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Antiviral options for biodefense

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A key to biodefense strategies is an assessment of current therapies available as well as the expedited development of new antiviral therapeutic options. Viruses make up the majority of the National Institute of Allergy and Infectious Diseases (NIAID) Category A Priority Pathogens, agents that are considered to pose the greatest risk to public health and national security, and yet there are currently no approved treatments for most of these viral biodefense threats. A review of the Category A viral biothreat agents and strategies for the development of new therapeutics are presented here.

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Introduction

Throughout history, microorganisms have been used as agents of biowarfare. Well-known examples include catapulting plague-infested rats into cities under siege during the Middle Ages and the distribution of smallpox-contaminated blankets to the Native Americans by the British in the 1800s. Whereas traditionally, biowarfare was conducted between armies or populations, the unfortunate anthrax attack of 2001 in the U.S. made it clear that an individual or group of individuals could use pathogenic microorganisms to create terror (bioterrorism) in a target population. In many respects, bioterrorism represents a more serious threat than chemical or nuclear weapons, where the affected population is localized. In contrast, microorganisms can replicate and spread, potentially turning a focal attack into a global pandemic in the absence of effective containment strategies. Although there are a number of types of pathogenic microorganisms (bacteria, fungi, viruses) that might be (mis)used in this manner, viruses represent perhaps the greatest danger due to their diversity and the lack of available countermeasures.

Viral biothreat scenarios

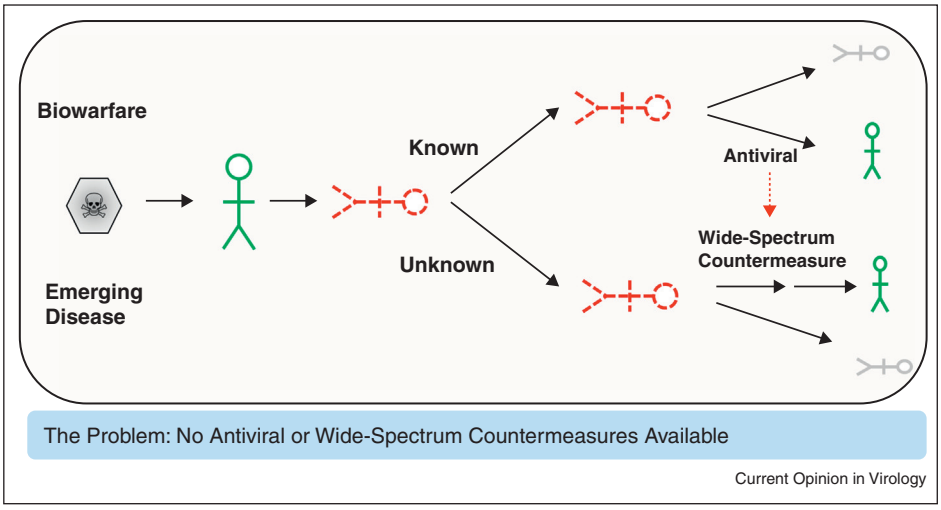
As shown in Figure 1, regardless of the source of a viral biothreat, when encountered by a susceptible individual, it will likely cause illness. If this is a known agent and an effective treatment is available, it can be deployed and hopefully effect a positive outcome. In the event that it is an unknown agent, broad-spectrum countermeasures that stimulate the host innate immune system to confer some level of resistance could be employed to provide time for appropriate diagnostic assays to be performed. In the event the agent is identified and specific antivirals are available, they can now be deployed. If there are no specific antivirals available, the hope is that infection can be held in check long enough for the host's acquired immune system to be activated and eradicate the infection. While this is a plausible defense scenario there are a couple of limitations. First, viral diagnostic assays for many viral biothreat agents are still in development. Second, for most of the viral biothreat agents there are no approved antivirals or broad-spectrum countermeasures available.

Antiviral development challenges

Severe viral infections that can be easily transmitted or disseminated are considered biothreat agents due to their ability to cause high morbidity and mortality as well as social disruption. There are many challenges in the development of antiviral therapeutics for these agents. Many of these viral infections are most prevalent in developing regions and pose a huge unmet medical need, yet there is very little financial incentive for development of effective countermeasures. The estimated cost to develop a drug from discovery to approval is $1.2 billion [1], making drugs without an established market less appealing to develop. In addition, many of the diseases caused by biothreat agents are rare and sporadic, making clinical evaluation of potential therapeutics complicated. In cases where clinical efficacy studies in humans may not be ethical or possible the Food and Drug Administration (FDA) has allowed animal efficacy data along with human safety data to be used to support drug approval; however, finding animal models that recapitulate human disease can be challenging. For many of these diseases, the host response to infection can contribute to the disease pathology, suggesting that effective treatment may require targeting both viral and host factors. Finally, conducting research with the most dangerous viruses requires high-level biocontainment facilities with extremely limited access. Despite these many challenges, there has been significant recent progress in the development of antiviral options for biodefense pathogens.

Viral biothreat agents have been classified by the National Institute of Allergy and Infectious Diseases

Figure 1



Viral biothreat scenarios.

(NIAID) into Category A (most dangerous), B and C (Figure 2).

Category A viral pathogens

The NIAID Category A viral pathogens are those that are considered to pose the greatest risk to both national security and public health and include poxviruses and hemorrhagic fever viruses (HFV). Below, the state of antiviral development for each agent is summarized (Table 1).

Smallpox antiviral development. Variola virus, the causative agent of smallpox, is considered to be one of the most severe biothreat agents. Although smallpox was declared eradicated in 1980 by the World Health Organization, stocks of the virus have remained in several repositories, and there is concern that the virus or an engineered poxvirus could be used as a bioterrorist weapon. In addition there are several poxviruses that cause natural infection, such as monkeypox and cowpox, for which no approved treatment currently exists. ST-246 (Arestvyr^{TM}) is a small synthetic antiviral compound being developed to treat pathogenic orthopoxvirus infections of humans [2,3•]. The antiviral activity is orthopoxvirus-specific and targets p37, a viral protein highly conserved amongst all the orthopoxvirus pathogens that is required for envelopment and secretion of extracellular forms of virus [4,5]. The compound is orally bioavailable and protects multiple animal species from lethal orthopoxvirus challenge [6–10]. Human clinical trials have shown that ST-246 is safe and well-tolerated in healthy human volunteers [11–14]. SIGA Technologies recently made its first delivery of finished product (ST-246) into the Strategic National Stockpile.

CMX-001, the dexadecyloxypropyl ester of cidofovir, is another candidate drug in development for use against double-stranded DNA viruses, including poxviruses. Cidofovir inhibits the viral DNA polymerases. ST-246 and CMX-001 act synergistically when used in combination [15]. These compounds have shown promise in the treatment of eczema vaccinatum and progressive vaccinia as a consequence of smallpox vaccination complications [16,17••,18,19].

HFV. The HFV are actually a diverse group made up of four different virus families (Arenaviruses, Bunyaviruses, Filoviruses, and Flaviviruses). Within a single virus family there can be multiple Category A agents (e.g. Arenaviruses have Lassa, Junin, Machupo, Sabia, and Guanarito). There are currently no approved antiviral drugs or vaccines available for treatment or prevention of HFV infection.

Arenaviruses are RNA viruses associated with rodents that are divided into two groups: Old World (including the Category A agents Lassa and lymphocytic choriomeningitis virus (LCMV)) and New World viruses (including Junin, Guanarito, and Machupo) and cause a range of diseases. Ribavirin has been used for treatment of Lassa fever and has been shown to reduce fatality if administered early [20]. Several broad-spectrum arenavirus inhibitors with efficacy in animal models have recently been described, including ST-193, a viral entry inhibitor with efficacy in a guinea pig model [21–23], peptide-conjugated phosphorodiamidate morpholino oligomers (PMO) with activity in a mouse model [24], and T-705, 6-fluoro-3-hydroxy-2-pyrazinecarboxamide, with activity in hamsters [25].