Repurposing Drugs: A therapeutic option to control the outbreak of new infective pathogens

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Abstract  
There has been limited development, approval and manufacturing of new medicines for the chemotherapeutic intervention of diseases caused by viral infections. The limited development could be due to multitudinous reasons such as a sudden outbreak of pathogenic microorganism, or a lack of financial incentives by the industry to invest in development and clinical trials. Drug repurposing (DR) is one of the drug development strategies adopted by the healthcare system to combat diseases caused by the sudden outbreak of pathogens characterized by its pandemic potential or a rare form of cancer, for which there is no effective therapy available. However, there are possible limitations to this strategy such as legal or regulatory barriers, intellectual property rights linked to the original drug, an increase in the manufacturing capacity or a negative perception towards the use of repurposed drugs by clinicians and patients. In this opinion paper, we have summarized the repositioning of the off-label generic drugs as a possible therapeutic avenue to combat microbial infections such as the recent outbreak of Coronavirus infection, COVID-19.

Key words: Cost saving, Drug repurposing, Generic drugs, Infective pathogen, Virus

Introduction  
There has been limited development, approval and manufacturing of new medicines for the chemotherapeutic intervention of diseases caused by viral infections. The limited development could be due to multitudinous reasons such as a sudden outbreak of pathogenic microorganism, a lack of financial incentives by the industry to invest in development and clinical trials. Drug repurposing (DR) is one of the drug development strategies adopted by the healthcare system to combat diseases caused by the sudden outbreak of pathogens characterized by its pandemic potential or a rare form of cancer, for which there is no effective therapy available.¹ In DR, an existing well-characterized clinically approved drug could be used in such cases by exploring a new mechanism of actions, new indications or new targets for the intervention. Additionally, the chances of repurposed drugs to fail are lower than the novel drug due to the availability of pre-clinical and clinical data of the original off-patent and off-label drugs. Hence, repurposed drugs require a shorter clinical trial and abbreviated regulatory approval. This approach of drug repositioning could be a time and cost effective alternative to a traditional drug discovery process.² These drugs could also be allowed for the compassionate use due to the lack of an effective treatment to circumvent sudden outbreak of diseases. However, there are possible limitations to this strategy such as legal or regulatory barriers, intellectual property rights linked to the original drug, an increase in the manufacturing capacity or a negative perception towards the use of repurposed drugs by clinicians and patients. In this opinion paper, we have summarized the repositioning of the off-label generic drugs as a possible therapeutic avenue to combat microbial infections such as the recent
outbreak of Coronavirus infection (COVID-19), for which a specific vaccine or drug is not available at the moment in the market. Repurposed drugs recommended for the use has been published in a recent paper. This scientific article aims to describe briefly, the general value propositions of drug repurposing, with specific examples of a few drugs which could be potentially used to control the rapid outbreak of coronavirus infection in India. We have also provided a few more examples to illustrate DR to treat other diseases. Finally, we have also proposed concerted actions which should be adopted by healthcare stakeholders to improve the uptake of repurposed drugs in other therapeutics and possible challenges encountered to develop repurposed drugs for other therapeutic indications.

COVID-19 and current opportunities to use repurposed drugs
The majority of FDA approved drugs since 2013 to treat viral infection are against the hepatitis C virus, followed by HIV, cytomegalovirus, and influenza virus. The Coronavirus (CoV) are RNA viruses, such as severe acute respiratory syndrome CoV (SARS), Middle East respiratory syndrome CoV (MERS-CoV), COVID-19 causes severe respiratory infections, which could be life-threatening. An outbreak of COVID-19 was declared as a public health emergency by WHO on 30 January 2020 stating that “the potential for the virus to spread to countries with a weaker health system”. There is a lack of an effective treatment protocol to control the outbreak of COVID-19, resulting in significant morbidity and mortality. Additionally, there is an emergence of new strains of this virus, which shows animal adaptation, a wide range of intermediate hosts, and likely possibility by the virus to develop resistance to the therapy. Hence, it is important to control the high potential pandemic transmission of COVID-19 infection. There are no chemical drugs available yet to treat the coronavirus infections or vaccines to control the coronavirus.

Efforts are underway to repurpose the existing therapeutic options to circumvent this global emergency. Clinically approved medicines used as an antiviral or other indication could also be used to treat infection caused by the COVID-19. Antiviral medicines interfere with the cellular pathway of the host, which is necessary for the viral replication. For instance, Cipla is repurposing their antiretroviral medications - Lopinavir and Ritonavir - to treat COVID-19. These are protease inhibitors which were designed to block HIV replication. These drugs have been in the market for about 10 to 15 years and are currently off-patent and the combination is sold under the brand name Lopimune in India. Indian Council of Medical Research had received approval for “restricted use” of fixed dose combination of Lopinavir and Ritonavir in vulnerable COVID-19 cases. However, the drug may face a problem with availability, as the present demand for these two molecules is relatively low to block HIV replication. There could be a potential drug shortage if used for growing number of COVID-19 cases. AbbVie’s Kaletra, also known as Aluvia, containing the same molecules is also recommended for the treatment of pneumonia caused by COVID-19. Although there is no evidence that this combination drug can treat coronavirus infection, the treatment has been proved to be efficacious in one such case of the recent outbreak. Moreover, in a study performed in 2004, the combination of these two molecules was associated with substantial clinical benefit among SARS-CoV. Gilead Sciences is also considering repositioning Remdesivir, a NUC (nucleotide/nucleoside analogue) inhibitor, for the treatment of coronavirus. This molecule was initially developed for the treatment of West African Ebola virus outbreak in 2013. Evidence of early stage tests published in 2018 has established use of Remdesivir against coronavirus. These tests serve as preliminary evidence to support that Remdesivir inhibits murine hepatitis virus and MERS-CoV. In animal models, scientists have found that Remdesivir can knock down similar coronaviruses, such as the ones that cause MERS and SARS. Further, an evidence in animal models suggests that Remdesivir can inhibit CoV infection which causes MERS and SARS”.

There have been previous successes in repurposing anti-microbial drugs for the treatment of infectious diseases. A few notable examples include Delamanid, a drug for tuberculosis which showed activity against visceral leishmaniasis and Niclosamide - an anthelmintic, showed activity against Zika virus. Additionally, drugs that were not originally
developed to treat infectious diseases have also exhibited activity against various infective pathogens. Examples include Auranofin, a gold containing compound which was used against rheumatoid arthritis, has been repurposed to inhibit several pathogens such as multidrug resistant bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) and *K. pneumonia*. Additionally, Auranofin could be used for the treatment against diseases such as HIV/AIDS, and some parasitic diseases, as well as Alzheimer’s diseases, Parkinson’s disease, and cancer. Other examples include Loperamide, a diarrhoea drug, which has been repurposed to treat infections caused by *Salmonella enterica* and Tamoxifen, a breast cancer drug, which has been repurposed to treat infections by Hepatitis C virus. Specific example of the use of drug repurposing in India includes the use of Paromomycin and Miltefosine for kala-azar post clinical trials, that benefited a large number of patients suffering from kala-azar. In addition to this, scientists of National Chemical Laboratory and National Centre for Cell Sciences discovered ant-glycating activity in Rifampicin (an antitubercular drug), which is suggestive of its potential use in controlling diabetic complications. Researchers have also reported that Thiazolidinones, compound with antibacterial activity, has potent anti-HIV activity.

**Other advantages of repurposed drugs**

There are other values offered by repurposed drugs such as cost saving, which is linked to the development cost and comparatively lower price when compared to the novel drug. This value is also integrated to other value propositions such as an increase in market access, patient access and affordability by the healthcare system. Cost saving incurred by the repurposed drugs could provide budget latitude and head room for novel therapies for new disease areas.

Repurposed drugs could further be explored for the development of a wide spectrum of antiviral therapeutics. There are several strategies which could be adopted to identify drugs with a repurposing potential such as screening small molecule libraries with known bioactivity. These libraries are available either in a public domain or for commercial use. Public-private partnership and data sharing for research at a global level could help to identify potential drugs for repurposing. To repurpose an antiviral or an anti-cancer drug, *in vitro* and *in vivo* clinical studies are required for the approval. However, there are several challenges to repurpose a drug, such as dose optimization. The repurposed drugs may require higher doses compared to the originally targeted therapy for the optimal outcome, which may cause toxicity or adverse events. Additionally, the route of administration should be carefully designed to be effective. A combination therapy with two or more drugs with different mode of actions could be considered for the use to reduce toxicity and resistance to the treatment.

**Conclusion**

Despite several values of repurposed drugs, there has been low uptake of these drugs due to low acceptance, strategic decisions by healthcare decision makers, and strategic pricing policies by the manufacturing companies. Thus, it provides an impetus for a coordinated engagement of the researchers, global health organizations, national health authority, policy makers, pharmaceutical industries, clinicians, and patients. Scientific-based arguments could increase the uptake of repurposed drugs which are both cost and time effective, in this era for limited healthcare resources. However, future case studies are required to address values and challenges which are not illustrated in this report such as drug shortages due to the sudden increase in the demand of repurposed drugs, pricing and reimbursement of repurposed drugs, and the willingness of physicians to use these drugs in the absence of a robust clinical evidence. An assertive action plan and implementation is required based on scientific evidence from WHO to use repurposed drugs to counteract global emergency such as high pandemic transmission of virus. In short, DR holds the potential of contributing safe, timely, and affordable access to the treatment to control the outbreak of coronavirus.

**Conflict of interest:** None declared

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