pathology, current therapy options available for a wide spectrum of diseases, the role of drug delivery sciences, advances in new techniques, diagnostic tools, and new drug research of various infectious diseases.

Total *four volumes* are compiled to accommodate vast available information.

Volume 1—Malarial drug delivery systems (MDDS)
Volume 2—Tubercular drug delivery systems (TDDS)
Volume 3—Viral drug delivery systems (VDDS)
Volume 4—Infectious disease drug delivery systems (IDDDS)

[1] Are there really 10,000 diseases and just 500 'cures'? – *The Washington Post*. https://www.orpha.net/

Volume 1: MDDS

Malaria is a disease caused by the parasite Plasmodium. The parasite spread to humans through the bites of infected mosquitoes causing high fever, nausea, vomiting, diarrhea, body pain, rapid heart rate, and shaking chills. Each year millions of people get infected by malaria, and many hundred-thousand people die. Some of the most significant risk areas include Sub-Saharan Africa, South and Southeast Asia, Pacific Islands, Central America, and Northern South America. The treatment of malaria mainly comprises the most common antimalarial drugs like chloroquine, primaquine, etc. In the case of drug resistance, artemisinin-based combination therapies (ACTs) are preferred. ACT is an amalgamation of two or more drugs that work against the malaria parasite using a different mechanism of action.

Volume 2: TDDS

Tuberculosis (TB) is a potentially severe infectious disease that affects the lungs and, in some cases, the kidney, spine, and brain. *Mycobacterium* causes tuberculosis via air route. As a result, two TB-related scenarios are possible: latent TB infection (LTBI) and TB disease. If not treated properly, TB disease can be fatal. TB bacteria usually grow in the lungs (pulmonary TB). The typical test used to diagnose TB is the Mantoux tuberculin skin test (TST). The medications used to treat latent TB infection include Isoniazid, Rifapentine, and Rifampin. Classically, the patient may undergo several treatment regimens (1st/2nd /3rd line) recommended as per disease condition and health policy of that specific country. TB treatment can take 4, 6, or 9 months depending on the regimen.

Volume 3: VDDS

Viruses are very tiny infectious germs, which cause infectious diseases such as the common cold, flu, and wart to severe illnesses such as HIV/AIDS, Ebola, and Covid-19 (which caused the recent pandemic where millions of people lost life). They invade living, normal cells and use those cells as host. Depending upon the type of virus, the target body cells are different. Virus infections and diseases are categorized under ten other groups, i.e., contagious, respiratory, gastrointestinal, exanthematous, hepatic, transmission, cutaneous, hemorrhagic, neurologic, and rest of the viruses not in these categories. All viruses have a protein coat and a core of genetic material, either RNA or DNA; unlike bacteria, viruses can't survive without a host. The diagnosis of viral diseases/infections can be performed by viral culture, serological tests, virus antigen detection, and viral nucleic acid or antibody detection. The treatment of viral diseases/infections depends on the type of viral

infection. Antibiotics do not work for viral infections. FDA has already approved several antiviral medicines for the treatment of certain illnesses.

Volume 4: IDDDS

Each infectious disease has its specific signs and symptoms. Diagnosis of infectious diseases needs lab testing. Samples of body fluids, e.g., blood, urine, saliva, etc., can reveal evidence of the particular microbe that is causing the illness. While imaging, scans using X-rays, computerized tomography, and magnetic resonance imaging can help pinpoint disease states. Often, local tissue biopsies provide helpful information on the state of infection and adverse observations of disease (if any). This volume is focused on diagnosis, detection, disease models, the link between two or multiple infectious diseases, and vaccine development for the treatment of infectious diseases

This book series compiles all the new treatment avenues that have been explored to treat malaria, tuberculosis, viral infections, and other infectious diseases like Ebola and hepatitis. This series covers various aspects of drug delivery advances for disease targeting, new drug molecules, analysis of currently ongoing clinical trials, vaccine development, and availability of disease models to evaluate drug performance. Dedicated chapters are included on herbal treatment opportunities for each disease. In addition, readers can refer to information on global disease health scenarios, cellular pathophysiology, and drug resistance, full coverage on polymeric nanoparticles, solid lipid nanoparticles, dendrimers, liposome, and micro/nanoemulsions as drug delivery carriers.

Experts from all over the world have shared their knowledge to generate this one-stop resource. This book series is destined to fill the knowledge gap through information sharing and organized research compilation between the diverse area of pharma, medicine, clinical, chemist, and academics to fulfill following specific objectives:

- To discuss opportunities and challenges in the treatment of infectious diseases
- To enlist current efforts by researchers and experts
- To facilitate the insight and knowledge sharing
- To highlight innovative, cutting-edge micro and nanotechnology research
- To establish collaborations between academic scientists, industrial, and clinical researchers

In summary, we are sure this book series will provide you great insights into drug delivery sciences (conventional, micro-nanomedicines, upcoming drug delivery trends) along with updates on clinical and chemical drug research for the treatment of infectious diseases.

Tübingen, Germany — Ranjita Shegokar
Tampa, FL, USA — Yashwant Pathak

Contents

Global Health and Viral Diseases: Past, Present, and Future

Sarika Chauhan, Surya Sankineni, Ranjita Shegokar, and Yashwant Pathak

Abstract Viral diseases are one of the most common and rapidly contagious ways to impair one's health. Hence, finding new ways to combat the spread and treat the viruses can be beneficial to global health overall. Some of these common and dangerous viral diseases include influenza, HIV/AIDS, HPV, and measles, mumps, and rubella (MMR). Prior to modern medicine, thousands faced death at the hand of these diseases; however, today, we can develop interventions and technology that could save most from their devastating effects. Although most of these diseases are highly preventable either via vaccines or preemptive safe practices, their access globally is highly limited by a nation's finances, resources, and initiatives. In order to accomplish the task of eliminating and reducing the spread of viral diseases, the HPV and MMR vaccines must be widely distributed to target populations, perhaps even made a requirement for school admission. Supplementary immunization activities (SAIs) are also recommended to maintain and enforce immunization strategies. For viruses that result in sexually transmitted diseases (STIs), educational resources as well as screening opportunities are needed to aid in the accurate recording of transmission and to execute preventative measures. Viral diseases prove fatal for many all around the world. By initiating plans for intervention and treatment of viral diseases that affect those around the world, we can significantly improve global health access and quality.

Keywords Viral disease · Influenza · HPV · HIV · Mumps · Rubella · Measles · Global

S. Chauhan · S. Sankineni · Y. Pathak (✉)
Nova Southeastern University, University of South Florida, Tampa, FL, USA

R. Shegokar
CapnoPharm GmbH, Tübingen, Germany

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1 Introduction

Understanding viral diseases, their risk factors, and available treatment options is essential to improving health outcomes at the global level. These infectious agents pose such a threat to human health because they are inert and as such can use the biology of a host cell to replicate nearly indefinitely [1]. Through initiatives like the World Health Organization's (WHO) Global Influenza Programme, Cervical Cancer Elimination Initiative, and UNAIDS, public health officials around the world have come together to address the spread of some of the most common—and most fatal—viral diseases.

2 Types of Viral Diseases

The first of these viral diseases is the influenza virus, which has the ability to infest many vertebrates. In humans, the virus invades the respiratory epithelium. There are four variants of the virus that differ depending on their source and effects: *Influenza A virus* (IAV), *Influenza B virus* (IBV), *Influenza C virus* (ICV), and *Influenza D virus* (IDV). The first three types of the influenza virus are extremely transmissible human respiratory pathogens, which eventually allow the reproduction of the viral genome within the host's nucleus. One of the most severe viruses is HIV, or human immunodeficiency virus, which results in acquired immunodeficiency syndrome (AIDS). It is a sexually transmitted infection (STI), meaning it is transferred perinatally and via bodily fluids. The HIV is a *Lentivirus* of the retrovirus family, meaning that the virus is characterized by long incubation periods and leads to long-term expression. Since the syndrome decreases an individual's immunity drastically, it may render them unable or not as fit to fight other illnesses [2].

Another viral disease that is categorized as a STI is the human papillomavirus, HPV. Like HIV, HPV can be spread via sexual contact even though there may be no symptoms present. HPV is most notable for causing cervical cancer as well as several others [3]. Measles, mumps, and rubella (MMR) can be both prevented via the MMR vaccine; it is often given within the first few years of birth to prevent the spread of the viral diseases. Measles is common throughout the world but highly contained in some countries like the United States with the use of the vaccine. However, global control of the diseases is insufficient as vaccine coverage needs to be more widespread [4]. Rubella and mumps were also a very common viral disease before the introduction of the vaccine. One thing to note for rubella is prevention of contracting congenital rubella during pregnancy as it can result in severe defects. Mumps can seldom but notably result in sterility in older males due to the inflammation it causes on the testes; it also results in the inflammation of the ovaries, pancreas, and spinal cord [5].

3 Viral Diseases Across the World

3.1 Influenza

H1N1, more commonly known as influenza, is classified as an acute respiratory illness and has again and again proven to be in a class of its own in terms of genetic adaptability. Influenza has been a world health concern since the first identifiable description of an outbreak recorded between 1173 and 1174 in Europe [6]. The official discovery of swine influenza virus occurred in 1933 by Dr. Richard Shope of the Rockefeller Institute in Iowa who had been investigating hog cholera [7]. Following his discovery scientists, Wilson Smith, Christopher Andrews, and Patrick Laidlaw followed Shope's isolation methods to isolate this elusive virus in humans. Three of the most impactful influenza pandemics presented themselves in the twentieth century alone, beginning with the Spanish flu (H1N1) in 1918, followed by the Asian flu (H1N2) in 1957 and Hong Kong flu (H3N2) in 1968. The Spanish flu took approximately 675,000 lives in the United States alone and approximately 50 million worldwide. Influenza has yet to halt genetic evolution, exemplified with the emergence of the new extremely transmissible strain of avian flu (H7N9) in 2019 [8]. Nearly every year, new genetic variations of influenza continue to present themselves. Influenza B is generally a less virulent form of virus, while influenza C is even less harmful, resulting in mild illness at its worst [9].

3.1.1 Prevalence Worldwide/Rate of Infection

The 2020–2021 influenza season resulted in approximately 1675 tested cases of influenza recorded in the United States by the Centers for Disease Control and Prevention (CDC) [10]. This rate of prevalence is a historical record low for influenza in the United States and can be largely attributed to the general increase in personal health safety due to the COVID-19 pandemic.

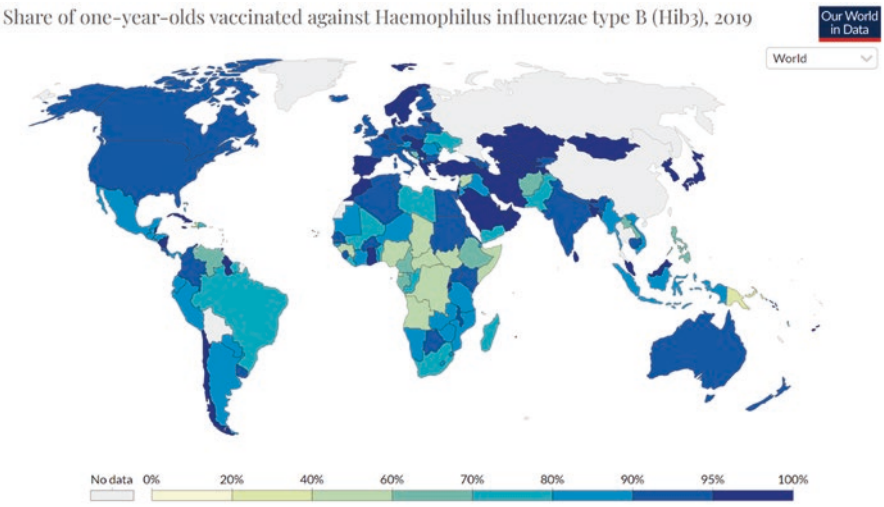
3.1.2 Treatments over Time

Since the isolation of the influenza virus, scientists have been diligently working to uncover various methods of treatment. Historically, herbal medications have recurrently been used to treat infections and flu-like ailments [11]. Maoto, an herbal mixture synthesized from four different plants is used in Japan as a regular method of treatment for standard influenza infection [12]. Alike Maoto, numerous herbal remedies exist for the treatment of influenza; however, one of the more common modern treatments can be found in the form of the neuraminidase inhibitor oseltamivir. Since it received Food and Drug Administration approval in 1999, oseltamivir has been surrounded in controversy with numerous studies pointing out that the risks weigh heavier than the paltry benefits [13]. Even still, oseltamivir was largely

at the forefront of influenza treatment between 1999 and the early twenty-first century. Before oseltamivir, the first neuraminidase inhibitor that was approved for use in the treatment of influenza had been zanamivir [14]. Numerous studies were conducted of the efficacy of zanamivir. An overarching review directed by Professor Carl James Heneghan in 2014 covered a total of 54 clinical trials and concluded that zanamivir is an effective treatment method for adults. However, the results of the review displayed insignificant results in the treatment of influenza for children. The herbal treatment using Maoto was compared to the effectiveness of oseltamivir or zanamivir through random trials in 2012 conducted by Shigeki Nabeshima [12]. These trials resulted in a surprising conclusion showing nearly equal results between both herbal and clinical methods.

3.1.3 Vaccine Landscape

Not only did 2021 record a low in infection rates but also a record high in immunizations. In 2021 alone, the CDC approximately distributed 198 million doses of the influenza vaccine, which was a record high, and as of February 25, 2022, another total of 174 million doses of the flu vaccine have been distributed by the CDC [10]. Currently, the World Health Organization recommends the use of quadrivalent vaccines. The recommendation includes egg-based or cell culture/recombinant-based vaccinations containing H1N1-like viruses, H3N2-like viruses, a Victoria lineage-type virus, and a Yamagata lineage-type virus [15].



Source: World Health Organization (WHO); UNICEF. OurWorldInData.org/vaccination • CC BY. Note: Haemophilus influenza type B is a bacteria responsible for severe pneumonia, meningitis and other invasive diseases almost exclusively in children younger than 5 years

3.2 HIV/AIDS

HIV is a species of immune-attacking retrovirus characterized by long incubation periods in humans and mammals [16]. The virus primarily occurs as two types—HIV-1 and HIV-2—which differ in rates of progression and degrees of transmissibility [16]. Left untreated, however, both subtypes can cause AIDS, a condition marked specifically by a CD4 T lymphocyte count of less than 200 cells/mm^3 [17]. Because CD4 cells are the primary mechanisms behind cell-mediated immunity, a patient whose HIV infection has progressed to the AIDS stage becomes dangerously susceptible to fatal opportunistic infections, certain cancers, and even common diseases that an otherwise healthy individual can fight [18]. Left untreated, a person with HIV usually progresses through three stages: stage 1, acute HIV infection (mild influenza-like symptoms and high rates of transmission); stage 2, chronic HIV infection (asymptomatic for at least a decade until viral load increases and CD4 count decreases beyond repair); and stage 3, AIDS diagnosis [19]. It is critical to diagnose HIV in the early stages, before the viral load further impedes the immune system's ability to produce CD4 cells.

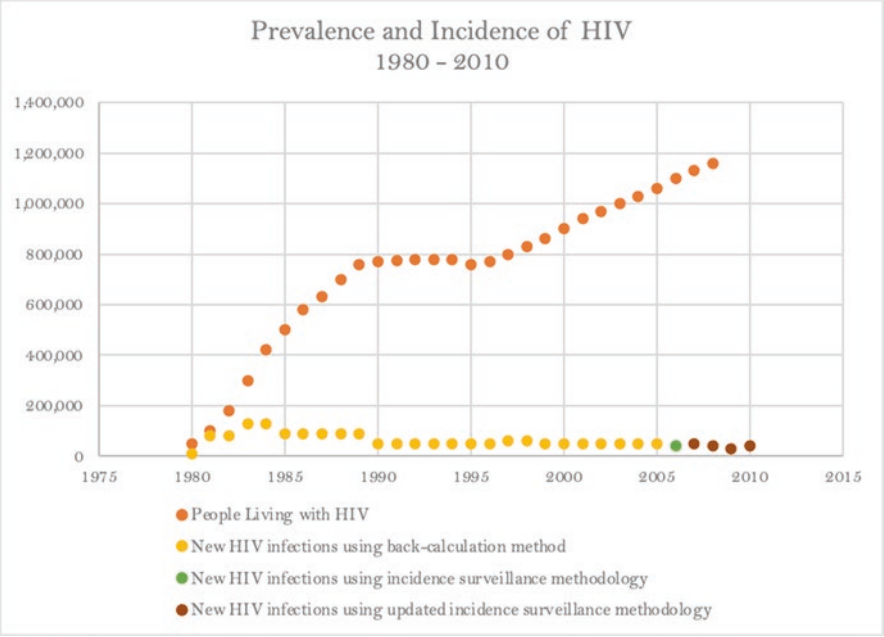
Early diagnosis and thereby efficient treatment of HIV is initially done with the availability of both at-home self-tests and rapid tests that produce same-day results in the lab. Following these tests, confirmatory testing at a healthcare center is necessary. These confirmatory tests measure levels of HIV antibodies in a patient's blood, which typically develop "within 28 days of infection". Due to the severity of this viral disease and its available treatments, the World Health Organization recommends people be retested prior to enrolling in treatment [18].

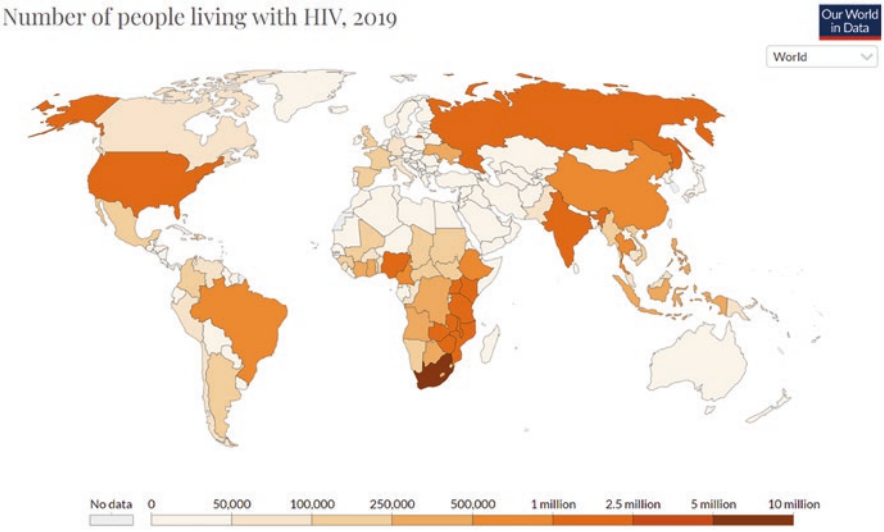
HIV is transmitted through bodily fluids such as blood, semen, and rectal or vaginal fluids. As such, it is most often contracted through unprotected anal or vaginal intercourse and sharing drug injection equipment such as syringes and needles [20]. The virus can also be passed perinatally from mother to baby during birth or breastfeeding [20]. Rarer forms of transmission include biting, oral sex, and transmission through pre-chewed food; usually, these modes involve a cut or abrasion in the mouth through which the virus can enter the bloodstream. Risk factors that increase an individual's likelihood of contracting HIV include having unprotected sex, receiving or performing unsafe injections, sharing contaminated needles, and accidental stick injuries in the healthcare setting [21].

3.2.1 Prevalence Worldwide/Rate of Infection

HIV is a major global health issue, having claimed over 36 million lives since the identification of the first case in 1981. At the end of 2020, there were "an estimated 37.7 million people" living with HIV [18]. Of these, 36 million were adults, and 53% were women and girls [22]; 25.4 million lived in the WHO African Region [18]. Since 2010, incident HIV rates have declined by 31%, thanks to increased access to treatment and educational resources worldwide [22]. In 2020, 1.5 million

people became infected globally, and 680,000 died from AIDS-related complications [23]. This is a marked (52%) decrease in incidence since the peak in 1997, when three million people were diagnosed in that year alone [23]. As the figures below indicate, sub-Saharan Africa is home to just 10% of the world's population but comprises nearly two-thirds of the world's HIV prevalence. In this region, HIV has become a generalized epidemic, meaning that it spreads through the population at large rather than just through at-risk groups such as sex workers and users of injectable drugs [24, 25].





Source: Institute for Health Metrics and Evaluation, Global Burden of Disease (**2019**). OurWorldInData.org/hiv-aids • CC BY

In terms of AIDS, mortality rates have declined by 53% among women and girls [26] and by 41% among men and boys since 2010 [23]. Since the AIDS peak in 2004, mortality has reduced by 64% [23]. Still, the epidemic is not over, and its effects continue to be compounded by the prevalence of other viruses—most recently, COVID-19. Studies from several countries (South Africa, the United Kingdom) have found that the risk of mortality from a COVID-19 infection was doubled in those with HIV/AIDS compared to the general population [23]. Despite this statistic, the regions with highest rates of infection—regions in sub-Saharan Africa, namely, Mozambique and Zimbabwe—have had least access to COVID-19 vaccines [27].

3.2.2 Treatments over Time

Although there is currently no cure for HIV/AIDS, there are effective treatment options that enable patients to live healthy long lives with the virus as a manageable chronic health condition rather than a life-defining fatality. The current treatment regimen for HIV includes "three HIV medications from a minimum of two drug classes" [28]. Different drugs from different classes must be used because the life cycle of the virus is complex and multistage; targeting the virus at each stage of its life cycle thus decreases the likelihood of viral replication throughout the host [29]. This multistage treatment regimen is known as antiretroviral therapy (ART) and must be followed daily for life to be fully effective [30]. Common FDA-approved drug combinations for HIV include two nucleoside reverse transcriptase inhibitors

and one non-nucleoside reverse transcriptase inhibitor, a protease inhibitor (PI), or integrase inhibitor (II) [28].

The first antiretroviral drug to reach FDA approval, in 1987, was zidovudine, a nucleoside reverse transcriptase inhibitor; in 1996, clinical studies found that combining zidovudine with other classes of medicines increased inhibition efficiency [28]. Since then, further research has shown that three-drug ART has led to an approximate 60% to 80% decrease in the rates of AIDs, hospitalization, and death [28]. In the United States specifically, the CDC plans to implement a 90-90-90 plan by 2030, wherein 90% of cases are HIV-diagnosed, 90% are on ART, and 90% have nearly fully suppressed the virus [28].

HIV prevention options have also become widely available. PrEP, or pre-exposure prophylaxis, is a medicine that at-risk individuals can take to prevent getting HIV through unprotected sex or use of contaminated needles [31]. There are currently two approved PrEP medications, Truvada and Descovy, the latter of which is not approved for those assigned female at birth [31]. Daily PrEP use can reduce the risk of sexually contracting HIV by 90% and the risk of contracting HIV through needles by 70% [32].

3.2.3 Vaccine Landscape

Research for an effective HIV vaccine is currently underway and has been for several decades. The difficulty scientists have faced in creating an effective HIV vaccine is the virus' rapid mutation rate and ability to evade the immune response. Yet as of March 2022, the National Institute of Allergy and Infectious Diseases launched a phase I clinical trial examining a potential mRNA vaccine for HIV, citing the effectiveness of the mRNA COVID-19 vaccine as support for the research [33].

3.3 HPV

Human papillomavirus, commonly known as HPV, is a common sexually transmitted disease that is associated with numerous cancers—cervical cancer, head and neck squamous cell carcinoma, and anal cancer [34]. There are over 200 types of the virus that exist. HPV infections can be categorized as low-risk infections and high-risk infections. Low-risk infections consist of causing genital warts, whereas high-risk infections may cause cervical and other types of cancers [35].

The biological structure of papillomaviruses can be described as "small, non-enveloped, epitheliotropic, double-stranded DNA viruses" [36]. Human papillomaviruses result in mucosal and cutaneous epithelial lesions and cancers [37]. Risk factors for HPV include having "multiple sex partners, sex at an early age, a history of sexually transmitted infections, and smoking" [35].

3.3.1 Worldwide Prevalence/Rate of Infection

Worldwide, HPV is found in 11–12% of women without cervical abnormalities [38]. Sub-Saharan Africa had the highest HPV prevalence of 24% [39] in cytologically healthy women. However, the highest prevalence of HPV infection in all women was in Asia; specifically, a large number of Eastern and Central and Southern Asian women were carriers [39]. Additionally, there appears to be a trend of higher HPV infection rates in developing regions rather than in developed regions [39]. In the United States, HPV is considered the "most commonly sexually transmitted infection" and has been associated with increased risk of cervical cancer and genital warts [40]. Adolescent girls and women under 25 are the most infected with HPV [39]. There is a peak prevalence of HPV in women around their early 20s [35]. Up to 79% of sexually active women are likely to acquire an HPV infection at some point during their lifetime [35]. On the other hand, genital warts is only prevalent in about 1% of sexually active Americans [37].

With more than 100 types of HPV strains, the HPV infection is categorized based as non-genital, mucosal or anogenital, and epidermodysplasia verruciformis [37]. Of these strains, HPV 6 and 11 are responsible for "approximately 90% of" genital warts, and HPV 16 and 18 are associated with "approximately 70% of cervical cancers" [40]. HPV 16 and 18 are considered the most prevalent strains of HPV [38]. HPV is transmitted when in contact with infected genital skin or mucosa [35]. Other possible routes of infection are orally or perinatally. While oral infection of HPV is possible, there is a low risk of transmission [35]. Similarly, perinatal transmission of HPV is rare [35].

3.3.2 Treatments over Time

Preventative care for HPV infection consists of two FDA-approved HPV vaccines. Gardasil is the quadrivalent recombinant HPV vaccine that was approved in 2006 and protects girls and women from ages 9 to 26 from HPV types 6, 11, 16, and 18 [35]. The second vaccine, Cervarix, was approved for girls and women from ages 10 to 25 and protects against HPV types 16 and 18 [35].

3.4 MMR

MMR, also known as measles, mumps, and rubella, are a group of single-stranded RNA viruses. Measles and mumps are negative sense paramyxoviruses, and rubella is a positive sense togavirus. This group of viruses has high transmissibility, with measles having a R0 of 12–18. This R0, also known as basic reproductive number, means that during the course of an infection, a person is likely to spread measles to 12–18 others. These specific viruses have had a spotlight in the public eye as of late, due to a now-defunct study linking the vaccine to autism. This negative press has

resulted in many choosing to not vaccinate their children, thus leading to outbreaks [41].

Measles virus, also known as *morbillivirus*, replicates in the cytoplasm of host cells and is spread primarily through respiratory droplets. It is known for its viral prodrome of cough, coryza, conjunctivitis, and Koplik spots, as well as its characteristic cephalocaudal spreading maculopapular rash. Virulence factors include hemagglutinin and fusion protein, which aid in infectivity. Finally, measles has late-stage complications such as pneumonia and subacute sclerosing panencephalitis [42]. Mumps virus also replicates in the cytoplasm of host cells. It has the virulence factors of hemagglutinin, fusion protein, and neuraminidase. Mumps infection can be hinted at on physical exam because of its characteristic reproduction within salivary glands. It is known to also cause orchitis in males, which can lead to infertility. An additional known complication of mumps is meningitis [43].

Rubella, also known as German measles, can sometimes be mistaken for measles because of its maculopapular rash's similar cephalocaudal spread [44]. It is generally a disease of childhood and has different symptoms depending on the type of infection, congenital or acquired. Congenital rubella crosses the placenta and causes a myriad of symptoms. The most common presentation for congenital rubella is the triad of congenital cataracts, sensorineural deafness, and patent ductus arteriosus. Additional signs of congenital rubella are the "blueberry muffin rash," jaundice, microcephaly, and pulmonic stenosis [45]. Acquired childhood rubella signs include the cephalocaudal rash and posterior auricular and occipital lymphadenopathy. Rubella has been linked with arthritis. Rubella is also spread primarily through respiratory droplets.

3.4.1 Worldwide Prevalence/Rate of Infection

Measles is an extremely contagious disease and thus can have high rates of spread. It is estimated that there is a 90% chance of infection, if exposed to the virus [46]. Despite the high levels of contagion, the prevalence remains low due to the existence of MMR vaccine. The highest rates for measles can be seen in Africa and India; however, there are also large rates in Brazil. In 2019, there were an estimated 11,371 confirmed measles cases in Brazil. The primary age group that was affected by measles was from ages 15 to 29, which comprised 45% of the cases in Brazil. Somali was reported as having the greatest number of cases, nearing around 6000 cases as of 2022.

Mumps also has a high rate of transfer and is generally caused by the paramyxovirus. Since the introduction of the mumps vaccine, the rates dropped; however, recently, there has been a surge in the number of outbreaks and cases. The country most afflicted is China. The number of cases in China has reached around 130,000 by 2020 and has been increasingly seen in vaccinated patients. The number of cases of mumps in the United States has dropped greatly from 150,000 in 1967 to 2251 cases in 2018 (Lau, Roger, and Michael Turner) [47].

Rubella is an acute contagious disease that previously had a high prevalence but decreased by more than 95% from the vaccine. India has only recently seen a decline in the prevalence due to only launching the vaccine in 2017 [48]. Despite the introduction of the vaccine, there are still thousands of cases in India. Globally, however, the rates are extremely low, and it is only found in around 14 countries.

3.4.2 Treatments over Time

Measles virus, as it is known today, was first documented in the ninth century by a Persian doctor named Rhazes. Measles treatment has had some changes over the course of time, but much of its treatment remains the same. Historically, measles was treated supportively with antipyretics and hydration [49]. Today, treatment for measles is still largely supportive. Aimed at reducing complications, measles treatment largely consists of supportive fluids and analgesia. However, studies have demonstrated efficacy in vitamin A treatment. Vitamin A reduces mortality in measles patients less than 2 years old. This has now become a standard of care in this group. Vitamin A is efficacious due to its function as an immunomodulator, which increases antibody response against the virus. Post-exposure prophylaxis includes one dose of the MMR vaccine and immunoglobulin if the exposure was within 72 hours [50].

Mumps and rubella currently do not have any specific medications or drugs that can be taken as treatment; however, there are practices that can reduce the symptoms. Most symptoms should go away after 1–2 weeks, especially through the addition of hydration of fluids. There are some drugs, such as acetaminophen or ibuprofen, that can be taken to alleviate fever symptoms. Decreasing inflammation of the glands can be alleviated by utilizing heating or ice packs on the areas of inflammation [51].

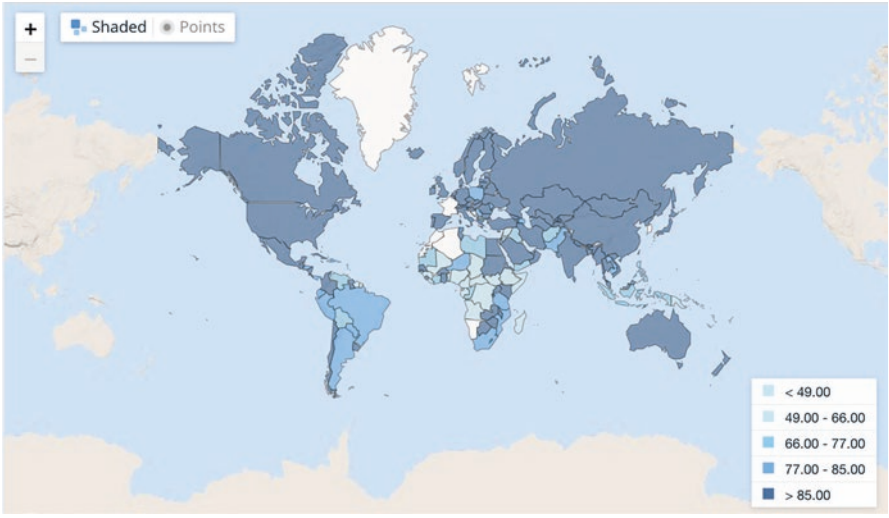
3.4.3 Vaccine Landscape

Measles, mumps, and rubella vaccine is given in two doses. The first is given to children at 12–15 months of age, and the second is given from 4 to 6 years of age. The vaccine itself contains strains from each of the three viruses and has an extremely high efficacy rate, above 95%. The vaccine is slightly less effective for mumps but still results in an efficacy rate above 85%. Measles is currently labeled as eliminated in the United States due to the vaccine in 2016. However, low-income countries still have these diseases due to the lack of distribution of the vaccine. There have been speculations about autism being linked to the MMR vaccine; however, there is no evidence that can support this (Table 1).

Table 1 Viral diseases with their year of emergence and whether they have a treatment or vaccine available for use

Viral disease	Year emerged	Treatment available	Vaccine available
Chickenpox [52]	1691	Yes	Yes
Flu (influenza) [53]	1918	Yes	Yes
Herpes [54]	1.6 million years ago	Yes	No
HIV/AIDS [55]	1981	Yes	No
HPV [56]	500,000 years ago	No[a]	Yes
Infectious mononucleosis [57]	1880s	No	No
MMR [58]	Ninth century	No	Yes
Shingles [59]	1888[b]	Yes	Yes
Viral gastroenteritis (stomach flu) [60]	1972	Yes	Yes
Viral hepatitis [61]	100,000 years ago[c]	Yes	Yes
Viral meningitis [62]	1805	Yes	No
Viral pneumonia [63, 64]	1938[d]	No[e]	Yes

[a]Associated genital warts can be treated
[b]Although not distinguishable from smallpox, the emergence dates back to the fifteenth century
[c]HBV specifically has been estimated to originate between 3000 and 100,000 years ago
[d]Viral pneumonia has been common throughout human history along with most of the diseases in the table
[e]Most viruses responsible for pneumonia are not treatable (they resolve on their own), but there are some exceptions



"Immunization, Measles (% of Children Ages 12–23 Months)." *The World Bank*, https://data.worldbank.org/indicator/SH.IMM.MEAS?end=2020&start=1980&view=chart

4 Conclusion

Global initiatives taken by organizations like the UNICEF and the World Health Organization have not been effectively implemented in several countries due to the dearth of the country's ownership and limited will, which is seen by their insufficient resources [65]. For the effect expansion of MMR treatment, there needs to be greater political support as well as a dependency on supplementary immunization activities (SIAs). A measles eradication plan should include the assurance of two measles-containing vaccine doses along with the SIAs. Using the MMR vaccine as a school entry requirement could also contribute to increasing the immunity withing target populations. Accurate reporting of cases on at least a weekly basis in affected countries could indicate areas that are spiking and need immediate containment or intervention. The strengthening of global immunization programs is crucial to achieving the eradication goals for measles, mumps, and rubella.

For all the aforementioned viral diseases including HPV and HIV, there must be adequate human, financial, and technical resources to investigate outbreaks and their causes. Since HPV presents major concerns for cervical cancer, routine screening for women with HPV must also be taken into consideration in target countries along with preventative transmission efforts (HPV vaccine) [41]. For both HPV and HIV, a national push toward breaking the stigma on STIs as well as providing educational programs in schools would prove beneficial as more people can recognize the symptoms and speak on the subject. Affordable STI screenings for those that are sexually active should also be highlighted as a global effort to further bring light to the diseases (and those affected) and help eliminate its transmission. There are affordable ways to prevent these viral diseases; however, they must be implemented and initiated at a global, national, and regional level in order to decrease or eliminate transmission.

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Drug Resistance in Antiviral Therapy

Seth Kwabena Amponsah and Benjamin Tagoe

Abstract Drug resistance in antiviral therapy is a major public health challenge. This resistance can occur among immunocompromised patients where persistent viral replication and protracted drug exposure result in selection of resistant strains. Consequences of drug resistance range from toxicity inherent in the use of second-line antiviral agents, severe disease, and even death (from progressive viral infection when no effective alternative treatment is available). Although scientific technology has identified a number of these proximal mechanisms of antiviral resistance, bigger evolutionary trends of the viruses remain obscure. New metrics for evaluating mutations, recombination rates, demographic histories of transmission, and selective forces during viral adaptation to antiviral drug treatment have been developed. Understanding levels of resistance and cross-resistance conferred by diverse mutations is required for accurate interpretation of genotypic assays. Identification of viral resistance to drug therapy is possible by linking distinctive viral alterations (phenotypic resistance) to a number of antiviral drugs. To reduce antiviral resistance, there is the need to optimize drug administration, select alternate therapy based on knowledge of resistance mechanisms, and develop novel antivirals. Experimental drugs with various viral targets are being investigated, and these agents may offer better treatment options. In this chapter, we delve into the mechanisms of viral resistance, manifestation of antiviral resistance, detection of antiviral resistance, and clinical implications of drug resistance in viruses.

Keywords DNA polymerase · Famciclovir · Hepatitis B virus · Lamivudine · Resistance · Varicella-zoster virus

S. K. Amponsah (✉)
Department of Medical Pharmacology, University of Ghana Medical School, Accra, Ghana

B. Tagoe
Fulfilment Operations and Academy, Zipline Ghana, Accra, Ghana

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1 Resistance as an Evolutionary Process

Just like most cell-based organisms, viruses undergo evolution and natural selection. Currently, monitoring of viral evolutionary processes has become more streamlined due to availability of molecular data on strength of selection and nucleotide diversity [1, 2].

Over the last few decades, drugs that target mechanisms of viral replication have been widely used to treat viral infections. Generally, viral genomes are not likely to replicate if treatment is robust [3]. A less effective therapeutic regimen may result in successful replication of some viral genomes, which may ultimately lead to rapid adaptation towards resistance. Resistance to antiviral drugs is further worsened by high rates of mutations within viruses. Pharmaceutical companies and research laboratories have been forced to remain innovative in the process of drug discovery and development.

2 Clinical Definition of Antiviral Drug Resistance

Antiviral drug resistance occurs when viruses become less susceptibility to antiviral agents. This is usually confirmed by in vitro testing, with confirmation via genetic and biochemical analysis. In chronic hepatitis B, for example, definitions for first-line (main) and secondary antiviral drug failure exist [4]. First-line antiviral failure (sometimes referred to as non-responsiveness) occurs when there is the inability of an antiviral drug to decrease hepatitis B virus (HBV) deoxyribonucleic acid (DNA) viral load beyond 1.0 $\log_{10}$ IU/ml within the first 3 months of treatment. This is frequently caused by problems with efficacy of pharmacological or antiviral agents [5]. Second-line antiviral treatment failure occurs when there is an increase in viral load from nadir of at least 1.0 $\log_{10}$ IU/ml following two blood samples that are taken within 1 month. There is the possibility that patients who show efficacy to antiviral therapy may experience this second-line antiviral treatment failure sometime later. It is, thus, recommended that viral load is estimated at the beginning of therapy. In order to identify viral rebounds that may occur with antiviral resistance, an assay that is specific and sensitive (1000 IU/ml) to HBV DNA viral load is recommended. A recent international summit recommended that HBV DNA viral load testing be undertaken every 2–3 months, if health resources permit [4]. Patients on antiviral drugs should be monitored on a regular basis. This is especially important in individuals with advanced disease, since it is necessary to maintain viral suppression for an extended period.

This book chapter seeks to discuss variations in antiviral resistance mechanisms, resistance to common antiviral drugs, and identification of resistance. Additionally, information on infections caused by hepatitis B and C viruses, herpesvirus, human cytomegalovirus, varicella-zoster virus, and human immunodeficiency virus is reviewed.

3 Antiviral Drug Resistance

3.1 Variation in Viral Resistance Mechanisms

Due to differences in replication among viruses, development of antiviral drugs in modern times has primarily focused on targeting different stages of viral life cycle. This approach is relevant in reducing evolution of viruses toward resistance. Understanding the different mechanisms of viral resistance is key in antiviral drug development.

The mutation rate of hepatitis C virus (HCV) is relatively high, and this is further aided by repeated replication and poor censoring of encoded ribonucleic acid (RNA) polymerase [6]. Replication of HCV is close to the allowed maximum error rate before the loss of genomic integrity. Antiviral drugs that inhibit activity of protease or polymerase are usually used to treat HCV infections. A few mutations in HCV genome could result in resistance toward protease or polymerase inhibitors. It is likely resistant strains of HCV already exist in the population, considering its high mutation rate. Regardless, the HCV appears to be susceptible to new antiviral drug combinations such as ledipasvir and sofosbuvir. Research has shown that there is little to no cross-resistance between the two drugs; hence, these two agents could have promise in the future [7].

Herpesvirus (HSV) is known to have low diversity, partly due to its low rate of recombination [8]. HSV may occasionally have latent periods and also viral shedding while preserving its transmissibility even in asymptomatic individuals. Nucleoside inhibitors such as acyclovir are commonly used to manage HSV infections in immunocompromised patients. Therapy with acyclovir for systemic viral infections either target DNA polymerase or a thymidine kinase required for prodrug activation [9]. Infections caused by human cytomegalovirus (HCMV), which are HSV, could start in saliva (occupying a one compartment) before moving to other compartments. HCMV infections are generally asymptomatic; however, there is cause for concern among congenitally infected infants and immunocompromised hosts. Differentiation persists after compartmentalization to the point where viruses found in different compartments within a host may be very diverse [10].

The HCMV has polymorphism levels comparable to RNA viruses, despite the fact that usually DNA polymerases have high fidelity compared to RNA polymerases [11, 12]. Positive selection signatures can be found in a low percent (5%) of open reading frames of HCMV. Due to the fact that envelopes of HCMV assist to escape host immune defense, loci that are associated with envelope proteins appear to have elevated ratio of non-synonymous to synonymous substitutions (dN/dS). However, loci associated with replicative proteins are usually conserved. During treatment of HCMV infections, antivirals that act as nucleoside analogs, such as ganciclovir and cidofovir, are usually used. Resistance can occur in the viral kinase that is needed for the phosphorylation of prodrugs [13].

Neuraminidase (NA) and hemagglutinin (HA) are the virion-surface proteins found in *Influenza A virus* (IAV). These virion-surface proteins are encoded in the

short genome of IAV. In IAV, HA and NA are used to bind and detach from the cell membrane of a host. The dN/dS ratio of HA and NA are substantially larger than those of the other viral proteins because they are surface antigens under diversifying selection [14, 15]. NA inhibitors, which have the tendency to disrupt viral envelope detachment from host cell membrane, are the most utilized antivirals in the treatment of IAV. IAV that have H274Y NA enzymes are known to be resistant to oseltamivir [16, 17]. It is possible that the difficulty of administering zanamivir, another NA inhibitor, has led to relatively few resistant viral strains [18]. As a recently synthesized antiviral agent, favipiravir is expected to induce mutagenesis in the IAV genome. So far, there has been little to no reports of viral resistance to favipiravir [19, 20].

Human immunodeficiency virus (HIV) is a retrovirus with an RNA genome. Once HIV infects a host, there is duplication of genome by reverse transcription that leads to the formation of a double-stranded DNA. This DNA is inserted into genome of the host and then reverted to RNA. During drug treatment, the process of reverse transcription is highly error-prone, and this can lead to a number of mutations and increased population diversity [21]. In fact, it is expected that at the start of pharmacotherapy, there exist mutations in the genome of HIV that are present in at least one infected cell [22, 23]. Multi-drug regimen is the most appropriate approach in HIV treatment today, where antivirals from varied classes, and without known cross-resistance mutations, are used [24]. A regimen like this decreases the likelihood for resistance to occur. Combinations with the various antiretroviral agents (integrase strand transfer inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, etc.) are recommended.

HBV is a DNA virus and replicates (by transcription) into intermediates of RNA. HBV then undergoes reverse transcription back to DNA. HBV is assumed to live as a quasi-species despite its DNA genome. In HBV, there is high level of population variation, which occurs due to lack of proofreading during the process of reverse transcription. Hence, there is often HBV with mutations that can lead to resistance to antiviral therapy [25, 26]. Lamivudine, a reverse transcriptase inhibitor, is typically used to treat HBV infections. However, a number of lamivudine-resistant HBV have been identified, often with low genetic barriers. As a result of the aforementioned, an additional reverse transcriptase inhibitor is frequently added [26]. Care must be taken when drug switching is done, especially if it is within same drug class because there is the likelihood of HBV-resistant mutations occurring. Although a few clinical trials have combination therapy in the treatment of HBV infections, this is often not the standard treatment [4, 26, 27].

3.2 Resistance to Common Antiviral Agents

Most drugs currently indicated for HSV infection treatment inhibit DNA polymerase in the virus. Nucleoside analogs such as ganciclovir and acyclovir are usually used to treat infections caused by HSV. Despite possessing weak activity against HCMV, famciclovir, valacyclovir, and acyclovir are used to manage other viral

Table 1 Mechanism of viral resistance to widely used drugs

Antiviral agent	Resistance mechanism	References
Cidofovir	Altered DNA polymerase	[33]
Famciclovir	Altered DNA polymerase or viral thymidine kinase	[34]
Acyclovir	Altered DNA polymerase or deficient viral thymidine kinase	[34]
Valacyclovir	Altered DNA polymerase or deficient viral thymidine kinase	[34]
Ganciclovir	Diminished drug phosphorylation or altered DNA polymerase	[33]
Vidarabine	Altered DNA polymerase	[35]
Foscarnet	Altered DNA polymerase	[33]
Zidovudine	Altered viral reverse transcriptase	[34]
Lamivudine	Altered viral reverse transcriptase	[36]
Didanosine	Altered viral reverse transcriptase	[36]
Indinavir	Altered viral protease	[36]
Nevirapine	Altered viral reverse transcriptase	[34]
Ritonavir	Altered viral protease	[36]
Saquinavir	Altered viral protease	[36]

infections such as varicella-zoster virus (VZV) infections. Other drugs like valganciclovir and ganciclovir are approved for HCMV infection. These drugs also possess in vitro activity against VZV and HSV [28–30]. The metabolism of acyclovir involves phosphorylation by viral thymidine kinase and subsequent conversion by host kinases to acyclovir triphosphate, which is the active form of the drug. Acyclovir triphosphate then inhibits viral (HSV and VZV) replication by chain termination. Ganciclovir is phosphorylated only once by viral kinases, and this makes the drug active against viruses [13, 28, 31].

Forscanet, a pyrophosphate analog, selectively binds to DNA polymerase of viruses. Eventually, DNA chain elongation is inhibited. Cidofovir, a nucleotide analog, requires phosphorylation by cellular enzymes. The activated form of cidofovir inhibits DNA polymerase of viruses. Second- and third-line HSV antiviral drugs, foscarnet and cidofovir, can be used when there is dose-limiting toxicities or suspected resistance to first-line drugs [32]. A summary of resistance mechanisms to the aforementioned antiviral drugs is outlined in Table 1.

4 Identification of Antiviral Drug Resistance

In order to discover drug resistance in viruses, mutations in their genome must be detected. These mutations should be validated via in vitro phenotypic assays, as being specifically related to drug resistance. A number of assays available in identifying resistance mutations include real-time polymerase chain reaction (PCR),