

# Pre-Exposure Prophylaxis for viral infections other than HIV

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## SUMMARY

The battle against human viral infections has historically relied on two medical strategies, namely vaccines to protect from contagion and antivirals to treat infected patients. In the absence of vaccines, antivirals have occasionally been used as peri-exposure prophylaxis, given either before (pre-exposure prophylaxis) or right after (post-exposure prophylaxis). In an unprecedented way, the use of antiretrovirals as chemoprophylaxis has triumphed in the HIV field. Indeed, oral antiretrovirals given either daily or at demand to HIV-uninfected individuals engaged in high-risk behaviors protect from contagion. More recently, the advent of long-acting formulations has allowed HIV protection following intramuscular injections every three months. Can

we envision a similar prophylactic strategy for other human viral infections?

The advent of such 'chemical vaccines' would fill an unmet need when classical vaccines do not exist, cannot be recommended, immune responses are suboptimal, escape mutants emerge or immunity wanes. In this review, we discuss the opportunities for antiviral chemoprophylaxis for viral hepatitis B and C, retroviruses HTLV-1 and HIV-2, and respiratory viruses influenza and SARS-CoV-2, among others.

**Keywords:** antiviral drugs, prevention, prophylaxis, hepatitis C, hepatitis B, HTLV-1, SARS-CoV-2, monkeypox virus, HIV, long-acting antivirals.

## INTRODUCTION

Since the advent of sulfamides and penicillin as first widely used antibiotics during World War II, viruses have steadily replaced bacteria as major infectious agents, particularly for globally spread microorganisms. Examples are pandemics caused by influenza, the human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV and HCV), Dengue, Zika and nowadays SARS-CoV-2, the coronavirus responsible for the COVID-19 pandemic [1].

The battle against human viral infections has historically relied on two medical strategies, namely

vaccines to protect from contagion and antivirals to treat infected patients. For different reasons, the development of effective vaccines and/or antivirals has been achieved for some but not all viruses (Table 1). Vaccines use immunogens that awake specific adaptive humoral and/or cellular immune responses in the host, preventing the acquisition of a given infectious agent. In contrast, antiviral drugs target either unique viral proteins or cellular molecules that are critical for viral replication. Antivirals that exclusively target viral enzymes benefit from having no expected effects on human proteins, and therefore less chances to produce adverse events [2].

In the absence of vaccines, antivirals have occasionally been used as peri-exposure prophylaxis, given either before (pre-exposure prophylaxis, PrEP) or right after (post-exposure prophylaxis). In an unprecedented way, the use of chemo-

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**Table 1** - Current antivirals and vaccines for confronting human viral illnesses (modified from ref. 7).

<i>Virus</i>	<i>Antivirals</i>	<i>Vaccine</i>
HIV	✓	✗
HAV	✗	✓
HBV	✓	✓
HCV	✓	✗
HTLV	✗	✗
Polio	✗	✓
Measles	✗	✓
HSV	✓	✗
VZV	✓	✓
CMV	✓	✗
EBV	✗	✗
Papilloma	✓	✓
Influenza	✓	✓
Ebola	✓	✓
Corona	✓	✓
Poxvirus	✓	✓

prophylaxis has been fueled in the HIV field as protection from contagion [3]. Two major reasons account for this phenomenon. Firstly, HIV vaccines have remained elusive to date despite huge efforts. Secondly, the development of long-acting formulations of potent antiretrovirals has shown to be very effective, protecting uninfected individuals with high risk behaviors [4-6]. Intramuscular or subcutaneous shots given a few times per year or even once yearly might work as 'chemovaccines' [7-10]. Can we envision such approach to protect from other human viral infections?

The advent of such 'chemical vaccines' would fill an immediate need in providing protection when classical vaccines do not exist, cannot be recom-

mended, immune responses are suboptimal, escape mutants emerge or immunity wanes (Table 2) [11]. In this review, we discuss the opportunities for antiviral chemoprophylaxis for viral hepatitis B and C, retroviruses HTLV-1 and HIV-2, and respiratory viruses influenza and SARS-CoV-2.

## ■ HEPATITIS B

Roughly two billion people have been exposed to the hepatitis B virus (HBV) worldwide. Estimates for chronic hepatitis B patients are of 290 million people. The number of global deaths caused each year by HBV due to decompensated cirrhosis or liver cancer approach one million. These high numbers are paradoxical considering that effective protective HBV vaccines exist for more than 40 years. Suboptimal global HBV vaccine coverage largely explains it [12].

Antiviral agents to treat HBV have also been available for decades. Nowadays tenofovir and entecavir have replaced lamivudine as oral anti-HBV agent. Although viral suppression is achieved in most treated patients, HBV is not eradicated from carriers and therefore oral treatment is lifelong. Patients with chronic hepatitis B under long-term tenofovir experience a reduced risk of liver disease progression and hepatocellular carcinoma. In addition, viral suppression is associated to halted HBV transmission, a benefit known as '*treatment as prevention*' [3].

The first observations about a protective effect of tenofovir on HBV acquisition come from studies conducted in HIV patients on antiretroviral therapy [13, 14]. Sexually active men having sex with men (MSM) that received tenofovir had a lower chance of HBV infection than those that did not receive the drug. Thereafter, this protective effect was confirmed in both HIV-infected individuals under tenofovir-based antiretroviral therapy and in HIV-uninfected persons at risk undergoing PrEP with tenofovir. Based on this finding, the increasing trend in HIV therapeutics for using mono or dual regimens sparing tenofovir is worrisome [15]. It might be associated with a rebound of incident HBV infections.

Although HBV vaccines are effective, individuals with immunosuppression may experience more frequently suboptimal responses and/or waning of antibodies following immunization [16]. Moreover, circulation of HBV vaccine escape mutants

**Table 2** - Major indications for prophylaxis with antivirals.

No vaccines available (i.e., HIV or HCV)
Vaccines not recommended (i.e., attenuated live vaccines in immunosuppressed patients, allergies, etc.)
Suboptimal response to vaccines (i.e., HBV in immunosuppressed individuals)
Emergence of vaccine escape mutant viruses (i.e., HBV)
Vaccine immunity waning (i.e., SARS-CoV-2, HBV)

is occasionally responsible for paradoxical acute HBV infections in vaccinated individuals [17]. For all these considerations, the use of tenofovir as chemoprophylaxis might be discussed in certain populations to avert breakthrough HBV infections. We postulate that this could be the case for immunodeficient individuals engaged in high risk behaviors, including injection drug users (IDUs) that share needles, MSM and persons with multiple sexual partners (Table 3). The advent of long-acting formulations of tenofovir could facilitate this option [18]. 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 [18, 19].

## ■ HEPATITIS C

For long time, infection with the hepatitis C virus (HCV) has been one of the most frequent causes of decompensated cirrhosis and liver cancer worldwide and particularly in developed countries. The advent of new oral direct-acting antivirals during the last decade has transformed the HCV

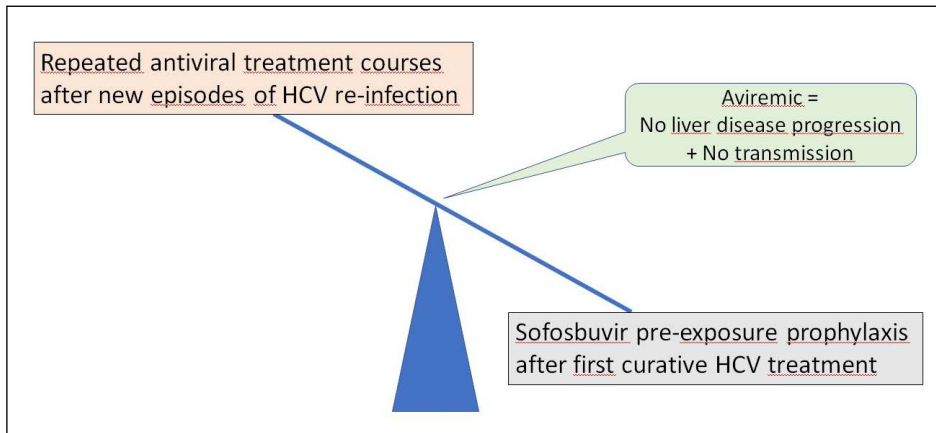
landscape [21]. Oral treatments generally given for three months can cure (eradicate) hepatitis C in most treated patients.

Global estimates for HCV viremic persons have declined from 70 million to 50 million as result of the widespread use of oral new HCV therapies. Successful plans at country level, such as in Egypt or Georgia, highlight this historical benefit Egypt has been the first country to eliminate hepatitis C, curing more than 4 million patients [22, 23].

Treatment failures to new oral anti-HCV agents are very rare and generally associated to poor drug adherence and/or selection of drug resistance. On the other hand, HCV re-infections may occur in persons with high risk behaviors since there is no protective HCV immunity [24]. However, anti-HCV re-treatment even with the same regimen that cured the first HCV episode, is generally successful again [25]. Thus, any consideration about prophylaxis with antivirals is less appealing for HCV than for hepatitis B or HIV, given that any course of HCV therapy generally leads to hepatitis C cure. However, in certain risk populations, such as IDUs sharing needles and MSM with multiple sex partners, repeated episodes of HCV re-infec-

**Table 3 - Pre-exposure chemoprophylaxis in viral infections other than HIV.**

<i>Virus</i>	<i>Target population</i>	<i>Comments</i>
HBV	- Persons with immunodeficiency and - High-risk exposure behaviors (multiple sex partners & injection drug users)	- Despite HBV vaccine prioritization in these groups, be aware of potential contraindications, suboptimal responses, immunity waning and vaccine escape mutants.
HCV	- Recipients of HCV+ viremic transplant donors, and - Certain individuals engaged in high-risk behaviors	
HTLV-1	- Sexual partners of HTLV-1+ persons and - Individuals with sexually transmitted infections	- Second-generation integrase inhibitors inhibit HTLV-1 replication in vitro
HIV-2	- Individuals with HIV-2 sex partners or - Living in HIV-2 endemic regions and engaged in risky behaviors	- HIV-1 does not protect from HIV-2 superinfection - Both tenofovir and cabotegravir used as HIV-1 PrEP would reduce HIV-2 acquisition
Influenza	- Population at risk for influenza A complications includes pregnant and postpartum women, the elderly, children, immunosuppressed patients, health care workers, and long-term residents at institutions. - Close contacts and earlier on seasonal outbreaks are additional considerations	- Oral oseltamivir and inhaled zanamivir are the preferred choices as prophylaxis.
SARS-CoV-2	- Individuals at increased risk for severe COVID-19, include the elderly, obese, diabetics and immunodeficient patients	- Nirmatrelvir is the most potent antiviral
MPXV	- Children, pregnant women and immunosuppressed individuals are at increased risk for severe clinical forms.	- Data about the efficacy of tecovirimat as prevention are scarce.



**Figure 1** - Management of hepatitis C in persons engaged in high risk behaviors.

tion (occasionally more than 6) have urged to reconsider this strategy [26]. Given that the clinical consequences of chronic hepatitis C are generally seen only after decades of infection, some authors advise against immediate anti-HCV treatment risk behaviors persist. On the other hand, being viremic means to be potential source of contagion for others [27, 28]. In this scenario, the consideration of sofosbuvir as prevention of new HCV infections in persons engaged in risky behaviors and/or in prisons could be defended (Figure 1). Sofosbuvir is an attractive agent for this objective, given its high potency, good safety profile, scarce drug interactions and high barrier to resistance. After becoming HCV-negative following a first course of therapy, sofosbuvir chemoprophylaxis could avert HCV re-infections. Furthermore, if long-acting forms of HCV drugs become available, this option could be even more appealing [29].

A different scenario for considering HCV chemoprophylaxis is represented by recipients of HCV+ organ transplants (kidney, liver, etc.). Although HCV donors were traditionally discharged, they are increasingly being accepted given the shortage of organs for transplantation and the fact that early administration of HCV antivirals precludes new onset hepatitis C in the recipient [30].

## ■ HTLV-1

Other retroviruses than HIV-1 may cause human diseases. HTLV-1 infects 15-20 million people worldwide and may produce two characteristic illnesses in 10% of carriers, namely a subacute myelopathy known as tropical spastic para-

paresis (or HTLV-associated myelopathy) and adult T-cell lymphomas. The virus is transmitted throughout sexual contact, from infected mothers to newborns mostly through breastfeeding, and following parenteral exposure (transfusions, organ transplantation and injection drug use) [31]. Despite being present globally, hot spots of endemicity exist for HTLV-1 in Latin America, the Caribbean basin, West Africa, South of Japan, North-east Iran, Australia and Romania [31]. Following large population migration flows, HTLV-1 is currently been reported in North America and the European Union, mostly among foreigners coming from endemic regions [32]. Moreover, new HTLV-1 diagnoses among natives are increasingly been reported in sexual partners [33]. Given that there is neither protective vaccine nor effective antivirals to treat HTLV-1 infection or its complications, early diagnosis has become an important tool. Only in this way, asymptomatic HTLV-1 carriers can be unveiled, start periodic clinical follow-up and be informed about the risks of transmission. In this regard, testing of sex partners and avoiding breastfeeding are very effective measures [34].

The incidence of sexually transmitted infections (STI) is on the rise during the last decade. The loss of fear to HIV contagion following the success of PrEP has largely contributed to it [35]. In response to this 'compensatory effect', current guidelines recommend STI testing before starting and periodically in all individuals on HIV PrEP. Besides classical STI agents, i.e. syphilis, gonorrhea, chlamydia and mycoplasma, testing for other less frequent etiologies is increasingly becoming cost-effective and informative in terms of public health.

We and others support that this should be the case for HTLV-1; which should be added into the STI screening list [34-36].

Antiretrovirals used as HIV PrEP include nucleos(t)ide reverse transcriptase inhibitors and integrase inhibitors. There is a lack of HTLV-1 seroprevalence studies among HIV PrEP-using groups, including MSM, IDUs, and female sex workers. These HTLV-1 serosurveys should be performed to recover any evidence in favor of a protective effect of antiretrovirals on HTLV-1 acquisition. This information would be particularly relevant in cabotegravir users, since this drug has shown potent antiretroviral activity in vitro against HTLV-1 [37, 38].

## ■ HIV-2

Around 1-2 million people are infected with HIV-2 worldwide. Endemic areas exist in West Africa, Brazil, India and Portugal. HIV-2 has also been described in Western countries with a large immigrant population from HIV-2 endemic regions. In this way, nearly 500 cases of HIV-2 have been reported in Spain [39].

HIV-2 may cause AIDS but slowly than HIV-1. Although many antiretrovirals used to treat HIV-1 are active against HIV-2, neither non-nucleoside reverse transcriptase inhibitors nor entry inhibitors are active. Moreover, some HIV-1 protease inhibitors are less effective against HIV-2. Finally, drug resistance mutations in HIV-2 depict unique profiles [40].

Both daily and on-demand antiretroviral regimens have been proven effective as PrEP in HIV-1, but scarce data exist about protection exerted on HIV-2. Overall, HIV-2 is less transmissible than HIV-1 following sexual contact [3, 41, 43]. It is noteworthy that tenofovir and integrase inhibitors used as HIV-1 PrEP may protect from HIV-2 infection. In this regard, long-acting formulations of cabotegravir might prevent from sexually transmitted HIV-2 in endemic regions or in persons with an HIV-2 sex partner. The use of other antiretroviral agents, however, could not prevent HIV-2 acquisition [43].

## ■ INFLUENZA

Influenza viruses of types A and B attack 5-10% of adults and 20-30% of children, thereby causing

millions of acute respiratory infections annually. A significant number of these episodes are associated with complications such as pneumonia and bacterial superinfections that require hospitalization and might lead to death [44]. Vaccination is the most effective way to prevent influenza. If vaccination is not available, e.g., upon emergence of a new variant or in vulnerable groups with diminished immune responses, prophylaxis and/or early treatment with antivirals represents an alternative option [45]. The timely prescription of antiviral drugs may shorten viral shedding, reduce symptoms, and diminish contagiousness. There are currently three classes of antivirals for treatment and prophylaxis of influenza: neuraminidase inhibitors (oseltamivir and zanamivir), M2 ion channel inhibitors (adamantanes), and 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 [46]. Treatment of influenza with neuraminidase inhibitors is recommended for patients at high risk for developing severe illness or infected with avian influenza viruses like 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. Usually, the dosage of neuraminidase inhibitors used for prophylaxis is only half of that used for treatment. Interestingly, there is no cross-resistance between oseltamivir and zanamivir [46].

Baloxavir is an oral prodrug administered as a single dose for the treatment of acute uncomplicated influenza. Baloxavir blocks the viral RNA-dependent RNA polymerase. It has a broad spectrum coverage and represents an option for patients with infections caused by drug-resistant influenza viruses. However, itself depicts a 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% [46].

Influenza antivirals used as pre- and post-exposure prophylaxis represent an essential tool to stop outbreaks in institutions, such as hospitals or nursery homes. Oseltamivir remains the drug of choice for influenza treatment and preven-



tion nowadays. Antiviral treatment of influenza should be restricted to severe illness in critically ill hospitalized patients and should be considered for in- and outpatients who are at high risk for severe disease. In special cases, Baloxavir may represent an attractive option with a single dose oral regimen.

## ■ 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, known as 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 [47].

In clinical trials, both oral nirmatrelvir and molnupiravir, when administered during the initial stages of SARS-CoV-2 infection, have shown a reduction in the risk of hospitalization or death in high-risk adult outpatients with mild to moderate symptoms [48]. Paxlovid® is more potent than the other two drugs. It is currently being tested in standard-risk patients early after the onset of the disease, assessing the time interval to sustained symptom relief. The drug is also being evaluated for administration as post-exposure prophylaxis, in individuals exposed to symptomatic patients with laboratory-confirmed SARS-CoV-2 infection. 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 remains the 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 forms of antivirals [49]. Besides targeting the anatomic viral

entry site, this route might reduce systemic side effects and concerns on drug interactions.

## ■ MONKEYPOX VIRUS

Smallpox has been one of the most deadly human infections historically. It is 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 last case was reported in Somalia in 1977. The WHO declared smallpox as completely eliminated in 1980. Since then, vaccination was discontinued [50].

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 there was an outbreak in the United States of monkey poxvirus (MPXV) that affected more than 40 persons [51]. All sick patients were exposed to pets that had been growth in a farm where other small animals had recently arrived from West Africa, where MPXV is endemic.

Poxviruses are very large particles (up to 400 nm), even visible using the optic microscope. They contain a single double stranded large DNA ranging from 130 to 375 Kb. In contrast with retroviruses or hepatitis B, replication of poxviruses only takes place within the cytosol of infected cells.

In early May 2022, an outbreak of MPXV begun in Europe. Nearly 10,000 cases were confirmed during the next 3 months with a wide international distribution. Interestingly, most cases occurred among MSM, younger than 45 years-old, had genital and anal skin lesions, and self-limited within 2-3 weeks with very few deaths [52]. This MPXV epidemic form contrast with the endemic form in West and Central Africa, first described in the Democratic Republic of Congo by 1970. 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% [53].

Globally all individuals older than 45 years-old are vaccinated against smallpox and exhibit cross-protection against MPXV 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 MPXV contagion. In addition, there is an oral antiviral drug that is effective against MPXV, called tecovirimat. It is a specific inhibitor of the viral protein VP37, which is critical for viral replication. In adults, 600 mg twice daily are recommended for 14 days [54].

More severe forms of MPXV infection, including dissemination and multiorgan damage have been described in three populations: children, pregnant women and immunocompromised patients [55]. In these groups, PrEP with tecovirimat could be considered in the presence of close contacts with MPXV infection, i.e., sexual partners or relatives.

### ■ CAVEATS AND CONCERNS USING PREP FOR NON-HIV INFECTIONS

The use of antivirals as prevention rather than 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 advent of long-acting formulations may further encourage PrEP use with antivirals for infections other than HIV-1. However, enthusiasm unabated, several concerns require attention (Table 4). There are at least four major considerations.

Firstly, 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 [56].

**Table 4 - Major concerns using long-acting antivirals as prophylaxis of viral infections.**

Selection of drug resistance
Unexpected side effects
Drug interactions
Potential teratogenicity in women of child-bearing age
Cost

**Table 5 - Antivirals for pre-exposure prophylaxis.**

<i>Virus</i>	<i>Antiviral candidate</i>
Hepatitis B	Tenofovir Bulevirtide
Hepatitis C	Sofosbuvir
HTLV-1	Cabotegravir
HIV-2	Tenofovir Cabotegravir
Influenza	Oseltamivir Baloxavir
SARS-CoV-2	Nirmatrelvir
MPXV	Tecovirimat

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

Thirdly, the long-term side effects of antivirals used as extended released formulations must be monitored. Toxicities might appear in only a subset of treated patients and 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.

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 preventive measures. This has occurred with HIV risk behaviors and will occur with respect to risk exposures to other viruses. It seems reasonable to make efforts for providing proper information and education, and support safer life style changes in advance [3, 35, 57].

### ■ PREP WITH ANTIVIRALS IN THE ERA OF PRECISION MEDICINE

Precision medicine is moving the medical paradigm from producing a diagnosis for any disease

based on clinical symptoms/signs and complementary exams to predict the risk of illnesses in healthy persons based on individual genomics, biomarkers and imaging [58]. In the field of infectious diseases, precision medicine has become mostly personalized addressing the prevention of human infections. Tailoring the most convenient intervention for each individual may maximize the chances of success either for treatment or prevention [59].

The HIV field has been upfront in this new medical paradigm proving the efficacy of antiretrovirals as PrEP. The advent of long-acting antiretroviral formulations to be used as PrEP has proven very effective 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? [60-62]. We have identified distinct patient populations and specific clinical settings in which there is room for considering chemoprophylaxis for viral hepatitis B or C, retroviruses HTLV-1 or HIV-2, or respiratory viruses such as influenza or SARS-CoV-2.

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