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Pre-exposure prophylaxis of non-HIV viral infections and the role of long-acting antivirals

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Abstract

Viruses cause a large burden of human infectious diseases. During the past 50 years, antivirals have been developed to treat many pathogenic viruses, including herpesviruses, retroviruses, hepatitis viruses, and influenza. Besides being used as treatment, antivirals have shown efficacy for preventing certain viral infections. Following the success in the HIV field, a renewed interest has emerged on the use of antivirals as prophylaxis for other viruses. The development of formulations with extended half-life has pushed further this consideration in persons at risk for a wide range of viral infections. In this way, long-acting antivirals might behave as "chemovaccines" when classical vaccines do not exist, cannot be recommended, immune responses are suboptimal, escape mutants emerge, and/or immunity wanes. Five main caveats would temper its use, namely, selection of drug resistance, drug interactions, short- and long-term side effects, potential teratogenicity in women of child-bearing age, and high cost. Herein, we discuss the prospects for long-acting antivirals as prophylaxis of human viral infections other than HIV.

Keywords

Antiviral therapy. Prophylaxis. Pre-exposure prophylaxis. Pre-emptive therapy. Hepatitis B. Human T-cell lymphotropic virus type 1. Cytomegalovirus. Hepatitis C. SARS-CoV-2.

Introduction

The battle against human viral infections has historically relied on two medical strategies, namely, vaccines to protect from contagion and antivirals to treat infected individuals. Antivirals have generally been used in patients with ongoing viral infections, in an attempt to ameliorate clinical symptoms and when possible eradicate the virus[1]. However, when long-term antiviral therapy is required, as in HIV or chronic hepatitis B, keeping good daily drug adherence becomes an important challenge, as patients frequently forget to take medications. In this regard, drugs that only need to be given monthly or interspersing longer intervals have become very appealing for treating chronic infections. In this regard, the recent experience switching HIV-infected patients to long-acting antiretrovirals is reassuring, although some logistics need to be fixed[2].

In the absence of vaccines, antivirals have occasionally been used as peri-exposure prophylaxis, being prescribed either before (pre-exposure prophylaxis [PrEP]), or right after (post-exposure prophylaxis [PEP]) any potential viral

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exposure. In an unprecedented way, the use of chemoprophylaxis has been fueled in the HIV field to protect from contagion[3]. Two major reasons account for this enthusiasm. First, despite huge efforts, protective HIV vaccines have remained elusive to date. Second, long-acting formulations of antiretrovirals have shown high efficacy, protecting uninfected individuals with high-risk behaviors[4-7]. In this regard, intramuscular or subcutaneous shots of long-acting antiretrovirals given a few times per year or even once yearly might work as "chemovaccines"[8-11].

Can we envision such approach to protect humans from other viral infections? The advent of such "chemical vaccines" would fill an immediate need in certain scenarios, such as providing protection when classical vaccines do not exist, cannot be recommended, immune responses are suboptimal, escape mutants emerge, and/or immunity wanes (Table 1)[12].

The advantages of long-acting formulations of antivirals can be considered in four major clinical scenarios (Table 2). First, prevention of primary viral infections (i.e., HIV, hepatitis B virus [HBV], or human T-cell lymphotropic virus type 1 [HTLV-1]). Second, halt viral re-infections (i.e., hepatitis C virus [HCV]). Third, minimize viral reactivations using pre-emptive therapy (i.e., cytomegalovirus [CMV] or HBV). Finally, keep viral suppression in long-term treated patients favoring drug adherence and halting transmissions (i.e., HIV or HBV). In this review, we will focus on the opportunities for using long-acting antivirals as prevention of primary infections or reinfections for a wide range of human viruses. Given the unique differential features of monoclonal antibodies, they are excluded from this discussion.

Table 1. When antivirals may replace vaccines to prevent viral infections

- No vaccines available for certain infections (i.e., HIV, HCV, and HTLV)
- Vaccines not recommended in a subset of individuals (i.e., attenuated live vaccines in immunosuppressed patients, allergic, etc.)
- Frequent suboptimal response to vaccines (i.e., HBV in immunosuppressed individuals)
- Emergence of vaccine escape mutant viruses (i.e., HBV and SARS-CoV-2)
- Waning of vaccine protection (i.e., SARS-CoV-2 and HBV)

HBV: hepatitis B virus; HTLV: human T-cell lymphotropic virus.

Table 2. Clinical scenarios for long-acting antivirals

- Prevention of primary viral infections
  - HIV
  - Hepatitis B (and D)
  - Hepatitis C
  - Monkeypox
  - HTLV-1
  - Cytomegalovirus
- Prevention of viral re-infections
  - Hepatitis C
  - Influenza
  - SARS-CoV-2
- Prevention of viral reactivations
  - Hepatitis B
  - Cytomegalovirus
  - Herpes simplex
  - Varicela zoster
- Long-term treatment of infected persons
  - HIV
  - Hepatitis B

HBV: hepatitis B virus; HTLV: human T-cell lymphotropic virus.

Hepatitis B

Roughly, 2 billion people have been exposed to HBV worldwide. Estimates for chronic hepatitis B patients are of roughly 300 million people[13]. The number of global deaths caused each year by HBV due to decompensated cirrhosis or liver cancer exceeds 800,000[14]. These high numbers are paradoxical considering that an effective protective HBV vaccine exists for more than 40 years. However, global HBV vaccine coverage is largely suboptimal[15] and HBV immunity waning might be more common than expected[16].

Antiviral agents to treat HBV have been available for decades. Although viral suppression is achieved in most hepatitis B patients treated with either tenofovir or entecavir, HBV is not eradicated from carriers, and therefore, oral treatment needs to be lifelong. Patients with chronic hepatitis B under long-term tenofovir experience a reduced risk of liver disease progression and, in less extent, of hepatocellular carcinoma[17]. In addition, viral suppression is associated to halted HBV transmission, a benefit known as "*treatment as prevention*"[3], given that undetectable viremia translates into lack of contagiousness. This phenomemon was firstly described in the HIV field using antiretrovirals.

A protective effect of tenofovir on HBV acquisition was originally reported in studies conducted in HIV-infected patients on antiretroviral therapy[18]. Sexually active men having sex with men (MSM) that received tenofovir as part of their antiretroviral regimen had a lower chance of HBV acquisition than those that did not receive the drug[19,20]. More recently, this protective effect was also confirmed in HIV-uninfected persons at risk undergoing HIV PrEP with tenofovir. Based on these findings, the recent increasing trend in HIV therapeutics for using mono or dual regimens sparing tenofovir is worrisome[21]. It could be associated with a rebound of incident HBV infections.

For all these considerations, the use of tenofovir as HBV chemoprophylaxis might be considered in certain populations to avert breakthrough hepatitis B infections. This could be the case of immunodeficient individuals engaged in high-risk behaviors, including injection drug users (IDUs) that share needles, MSM, and other persons with multiple sex partners. Although HBV vaccines are effective, individuals with immunosuppression may experience more frequently suboptimal responses and/or waning of antibodies following immunization[22]. Moreover, circulation of HBV vaccine escape mutants has shown to be responsible for anecdotal cases of acute HBV infections in vaccinated individuals[23]. The advent of long-acting formulations of tenofovir[24] would represent an alternative option or a complementary intervention. An additional indirect benefit of using tenofovir chemoprophylaxis would derive from reducing the chances of hepatitis delta virus (HDV) acquisition since this virus requires HBV for transmission[25].

Besides tenofovir, another potent anti-HBV antiviral is entecavir. It has also been considered as HBV PrEP. Entecavir depicts a safer kidney profile compared to tenofovir. However, it has a lower resistance barrier and there is concern about selection of drug resistance in the mid/long term in patients with poor drug adherence. Anyway, entecavir could be a good alternative option in drug adherent patients with autoimmune diseases receiving rituximab, biological agents, cyclophosphamide, or high-dose corticoids or in transplant recipients, in all of whom renal toxicity needs to be closely followed. Rather than for PrEP, entecavir could be prioritized for preventing HBV reactivation. Research on long-acting forms of entecavir, however, is still too preliminary.

Hepatitis C

For long time, infection with the HCV has been one of the most frequent causes of decompensated cirrhosis and liver cancer worldwide, particularly in developed countries. Fortunately, the advent of new oral direct-acting antivirals during the past decade has transformed the HCV landscape[26]. Nowadays, oral treatments generally given for 2-3 months can cure (eradicate) hepatitis C in most treated patients.

Global estimates for HCV viremic persons have declined from 70 million to 50 million as result of the widespread use of new oral HCV therapies[27]. Successful plans at country level, such as in Egypt[28] or Georgia[29], highlight this historical benefit. Egypt has been the first country to eliminate hepatitis C nationwide, curing more than 4 million patients.

Treatment failures to new oral anti-HCV agents are very rare and generally associated to poor drug adherence and/or selection of drug resistance. However, HCV re-infections may occur in persons once cured that persist with high risk behaviors[30] since there is no protective HCV immunity. Anti-HCV re-treatment, even with the same antiviral regimen that cured the first HCV episode, is generally successful again[31]. Thus, any consideration about prophylaxis with antivirals for HCV could be less appealing than for hepatitis B or HIV, given that any course of HCV therapy generally leads to hepatitis C cure.

In certain risk populations, such as IDUs sharing needles and MSM with multiple sex partners, repeated episodes of HCV re-infection (occasionally more than 6)[32] have urged to reconsider the administration of repeated HCV courses. Given that the clinical consequences of chronic hepatitis C are generally seen only after decades of infection, advise against immediate anti-HCV treatment has been considered when risk behaviors persist. Against this view is the fact that being viremic means to be a potential source of HCV contagion for others[33,34]. In this scenario, some authors have defended the prescription of sofosbuvir as prevention of new HCV infections in persons engaged in risky behaviors and/or in prisons. Sofosbuvir is an appealing agent given its high potency, good safety profile, limited number of drug interactions, and high barrier to resistance. After becoming HCV-negative following a first course of therapy, sofosbuvir chemoprophylaxis could avert HCV re-infections in high-risk individuals. Furthermore, if long-acting forms of sofosbuvir become available[35], they could make more appealing this strategy.

A different scenario for considering HCV chemoprophylaxis is represented by recipients of HCV-positive organ transplants (kidney, liver, etc.). Although HCV donors were traditionally discharged; nowadays, they are increasingly being accepted given the shortage of

organs for transplantation. In this setting, the early administration of HCV antivirals precludes new-onset hepatitis C in the recipient[36]. Thus, the advent of long-acting formulations of HCV antivirals (i.e., sofosbuvir) might find room in this setting, where daily polypharmacy is challenging.

Hepatitis delta

Roughly, 5% of individuals with chronic hepatitis B are superinfected with the HDV. Of the estimated 15-20 million HDV carriers worldwide, hot spots have been noticed in West-Central Africa, Mongolia, Taiwan, Pakistan, Turkey, and the Amazon basin[37]. In addition, HDV has spread globally among IDUs[38]. This explains the disproportionate high prevalence of triple HIV-HBV-HDV coinfection[39].

HDV is a unique small defective virus that requires HBV for completing its replication cycle. The 1700 single-stranded circular RNA genome and a single antigen use the HBV envelope to form the HDV particle[40]. Hepatitis delta is the most severe form of chronic viral hepatitis, leading to cirrhosis and liver cancer in more than half of infected patients lifelong[41]. Until recently, only peginterferon-alfa was used to treat hepatitis delta. However, this drug is not well tolerated and only less than 30% of patients respond to therapy. Furthermore, a large proportion relapse on drug discontinuation[42].

Bulevirtide is an entry inhibitor for hepatitis B and D viruses. It blocks the NTCP receptor at the hepatocyte surface causing inhibitory competition with the physiologic substrate, the bile acids. As defective virus, HDV uses HBsAg as part of its envelope and in this way enters hepatocytes using the same receptor that HBV. Accordingly, despite 8 HDV genotypes exist, bulevirtide seems to be effective across all of them[43].

Phase 3 trials with lonafarnib as HDV therapy are ongoing[44]. This drug is already approved to treat progeria, a rare genetic disease. In hepatitis delta, lonafarnib specifically blocks the assembly of virions within hepatocytes. Development of lonafarnib, however, has recently been halted due to unexpected serious side effects. Peginterferon lambda is another antiviral drug currently been tested in phase 3 studies as hepatitis D treatment[45].

Since there is no stable cell reservoir for the HDV-RNA genome, viral clearance might hypothetically be achieved if complete blocking of viral replication occurs using antivirals for a minimum timeframe[46]. The combination of several specific anti-HDV agents will be required. This is what happens in hepatitis C combining direct-acting antivirals, that cure nearly all patients treated for 2-3 months. Hepatitis delta is a unique condition, and clearance of HDV-RNA genomes might occur despite HBV persistence as cccDNA or integrated HBV-DNA within hepatocytes (Fig. 1)[46]. Supporting this concept is cases of HDV elimination despite persistence of serum HBsAg following treatment with bulevirtide or lonafarnib plus peginterferon[47,48]. The advent of long-acting formulations for these drugs might hypothetically open the opportunity for considering the cure of hepatitis delta, perhaps using single shots[49].

Influenza

Each year influenza viruses of types A and B infect 5-10% of adults and 20-30% of children, thereby causing millions of acute respiratory infections. A significant number of these episodes are associated with complications such as pneumonia and bacterial superinfections that require hospitalization and might lead to death[50-52]. Vaccination is the most effective way to prevent influenza. If vaccines are not available or not expected to work, for example, on emergence of a new variant or in vulnerable groups with diminished immune responses, prophylaxis, and/or early treatment with antivirals represent an alternative option[53]. The timely prescription of antiviral drugs may shorten viral shedding, reduce symptoms, and diminish contagiousness of influenza.

There are currently three classes of antivirals for the treatment and prophylaxis of influenza: neuraminidase inhibitors (oseltamivir and zanamivir), M2 ion channel inhibitors (adamantanes), and the cap-dependent endonuclease inhibitor baloxavir. The efficacy of adamantanes (amantadine and rimantadine) is limited since they are not effective against influenza B viruses and high rates of drug resistance in influenza A are seen since 2004[54]. Treatment of influenza with neuraminidase inhibitors is recommended for patients at high risk for developing severe illness or infected with avian influenza viruses such as A(H5N1).

As PrEP, inhaled zanamivir is approved for 28 days, whereas oral oseltamivir is approved for up to 6 weeks in the general population, and for 12 weeks in immunosuppressed individuals[52]. Usually, the dosage of neuraminidase inhibitors used as prophylaxis is only half of the one given as treatment. Interestingly, there is no cross-resistance between oseltamivir and zanamivir[55].

Baloxavir is an oral prodrug administered as a single dose for the treatment of acute uncomplicated influenza. Baloxavir blocks the viral RNA-dependent

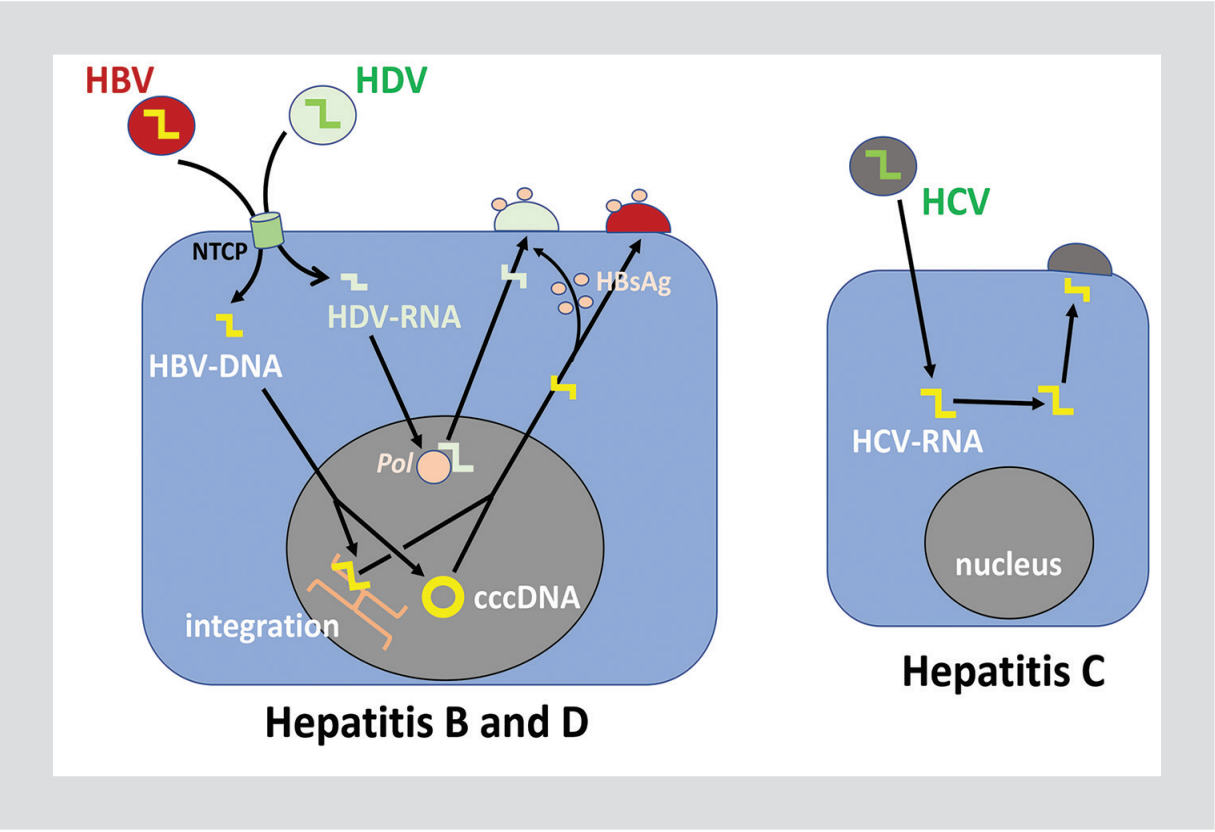

Figure 1. *Biological differences in the replication of hepatitis viruses.*
NTCP: sodium taurocholate cotransporter polypeptide; Pol: human RNA polymerase II.

RNA polymerase. It has broad spectrum coverage and represents an option for patients with infections caused by drug-resistant influenza viruses. However, it exhibits low barrier to resistance. In susceptible individuals, baloxavir shortens the length of viral shedding by a mean of 2 days. When used as prophylaxis, baloxavir reduces the risk of developing influenza by 86%[55].

Influenza antivirals used as pre- and post-exposure prophylaxis represent an essential tool for stopping outbreaks at hospitals and nursing homes. Nowadays, oseltamivir remains the drug of choice for influenza treatment and prevention. Antiviral treatment of influenza should be restricted to severe illness in critically ill hospitalized patients and only should be considered for in- and outpatients who are at high risk for severe disease. In special cases, baloxavir may represent an alternative option with a single dose oral regimen. The advent of long-acting formulations of these antivirals migh provide protective coverage to risky populations when influenza outbreaks peak in certain regions.

SARS-CoV-2

The unprecedented COVID-19 pandemic has transformed and accelerated drug discovery and marketing paths. Three antivirals have been approved so far against SARS-CoV-2, namely, remdesivir, molnupiravir, and nirmatrelvir. Remdesivir is an adenosine prodrug given parenterally that exerts moderate antiviral activity as chain terminator during SARS-CoV-2 replication. Molnupiravir is an oral prodrug form of the cytidine nucleoside, which can be metabolized and incorporated into the viral RNA, leading to viral mutagenesis and error catastrophe. Nirmatrelvir is an oral specific SARS-CoV-2 protease inhibitor, which blocks viral replication by inhibitory competition. It exerts the greatest antiviral activity on SARS-CoV-2[56].

In clinical trials, both oral nirmatrelvir and molnupiravir, when administered during the initial stages of SARS-CoV-2 infection, have shown to reduce the risk of hospitalization or death in high-risk adult outpatients with mild to moderate symptoms[57]. Paxlovid® is the most potent. The drug is being evaluated for administration as post-exposure prophylaxis, in individuals

exposed to symptomatic patients with laboratory-confirmed SARS-CoV-2 infection. Early prescription of nirmatrelvir could be prioritized in persons at increased risk for severe COVID-19[58].

Oral antivirals can strengthen the efforts to quell the health impacts of the COVID-19 pandemic, especially facing the continuous emergence of new SARS-CoV-2 variants, characterized by spike mutations and immune escape. Their role should be considered complementary to vaccination, which should remain key to tackling the COVID-19 pandemic.

Given that SARS-CoV-2 primarily infects the upper respiratory tract, there is much interest for exploring the performance of inhaled antiviral forms[59]. Besides targeting the anatomic viral entry site, this route might reduce systemic side effects and concerns on drug interactions. Long-acting formulations of nirmatrelvir might open the consideration for suing te drug as pre-exposure prophylaxis in persons institutionalized at risk for severe disease.

Monkeypox virus

Historically smallpox has been one of the most deadly human infections. It was caused by the variola virus that belongs to the poxvirus family. Vaccination begun two centuries ago and finally accomplished the objective of eradicating the disease. The famous Balmis journey during the XIX century extended from Spain across all continents the variolization procedure[60]. The last case of smallpox was reported in Somalia in 1977. The WHO declared smallpox as completely eliminated in 1980. Since then, vaccination was discontinued[61].

Other poxviruses, however, such as molluscum contagiosum, cowpox and monkeypox, remain in the natural environment and can infect both animals and humans. Poxviruses causing animal illnesses can occasionally jump to humans and produce outbreaks. In year 2003, more than 40 persons were infected in the United States by monkey poxvirus (mpox)[62]. All had been exposed to pets that had been growth in a farm where other small animals had recently arrived from West Africa, where mpox is endemic.

Poxviruses are very large particles (up to 400 nm), even visible using the optic microscope. They contain a linear double-stranded large DNA ranging from 130 Kb to 375 Kb. In contrast with retroviruses or hepatitis B, replication of poxviruses only takes place within the cytosol of infected cells. They produce acute, self-limited infections, although cutaneous lesions can be quite painful and encephalitis may develop occasionally.

In early May 2022, a human outbreak of mpox begun in Europe. Nearly 80,000 cases were confirmed during the next 6 months with a wide international distribution. Interestingly, most cases occurred among MSM, younger than 45 years old, and had genital and anal skin lesions. The illness self-limited within 2-3 weeks with very few deaths[63,64]. This mpox epidemic form contrast with the endemic form in West and Central Africa first described in the Democratic Republic of Congo by 1970[65]. African cases are seen occasionally as a zoonosis in persons with close contact with infected rodents, the natural reservoir. The mortality rate ranges from 3% to 10%[65].

Worldwide all individuals older than 45 years old had been vaccinated against smallpox and currently exhibit cross-protection against mpox infection. In this regard, the safer smallpox vaccine registered by Bavarian Nordic, a Danish biotech company that uses a non-replicative virus, largely protects from mpox contagion in young persons that never received the smallpox vaccine. In addition, there is an oral antiviral drug that is effective against mpox, called tecovirimat. It is a specific inhibitor of the viral protein VP37, which is critical for viral replication. In sick adults, 600 mg twice daily are recommended for 14 days[66].

More severe forms of mpox infection, including dissemination and multiorgan damage, have been described in three populations: children, pregnant women, and immunocompromised patients[67]. In these groups, PrEP with tecovirimat could be considered in the presence of close contacts with mpox infection, for instance sexual partners or relatives. The advent of long-acting formulations of this drug might provide protection using single shots.

Although public health measures (e.g., isolation, contact tracing, and quarantine) and vaccination have blunted the spread of mpox, cases are continuing to be reported around the world. With more than 100,000 people confirmed to be infected until November 2023, there is concern that mpox may become endemic outside of its original geographical area, leading to repeated human spillover infections or continue to be spread from person-to-person[68].

HTLV-1

The first human retrovirus was discovered in 1980 in a patient with lymphoma[69]. Globally, 15 million people are estimated to be infected with HTLV-1. Hot spots of endemicity have been reported in South Japan, Brazil, Peru, Colombia, the Caribbean basin, Iran, and West Africa[70]. High rates of infection have also been reported

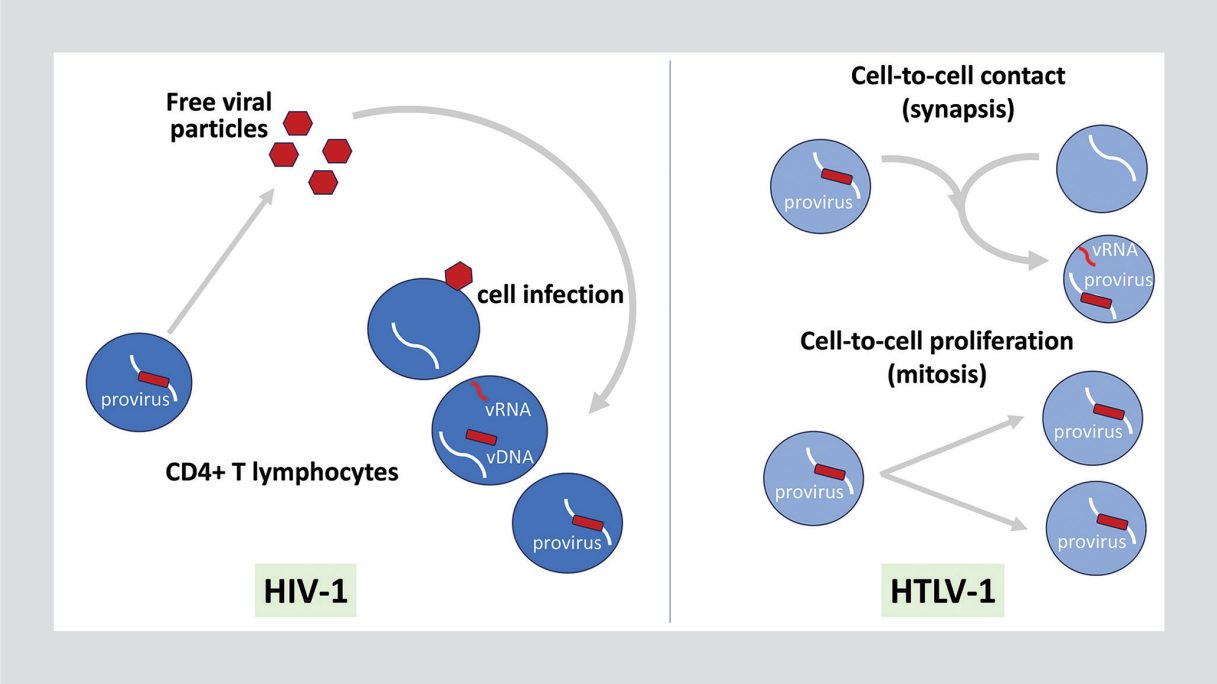

Figure 2. *Differences in the life cycle of human retroviruses.*

among Australian aborigens. HTLV-1 infection is lifelong, as the virus integrates its genetic material as provirus within infected CD4+ T lymphocytes. However, in contrast with HIV-1 that generally leads to immunodeficiency and AIDS in almost all carriers, only 10% of HTLV-1-infected individuals develop clinical symptoms. There are two major HTLV-1 diseases known as adult T-cell leukemia/lymphoma (ATLL) and HTLV-associated myelopathy. Survival in most patients with lymphoma is shorter than 1 year[71]. Roughly, half of individuals with the subacute myelopathy may end up in a wheelchair and with sphincters incontinence.

HTLV-1 is transmitted by sexual contact, parenteral exposure following blood transfusions or injections with unsterilized needles, and from mother to child, mostly throughout breastfeeding. Vertical transmission has been estimated to occur in 15% of babies breastfeed for longer than 6 months from infected mothers. Unexpectedly, HTLV antenatal screening is not recommended, even in many highly endemic regions, and the provision of milk feeding bottles is not ensured for infected mothers. Therefore, HTLV-1 vertical transmission remains significant in endemic regions and in countries that host migrants (including pregnant women) from these areas. As example, estimates in Europe for new HTLV-1 infections in babies annually are of 74 in the UK[72] and 35 in Spain[73].

The interest for antiretrovirals in the prevention of HTLV-1 infection has emerged following the recognition of viral replication through cell-to-cell contact during the first steps of primary acute infection[74]. Once the infection is established, the virus mostly expands clonally through proliferation (mitosis) of immortalized cells (Fig. 2)[75]. Thus, only during the first weeks following HTLV-1 acute infection, and before adaptive immunity develops, the virus may be susceptible to replication inhibitors[73]. At this time, HIV integrase inhibitors are the most potent HTLV-1 inhibitors *in vitro* and in animal models[76]. Given its good safety profile, long-acting formulations of cabotegravir have been considered for HTLV-1 PrEP[77]. We postulate that the medication could be given to HTLV-1-infected pregnant women during the last trimester of gestation before delivery and thereafter when breastfeeding is not expected to be avoided. The drug passes to the milk and is transferred to the baby. Long-acting cabotegravir already is available and is recommended as PrEP in uninfected persons at risk for HIV infection. The drug is given intramuscularly every 2 months.

CMV

Most herpesviruses infect humans widely. CMV has a global distribution with almost universal exposure in

children at younger age in low-income regions. In Western countries, half of the population has been exposed by 35 years of age. Acute CMV infection in immunocompetent persons if often asymptomatic. In youth and adults it may cause a mononucleosis-like syndrome resembling acute Epstein-Barr virus infection, with self-limited fever, headache, and rash. CMV is transmitted by mucosal and skin contact, sexual relationships, parenteral exposure, and vertically (intrauterine, at delivery or through breastfeeding). Children infected at kindergarden often transmit the virus to all family house contacts. During acute CMV infection, the virus is isolated from saliva, feces, urine, and blood[78].

CMV is an enveloped DNA virus with a large genome of 250,000 bp. Infection is lifelong, being the reservoir in the human body multiple cells, mostly of the hematopoietic lineage. In the presence of immunodeficiency, the virus can reactivate. In AIDS patients, typically in those with less than 50 CD4+ T-cells per microliter, it may cause retinitis, and less frequently other organ-specific complications, such as myelitis, hepatitis, esophagitis, and colitis. In patients with leukemia/lymphoma that undergo bone marrow transplantation, pre-emptive therapy is offered to those with evidence of relapsing CMV viremia[79]. Otherwise, they develop pneumonitis and/or other organ-specific CMV lesions. In solid organ transplants, the main concern is for those CMV-seronegative that experience acute CMV infection since they may experience symptomatic CMV disease. However, CMV-seropositive solid organ transplant recipients are also at greater risk for developing CMV disease. Pre-emptive CMV therapy given for those that surpass a CMV-DNA threshold effectively prevents disease[80].

Ganciclovir (iv) has been the drug of choice for treating CMV infection. An oral prodrug, valganciclovir, has been developed for managing long-term infections. Cidofovir (iv) is an alternative antiviral option with long half-life that can be prescribed every 2 weeks. Maribavir and letermovir are the newest approved antivirals active against CMV. They are better tolerated than the old ones[81].

Congenital CMV infection is nowadays the most common human congenital infection, affecting around 1 in 200 infants in high-income settings. It can have life-long consequences for up to one in four children, including sensorineural hearing loss and neurodisability[82]. Despite the frequency of congenital CMV and its severity in a subset of children, it is often forgotten by pregnant women, families, and healthcare providers[83]. Timely diagnosis of CMV infection in pregnancy is important to consider treatment with oral valacyclovir, which reduces the risk of CMV transmission to the fetus and ameliorate clinical manifestations for infected infants[84]. Ganciclovir and valganciclovir are contraindicated in pregnant women given its potential for teratogenicity. The advent of long-acting formulations of valacyclovir would maximize protective coverage against congenital CMV in recently infected pregnant women.

Table 3. Main concerns using long-acting antivirals as prophylaxis of human viral infections

– Selection of antiviral drug resistance
– Drug interactions
– Unexpected side effects
– Potential teratogenicity in women of child-bearing age
– High cost

Controversies using PrEP for non-HIV infections

The use of antivirals as prevention rather than as treatment of viral infections is steadily gaining support to prevent serious illnesses. Mimicking the protective effect of vaccines, PrEP with antivirals will reduce the chances of acquiring potentially life-threatening infections. The success of PrEP with long-acting formulations in the HIV field has encouraged the consideration of PrEP for viral infections other than HIV-1. However, enthusiasm unabated, several concerns require attention. There are at least five major considerations (Table 3).

First, selection of drug resistance may compromise the sustained benefit of antivirals, often used as monotherapies. For this reason, ideally drugs with high barrier to resistance must be considered as preferred candidates for PrEP. Suboptimal drug exposure in the presence of residual virus replication is the major mechanism for selection of drug resistance. This is the case for individuals that did not attend appointments on time for drug administration, even when recommended every 2-3 months. Lessons from the HIV field using long-acting cabotegravir may enlighten this caveat[85].

Second, drug interactions must be taken into consideration. Drug exposure cannot be interrupted abruptly in persons on long-acting antivirals. Both patients and their doctors must be aware of the potential risk of newly prescribed meds for any given medical condition. A careful assessment of potential drug interactions

Table 4. Proposal of viral infections, antiviral candidates for long-acting formulations, and target populations for pre-exposure prophylaxis

Virus	Antiviral drug	Target population
HBV	Tenofovir	HBV-seronegative at risk
HCV	Sofosbuvir	MSM with multiple sex partners, injections drug users
Hepatitis delta	Bulevirtide	Sex partners, injections drug users
Influenza	Oseltamivir, baloxavir	Persons at risk for severe disease during outbreaks
SARS-CoV-2	Nirmatrelvir	Persons at risk for severe disease during outbreaks
Mpox	Tecovirimat	Multiple sex partners (MSM, prostitute women), sex partners
HTLV-1	Cabotegravir	Positive pregnant women, positive sex partner
Cytomegalovirus	Valacyclovir	Pregnant women

HBV: hepatitis B virus; HTLV: human T-cell lymphotropic virus; HCV: hepatitis C virus; MSM: men having sex with men.

should always precede the introduction of new therapies. Safer drug alternatives should be chosen when potential drug interactions are expected.

Third, the side effects of antivirals used as extended released formulations must be checked in advance, when possible first prescribing the active drug during days weeks and excluding hypersensitivity or oother drug reactions. Long-term toxicities might appear in only a subset of treated patients and can be misrecognized if there is no close follow-up. Particular attention should be paid for establishing the safety and efficacy of very long-acting products in women of reproductive age, those who are pregnant, or are breastfeeding.

Fourth, the potential teratogenicity of the drug must be well characterized in advance, if women of childbearing age will be candidates to receive any long-acting antiviral formulation.

Finally, the cost of medications is an important caveat. Discussions are softened when drugs are needed as treatment and alternative options are scarce. However, prescription of drugs as prevention is always hesitant, as questions arise about what can be made to push other preventative measures. This has occurred with HIV risk behaviors[3] and will occur with respect to risk exposures for other viruses when behavioral actions can be made. It seems reasonable to make efforts in advance for providing proper information and education and support safer life style changes[86]. This strategy is cheaper and may rescue at least a subset of persons from risky behaviors.

Conclusion

Which are the prospects for non-HIV PrEP with long-acting antivirals? The HIV field has been upfront proving the efficacy of antiretrovirals as PrEP. The advent of long-acting antiretroviral formulations has shown to be very effective as PrEP using intramuscular or subcutaneous injections just once or a few times yearly. Are we ready to consider a similar approach confronting other common human viral infections?[87-89]

We have identified distinct patient populations and specific clinical settings in which there is room for considering chemoprophylaxis for hepatitis viruses B, C, or delta, respiratory viruses such as influenza or SARS-CoV-2, sexually transmitted agents such as monkeypox, and vertically transmitted viruses such as HTLV-1 and CMV. Hopefully, advances in pharmacology will end up in the development of long-acting antiviral formulations active against many of these viruses. In an orientative manner, table 4 records which antivirals would be preferred at this time and which would be the target populations for PrEP of distinct viral illnesses.

The advent of vaccines and the consideration of the above discussed 4 caveats (resistance, drug interactions, side effects, and cost) would make more or less appealing the development of PrEP strategies with long-acting antivirals in populations at risk for non-HIV viral infections.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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