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# COVID-19 and its impact on cancer, HIV, and mentally ill patients

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## 1 Introduction: SARS-COVID-19

The world is reeling from the unprecedented health emergency—COVID-19 disease—caused by the novel Coronavirus-2 infection. Irrespective of the health preparedness of developed and developing or underdeveloped countries, the effect and severity of the disease and its management is being felt at the same magnitude across the world and is testing the limits of health care infrastructure and management. As of July end, 2021, officially 195,886,929 confirmed cases are reported across the globe with an estimate of 4,189,148 deaths worldwide, with a total of 3,830,124,730 vaccine doses administered (WHO, 2021). As COVID-19 is progressing in to its second year, occurrences of second and third waves are creating further panic among the populace and administrations across the world. The resulting lockdowns curtailing the movement of people is creating an economic havoc, pushing untold number of people losing jobs, wages and pushing them in to forced poverty. Although, initially it affected more of the older population with premorbid conditions, however second and third waves of CoV-2 infections are proving to be increasingly effective with accompanied evolution of viral strains (B.1.1.7, i.e.,  $\alpha$ , B.1.351, i.e.,  $\beta$ , P.1, i.e.,  $\gamma$ , and B.1.617.2, i.e.,  $\delta$ ) over a broader range of age groups

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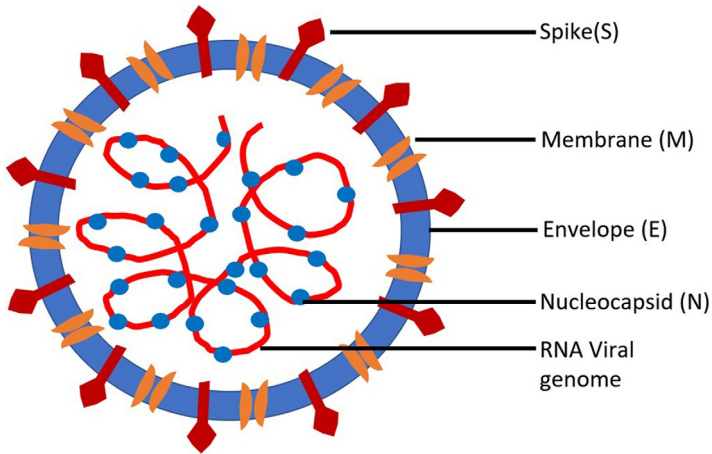
including younger population associated with longer recovery periods (long-COVID) (Blomberg et al., 2021; Venkatesan, 2021).

### 1.1 Pathophysiology of COVID-19: Infection, interactions

SARS-CoV-2 was identified as a causative agent of COVID-19 disease in late 2019 in Wuhan, China. Since its discovery and identification, the disease spread across the globe with almost half a billion infections and more than 4,189,148 deaths (WHO, 2021) reaching the status of a global pandemic. Initially, effects of infection of SARS-CoV-2 seemed to be relatively milder in younger population while older patients and patients with comorbid conditions were more vulnerable for severe disease and ensuing death (Sanyaolu et al., 2020). Although the infection rates are very high, the death rate is considerably low and only higher in older patients (Sanyaolu et al., 2020). Overall death rate is estimated to be around 1%–2% (Baud et al., 2020). Despite low death rate, rapid infectivity, less incubation time and consequent acute respiratory distress symptoms lead to the urgent need of health care facilities for many patients in a short span, causing severe strain and panic among administration and populations. Since the occurrence of COVID-19, intense research has led to the increased basic understanding of the causative agent that is SARS-CoV-2 and its relation to the already existing SARS and MERS viruses (Zhu et al., 2020).

SARS-CoV-2 belongs to the group of Coronaviruses, a diverse group of viruses infecting different variety of animals (Hu et al., 2021a). Most of them cause mild to severe acute respiratory diseases. Of all the Coronaviruses, SARS (2002), MERS (2012), the present SARS-CoV-2 (2019) seem to cause serious diseases (Gorbalenya et al., 2020). Among the Coronaviruses, SARS-CoV-2 is fast spreading and infecting an overwhelmingly larger number of people than either SARS or MERS (Zhu et al., 2020) within very short span of time.

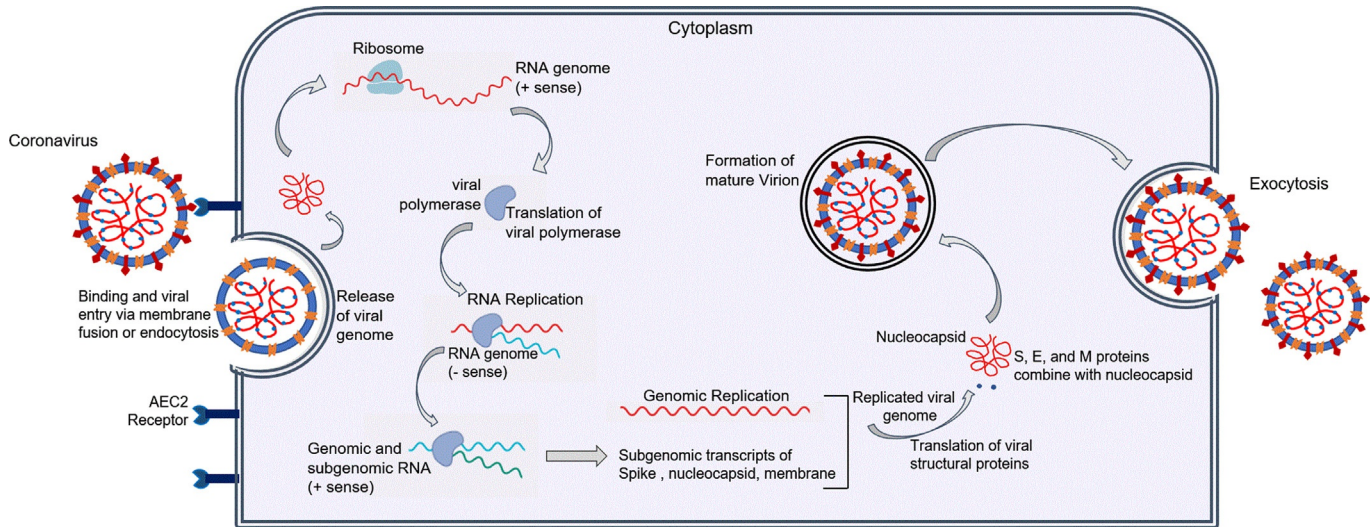
SARS-CoV-2 is a single stranded, positive sense RNA virus with an envelope for protecting its genome (Pal et al., 2020). SARS-CoV-2 genome is 80% similar to SARS-CoV and MERS-CoV (Lu et al., 2020; Zhang and Holmes, 2020; Zhou et al., 2020). The surface of the virus contains matrix (M) glycoprotein, envelope(E) protein and is richly coated with spike(S) protein (Zhang and Guo, 2020) (illustrated in Fig. 1). The transmission of infection is through the viral particles in the air released from the infected person or through contact with the surfaces with active virus particles. Usual mode of entry in the new host is through nasal cavities, eyes or any wounds for effective infection. The spike protein of the virus plays an important role in connecting and binding with receptors expressed on the host cell surface. Spike protein binds to angiotensin-



**Fig. 1** Schematic diagram of SARS-CoV-2.

converting enzyme 2 (ACE2), a surface receptor highly expressed on the surface of the tracheal epithelial cells of the host. Once the spike protein and ACE2 establishes the binding, another transmembrane host protease, TMPRSS2 cleaves the membrane helping in the internalization of virus by endocytosis. In the endocytic vesicle, proteases from host such as CTSL cleave the spike proteins and other viral surface proteins to release the viral RNA in the cytoplasm of the host cell (Pišlar et al., 2020) (illustrated in Fig. 2). After entering the host cell, the genome gets replicated through RNA dependent RNA polymerase. The viral genome is 30 kb, and consists of 14–open reading frames (ORFs) and ORF1a and ORF1b encodes for polyproteins, which produces 16 nonstructural proteins (NSP1–16) upon auto–proteolysis—and forms the replicase and transcriptase activity mainly. The rest of the genome codes for structural proteins; spike, envelope, membrane and nucleocapsid and also 9 putative accessory factors (Gordon et al., 2020). The translation of viral protein is processed in endoplasmic reticulum vesicles leading to the assembly of virion particles, consequently budding off from host cell. Thus, newly formed virions enter in to the interstitial space and thereby the blood circulation and starts to infect new host cells aggravating the infection and onset of the COVID-19 (illustrated in Fig. 2) (Snijder et al., 2006; Perlman and Netland, 2009).

The respiratory tract is the main route of infection for SARS-CoV-2, like for many other Coronaviruses. Airway and alveolar epithelial cells, vascular endothelial cells and alveolar macrophages are the primary target hosts' cells for viral infection (Hamming et al., 2004; Jia et al., 2005; Kuba et al., 2005; Ziegler et al., 2020). The most observable symptoms include



**Fig. 2** The life cycle of the SARS-CoV-2 from entry to exit of the host cell.

persistent fever or chills, dry cough, tiredness, fatigue and myalgia for a few days, loss of smell, taste and enteric problems such as diarrhea. The severe symptom includes trouble in breathing, persistent pain or pressure in chest and pale or gray, lips. All or some of them can be present in moderate or severe COVID-19. The disease could be very mild in some patients with very few or none of the above symptoms but they can still act as carriers. SARS-CoV-2 elicits strong immune response and activates all components of the innate and adaptive immune system. In severe COVID-19 cases, the immune system loses the battle to contain the virus and there is considerable reduction in CD4<sup>+</sup> T, CD8<sup>+</sup> T, NK, and B cell number leading to lymphopenia (Huang et al., 2020; Lippi and Plebani, 2020; Qin et al., 2020; Xu et al., 2020). In severe form of COVID-19, cytokines such as IL-2, IL-4, IL-6, IL-10, TNF $\alpha$ , and TNF- $\gamma$  elevates up to an alarmingly high level within short span of time and create a pathogenic condition called “cytokine storm” (illustrated in Fig. 3). As the disease progresses, severe acute respiratory distress syndrome (ARDS) occurs leading to shortness of breath requiring external supply of oxygen, hospitalization and in further extreme cases occurrence of multiple organ failure leading to death (Cattaneo et al., 2020; Huang et al., 2020). The current treatment regimens include usage of remdesivir (although its effect seems to be marginal and WHO is contemplating its removal from usage for COVID-19 treatment),

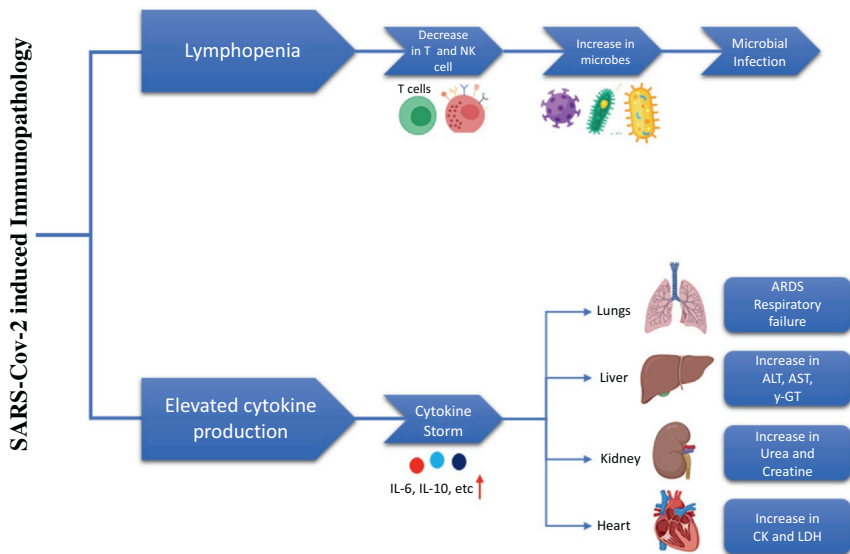


Fig. 3 SARS-CoV-2 induced immunology of severe form of COVID-19.

steroids and antibiotics to reduce the cytokine storm and opportunistic infections in severe cases, respectively. To contain ARDS, either external oxygen supply or ventilation is required in case of severe COVID-19. The rapid increase in infections across the globe and resulting fatalities forced development of vaccines for the disease on a war footing. Within a short span of less than a year, several vaccines have been developed and vaccination is administered rapidly across the globe hoping to achieve herd immunity and there by contain the disease.

In the context of COVID-19 pandemic, the treatment of patients with dreadful diseases like cancer, HIV, mental illness is challenging. In this chapter, we discuss the impact of COVID-19 on these patients and the managing strategies prevailed or emerged during this pandemic. We present the impact of COVID-19 on cancer patients in [Section 2](#). The effect of COVID-19 and its management on HIV patients is discussed in [Section 3](#). Subsequently, we discuss the impact of COVID-19 on mentally ill patients and patient management in [Section 4](#) and present a perspective on Ayurveda and its relevance in the context of COVID-19 treatment in [Section 5](#). Finally, we add a note on the available digital platforms or software tools for managing the COVID-19 patients in [Section 6](#).



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## 2 COVID-19 and cancer

In this section, we review the work related to cancer and its management in COVID-19 patients. More specifically, we present the treatment and managing the COVID-19 patients suffering from major types of cancers such as breast cancer, lung cancer, and hematologic neoplasms and malignancies.

Cancer is one of the prominent and persistent diseases of several types and affect almost all the tissues and organs with few exceptions. Despite intensive research, there is still no cure for many cancers and is one of the highly researched areas of modern medicine. Cancer is characterized by increased cell proliferation in tissues which leads the involved cell, tissue, and organ dysfunctional, leading to broad physiological disturbances in homeostasis of multicellular, multiorgan organisms with a final consequence in death. The cellular homeostasis of a tissue and organ is controlled by four cellular processes, *viz.*, self-renewal, proliferation, differentiation, and apoptosis which are in turn regulated by molecular determinants (gene/protein expression and genomic integrity), cell signaling, and biochemical regulation. Any changes in terms of genomic integrity leading to mutations, gene

amplifications, duplications affecting at least two of the cellular control processes, finally manifests into cancer. Thus, cancer is a multistep process which is accompanied by and is the result of the acquisition of the six biological capabilities such as sustenance of proliferative signaling, evasion of growth suppressors, resistance to cell death, replicative immortality, induction of angiogenesis, invasion and metastasis (Hanahan and Weinberg, 2000, 2011). Further to this it has been increasingly evident in the last decade that the progressively growing transformed cells/cancer tissue itself creates a hypoxic and inflamed microenvironment which pushes the cells to reorganize their metabolic states and evade immunity/or suppress it to thrive in the stress—essential for survival, which leads the cell for further transformation, and sets the stage for metastasis (Tennant et al., 2009; Cavallo et al., 2011; Prensner and Chinnaiyan, 2011; Fouad and Aanei, 2017; Tennant et al., 2009; Prensner and Chinnaiyan, 2011; Fouad and Aanei, 2017). The foundation of rationale for drug design/discovery to target at least two or more pathways with effective prognosis to achieve the disease free survival had been evident in last two decades with advent of targeted and semitargeted therapeutics (Fouad and Aanei, 2017). Nevertheless, most of the patients suffering from cancer need to visit the hospitals and also have to undergo various monitored therapeutic regimens which require several visits and hospitalization. However, due to the COVID-19 pandemic and the urgency to treat the patients, it is demanding a majority of the medical resources dedicated for treating COVID-19 patients. Therefore, it is very challenging to manage not only cancer patients but also patients suffering from other medical conditions. In this context we present the risk factors, scenarios and management of various types of cancers patients in COVID-19 pandemic.

## 2.1 COVID-19 and breast cancer

Breast cancer is prominent cancer type affecting more than 2 million cases across the world (Bray et al., 2018). Breast cancer is the most predominant cancer with very few or negligible number of male breast cancers. Breast cancer is highly heterogeneous at the molecular level, and requires different treatment approaches for major subtypes (Testa et al., 2020). Breast cancer is classified in subtypes based on the many genetic alterations (Radice and Pierotti, 1997). The most prominent one was proposed a couple of decades ago by Perou and Sorlie (Perou et al., 2000). Based on this classification, breast cancer is divided into various subtypes such as luminal A and luminal B, basal like (with no receptor expression) and



HER2 enriched (without ER expression). Clinical practice uses classification based on histological and molecular characteristics and thus, breast cancer is further classified into various types (do Nascimento and Otoni, 2020). When all the membrane-bound hormone receptors such as ER, PR, and HER2 are being expressed these tumors are called hormone receptor-positive breast cancers and if the receptor expression is completely absent, then those tumors are classified as receptor negative or triple negative breast cancers. Among all these cancer subtypes, targeted therapies are available for hormone positive breast cancers such as HER2 positive breast cancers (von Minckwitz et al., 2019). This cancer subtype can be treated with monoclonal antibodies against HER2 receptors and this therapy is proven to be effective (Baselga, 2001). However, triple negative breast cancers lack expression of any of the hormone receptors and are difficult to treat. Thus, they are more aggressive in recurrence with high fatality rates (Engelbraaten et al., 2013).

Although incidence of breast cancer is global, its distribution is skewed toward developed nations, and is more prominent in North America and Europe than in developing countries from Asia and Africa (Ferlay et al., 2015). This could be due to genetic factors as well as availability of better screening facilities for early detection (Winters et al., 2017). Less than 10% breast cancers are hereditary in nature and most prominent being the breast cancer with mutations in BRCA1 and BRCA2 tumor suppressor genes (Pruss et al., 2014). The incidence of breast cancer is also dependent on genetic, environmental, reproductive, and cultural factors (Rojas and Stuckey, 2016). Early pregnancy and breast feeding are shown to be inversely correlated with breast cancer incidences (Kotsopoulos et al., 2012). Obesity, alcohol consumption and less bodily exercises are considered to be positively correlated with occurrence of breast cancer (Australian Institute of Health and Welfare, 2012; Australian Bureau of Statistics, 2009, 2013). The histology and expression of the receptor dictates treatment regimens to be followed to treat various types of breast cancers.

Many breast cancer patients require regular visits to the hospital for consultations, surgeries, for radio or chemotherapies. COVID-19 is not only demanding most of the healthcare resources but also warrants social distancing and therefore cancer patients are advised to minimize hospital exposure to reduce risk of infections. Based on the urgency of requirement they are being categorized into Priority A, B, and C (Dietz et al., 2020). Priority A patients requires urgent hospitalization as the breast cancer is unstable and might result in poor prognosis if not intervened immediately. A short delay in medical intervention may not significantly affect the poor prognosis in

category B patients. Nevertheless, they may require hospitalization in the near future and can be subdivided based on the hospitalization requirement. Priority C patients may not require hospitalization for a considerable number of months and can be managed by remote consultations. Hospitalization can be deferred for these patients for a certain duration of time without affecting the outcome of the prognosis. For cancers such as triple negative breast cancer (BC) and HER2 positive cancers, surgery can be deferred by the option of neoadjuvant therapy (Sikov et al., 2015; von Minckwitz et al., 2019). Adjuvant and neoadjuvant therapy may not work with luminal A type, BC patients and they can be administered with endocrine therapy to delay immediate hospitalization. Metastatic breast cancer patients' doses and schedule adjustments could be made to reduce their hospital visits, blood work and side effects. Palliative care could be considered as an option if that relieves painful effects of the metastasis of the cancer. However, if the surgeries or progression of the disease to metastasis are imminent, then hospitalization of patients may be considered under strict COVID-19 guidelines (Dietz et al., 2020; Sheng et al., 2020). Many studies demonstrated that cancer patients that contract COVID-19 may have poor prognosis due to compromised immune system, radiation, and chemotherapies (Liang et al., 2020; Zhang and Guo, 2020). Most of the studies show that BC patients with COVID-19 may not be as vulnerable as other cancer patients to effects of SARS-CoV-2 infection.

## 2.2 COVID-19 and lung cancer

Lung cancer is highly prevalent next to colorectal and breast cancers with a high rate of fatality. Its high incidence is attributed to hereditary susceptibility, unbalanced diet, smoking, air pollution, radiation exposure, and an occupational exposure (Mao et al., 2016). One of the reasons for high mortality rate include the late detection of lung cancers by which time the cancer is metastatic or at an advanced stage (Spiro and Silvestri, 2005). Traditionally, lung cancers are classified as small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). NSCLC account for more than 80% of cases. SCLCs behave aggressively and are mostly treated nonsurgically, while treatment of NSCLC includes surgery and adjuvant therapies (Zheng, 2016). The diversity of NSCLC and SCLC has led to further subclassifications by World Health Organization (WHO). As per the 2015 WHO classification, lung cancers can be divided broadly into mesenchymal tumors, epithelial tumors, lymphohistiocytic tumors, tumors of ectopic origin,

and metastatic tumors. These classes are further subdivided based on their differences in immunohistochemistry (Pelosi et al., 2010). The major types of NSCLC include large cell carcinoma (LCC), squamous cell carcinoma (SSC/LUSC), and adenocarcinoma (ADC/LUAD), whereas SCLC is grouped with other tumors having neuroendocrine differentiation (Zheng, 2016). As mentioned earlier, the entry of SARS-CoV-2 virus into host cells occurs by binding of spike proteins to ACE-2 receptor. Further, the SARS-CoV-2 spike proteins are reported to be activated/primed by a number of mediators like transmembrane protease serine-2 and -4 (TMPRSS-2, TMPRSS-4), neuropilin-1 (NRP1), cathepsin L (CTSL) leading to infection in host cells (Katopodis et al., 2021). The physiological responses triggered by COVID-19 are amplified in the case of lung cancer patients due to the preexisting elevated levels of these molecules (Wan et al., 2010; Qian et al., 2013; Zhang et al., 2020). ACE-2 is primarily expressed in alveolar epithelial cells which play an important role in pulmonary gaseous exchange (Dobbs, 1989). Overexpression of ACE-2 in lung squamous cell carcinoma and lung adenocarcinoma has been reported. Aberrations of DNA methylation is considered as one of the causes for this abnormality in addition to histone modifications and glycosylation. Chai et al. (2020), Zhang et al. (2020), Kong et al. (2020), and Samad et al. (2020) explored the expression of *ACE2* and *TMPRSS2* with prognosis of COVID-19 in LUAD and LUSC. *TMPRSS2* is required for the binding of the spike protein (S protein) of SARS-CoV-2 virus to ACE-2. They reported that lung cancer patients at all stages and subtypes are highly prone to COVID-19 of which LUAD patients are highly susceptible. Tang et al. (2020) studied the expression levels of *ACE2*, *TMPRSS2*, and *AAK1* (endocytic regulator) in LUAD patients. They also studied the correlation of the expression of these genes and levels of immune infiltration caused as well as identified potential therapeutic targets and drugs for *ACE2*, *TMPRSS2*, and *AAK1*. They showed that expression of *ACE2* and *TMPRSS2* was high in case of LUAD which could be the reason for high susceptibility of these patients to COVID-19. They also reported that these patients showed higher infiltration of B cells, activated dendritic cells, memory T cells, and CD4 cells leading to the development of a “cytokine storm.” Hu et al. (2021b) have also reported a positive correlation between *ACE2* and *TMPRSS2* gene expression in lung cancer and the rate of immune infiltration.

In addition to the role of *ACE2* in COVID-19, the effect of other mediator proteins has also been studied. Yang et al. (2020) have reported the role of interferon gamma-induced protein 10 (IP-10) in COVID-19 infections.

IP-10 also known as CXCL10 (C-X-C motif10) is a proinflammatory cytokine known to be associated with pathological processes like infections and cancer. CXCL10 has been reported to be involved in the “cytokine storm” leading to tissue damage and ARDS. Hence has been also considered as an important biomarker for COVID-19 in addition to ACE2 receptor. [Xu et al. \(2020\)](#) and [Mahmood et al. \(2021\)](#) have analyzed in silico, the expression pattern, functional characterization and mutations of ACE2 and CXCL10 in LUSC and LUAD and have reported these are overexpressed. The overexpression of ACE2 gene might lead to higher degree of binding of the spike protein while high levels of CXCL10 might lead to alveolar collapse because of excessive cytokine secretions leading to increased fatality rate to COVID-19.

[Katopodis et al. \(2020, 2021\)](#) had studied the co-expression of TMPRSS-4 with other key SARS-CoV-2 cell entry mediators like ACE-2, ADAM17, and TMPRSS-2 in the bronchial epithelial cells of passive and active smokers. Further, TMPRSS-4 was found to be elevated in smokers. [Zang et al. \(2020\)](#) have reported the involvement of TMPRSS4 as a mediator for entry of SARS COV2 virus. They have observed that ACE2, TMPRSS2, and TMPRSS4 are co-expressed in cancer patients. Their finding indicates a predisposition to severe COVID-19 in these patients. Hence, a better understanding of the expression levels of these proteins and immune cell infiltration could aid in developing appropriate treatment strategies in cancer patients.

[Singh et al. \(2020\)](#) report a strategy for treatment of lung cancer patients during this pandemic. They report a workflow developed for treatment of NSCLC, SCLC, and lung neuroendocrine tumors (NETs) which relies on use of modern radiotherapy techniques for treatment and personalized treatment options. They recommend using image guided transthoracic biopsies instead of transbronchial biopsies for preliminary diagnosis. They also suggest use of computed tomography or Positron emission tomography for identification over invasive methods currently being used. They recommend mediastinoscopy over bronchoscopy in cases where invasive testing is needed.

For more details, it is recommended to visit websites of medical institutes of repute worldwide like British Columbia Cancer center, the European Society for Medical Oncology (ESMO), National Institute for Excellence in Health and Care (NICE), which have posted detailed information on patient handling and clinical management of lung cancer during the pandemic.

## 2.3 COVID-19 and the hematologic neoplasms and malignancies

The clinically manifested global infection rate of SARS-CoV-2 is 1%–2% and the rate of mortality in general population (noncancer patients) is 1%–5%, while >30% in cancer patients (Paul et al., 2021). SARS-CoV-2 can infect patients of all types of hematologic diseases. However, in early studies it was found that the risk of acquiring infection is higher for patients on immunosuppressive therapies, however the risk is lower in patients with chronic myeloid leukemia. Cattaneo et al. found that the mortality rate is 39.2%, compared to only 3% in not-infected hematologic controls and 23.5% in nonhematologic patients. The severe degree of respiratory syndrome combined with any type of active hematologic treatment was associated with worst prognostic outcome (Cattaneo et al., 2020).

Leukemia is a cancer of the hematopoietic system (HS). HS comprises the entire cellular compartment of the immune system derived from hematopoietic stem/progenitor cells (HSPCs)—through a tightly regulated interplay of the following cellular processes: (1) self-renewal of HSPCs, (2) proliferation, (3) differentiation and (4) apoptosis (Doulatov et al., 2012; Eaves, 2015; Bernitz et al., 2016; Arends et al., 2018; Zhang et al., 2018). It originates in bone marrow in adults and its mature-differentiated cells are present in the peripheral medium, which is blood, reaching each organ, tissue, and cells of the body. HS consist of the functional effectors and are the final frontiers of action to fight and clear off any foreign material or pathogens. The major cellular compartment of HS consist of HSPCs, multipotent progenitors (MPPs), myeloid (granulocytes), and lymphoid (agranulocytes—T and B cells) cells, which form the strong defense compartment to detect, alarm, digest and induce cellular and humoral immunity for future encounters with the pathogen (Dzierzak and Bigas, 2018; Boehm, 2011). The myeloid cells, i.e., granulocytes (mast cells, basophiles, neutrophils, macrophage, antigen presenting cells, erythrocytes, eosinophils) and the lymphoid cells, i.e., T-cells and B-cells and their differentiated progeny; series of T-effector and regulatory cells, NK cells, and memory and plasma cells, respectively—act through cross-talk with amongst themselves and cells of other tissues and organs, which is mediated through cytokines and chemokines upon interaction with the pathogen (Zhu and Emerson, 2002; Boehm, 2011). Interestingly, the receptor angiotensin converting enzyme 2 (ACE2), which is used by SARS-CoV-2 for entry into host cell (Hoffmann et al., 2020)—is expressed on monocytes, monocyte derived macrophages and also the cells of the bone marrow niche, which puts the

entire HS at risk of SARS-CoV-2 infection (Patnaik et al., 2020). HSPCs and progenitors can also stay in the same cellular state without differentiation for prolonged periods—some proportions even throughout lifetime. Thus, if these cells upon infection can lead to the generation of virus-persistence phase, which could stay asymptomatic till the HSPCs are not triggered to differentiate. Therefore, it is anticipated that—patients of Leukemia can serve as reservoirs of virus once these cells are infected with SARS-CoV-2 and also suffer secondary infections during the treatment and in relapse—most of the time leading to viremia and bacteremia. This is a regularly observed fact and is reflected in the patient data (Visentin et al., 2017; Pelland-Marcotte et al., 2020).

Leukemia are grouped and categorized in several groups depending on the cell types involved and the rate of cell division/or latency; for simplicity—here we take only two broad group—lymphoid and myeloid leukemia with acute and chronic category (which depends upon the rate of development of disease) (Arber et al., 2016; Swerdlow et al., 2016), which affect the overall functions of the respective compartment severely and thereby compromise immune functions. Leukemia patients can elicit inflammation or immune response or fail to do so depending on the type of leukemia—e.g., if granulocytes are involved, then these cells (transformed) are present at an alarming numbers—thus they can secrete varying quantities of cytokines needed for the first line of defense or fail to raise humoral immunity in lymphoid leukemia, depending on the proportions of transformed cells. This is complicated by the heterogeneous nature of the disease, that means the cell population also consist of various degrees of transformed cells—from leukemic stem cells, to normal cells to highly transformed cells (Stiehl et al., 2016; Beke et al., 2020). Therefore, the degree of these responses (in terms of overall inflammation) cannot be generalized or predicted, and needs to be monitored closely for each patient and treated accordingly to balance or to restore vitals of physiology for better prognosis and disease outcome.

In case of SARS-CoV-2, this is evident from a case study—of a chronic myelogenous leukemia; patient with immunocompromised state could shed the infectious virus for up to 70 days and the genomic and subgenomic RNA was detected till day 105 (Avanzato et al., 2020). Thus COVID-19, put the patients of leukemia in a unique category with short term personal benefit but at an impending risk to the other normal population, as they can serve as a reservoir of the SARS-CoV-2 (Truong et al., 2021).

This is being evident in patients and is an alarming concern as SARS-CoV-2 infection was found persistent in immunocompromised

patients—who can be reservoirs for replication and evolution—by accumulation of mutation and consequent emergence as novel strains which can have increased capacities of infectivity and evasion of immune response. It has been demonstrated in three patients with acute lymphoblastic leukemia (ALL) with persistent SARS-CoV-2 infection monitored by quantitative polymerase chain reaction and viral viability—through viral culture analysis over a period of 162 days. These results demonstrated broad spectrum infectivity and immune response (Truong et al., 2021). In another study consisting of 175 patients with myeloproliferative neoplasm (MPN) with clinically manifested COVID-19, the mortality was 48% with a median follow-up of 50 days compared to the general population. There was a significant co-relation between death and age, male gender bias, decreased number of lymphocytes, comorbidities, and myelofibrosis. This study also highlighted the increased risk for patients who discontinued ruxolitinib treatment during COVID-19 (Barbui et al., 2021).

Treatment and management of leukemia patients in COVID-19 presents us with unique challenges as homeostasis of the immune system—itsself is disturbed. Given the cellular homeostasis and the dynamics of molecular regulators and associated chemotherapy (targeted and semitargeted likewise) adds to increase the complexity of the treatment during the window period of risk of SARS-CoV-2 infection. Broadly, for the brief benefit of understanding: the line of treatment of leukemia are general chemotherapy or semitargeted chemotherapy (e.g., tyrosine kinase blockers-Gleevec/imatinib, or cell differentiators-like *trans*-retinoic acid for PML-RAR- $\alpha$  (promyelo monocytic-retinoic acid receptor alpha-leukemia and long list of other chemotherapeutics, etc.) or immunotherapy followed by hematopoietic stem cell transplantation (HSCT) and immunosuppression till graft acceptance (Lo-Coco et al., 2013; Dombret and Gardin, 2016; Piccolomo et al., 2020).

HSCT is a standard and most successful therapeutic treatment applied in all acute and chronic leukemia. This poses a challenge evident from the following cases, wherein the healthy allogenic donors (aged 22 years—a child of patient and 50 years—a sibling of patient) were tested negative—8 days before transplantation; however, they tested positive for SARS-CoV-2 but asymptomatic (RT-PCR tested on nasopharyngeal swabs only) on the day of collection. However, considering the benefit-risk balance in cases of acute myeloid leukemia, transplantation was opted. The recipients (patients of leukemia aged 60 and 64) were found negative and asymptomatic when tested twice a week for SARS-CoV-2 with nasopharyngeal swab and plasma

for 4 weeks posttransplantation. Nevertheless, recipients developed fever without any other symptoms—suggestive of COVID-19 (Leclerc et al., 2021).

The immunosuppressive treatment post bone marrow (or hematopoietic stem cell) transplantation, post chemotherapy—has immediate implications in COVID-19 pandemic, given that most of the bone marrow cells and its progeny's do express ACE2 receptor, thereby increasing the rate of infectivity of SARS-CoV-2. Therefore, the donors must be tested for persisting SARS-CoV-2 even in recovered survivor of COVID-19, and individualized decisions must be made depending on the risks of immunosuppression and other vital parameters (Jain et al., 2020; Weinkove et al., 2020; Truong et al., 2021). Thus, although COVID-19 is a life-threatening disease, but manageable compared to aggressive acute and relapsing leukemia—therefore, clinicians will have to weigh the “benefit-risk” assessment at a given point of time and location of patient (considering logistics of transplantation)—and administer the treatment without delay to pass through the window periods of mortal risk—which will definitely help to improve the outcome of leukemia patients with COVID-19.

The other effective front of leukemia treatment involves tyrosine kinase inhibitors (TKIs) and could be found fruitful in patients with leukemia suffering from COVID-19. A study of patients of Philadelphia-positive acute lymphoblastic leukemia (Ph<sup>+</sup>ALL) and chronic myeloid leukemia (CML) on TKIs (like nilotinib and imatinib) showed upregulation of “antiviral” genes, such as CD28 and IFN $\gamma$ , while less expression of “proviral” genes—ARG-1, CEACAM1, and FUT4, which is in congruent with the low occurrence of COVID-19 in Ph<sup>+</sup>ALL and CML patients (Galimberti et al., 2020). However, a conflicting in vitro report demonstrated no activity of imatinib or asciminib on SARS-CoV-2 replication (Zhao et al., 2020). In clinical setting, surveys from the Netherlands and Italian CML network (comprising of over 7000 patient data of CML and ALL) found very low incidences of COVID-19 in patients on TKIs, which is strong suggestive evidence of prospective potential to counter COVID-19 effectively (Ector et al., 2020; Breccia et al., 2020). Interestingly, imatinib's role of immunomodulatory effects are known and its target specific inhibition of ABL1/2 (nonreceptor tyrosine-protein kinase) and ABL1 is known for its function as a regulator of multiple pathological signaling cascades during infection. Imatinib also mediates inhibition of cytokine receptor signaling through PDGFR, c-Kit, and CSF1R (UniProt, 2021). Therefore, it is predicted that it can either inhibit or reduce



cytokine-induced inflammatory response and thereby the tissue injury as a consequence of the cytokine storm in COVID-19. This is evident in pre-clinical models leading to alleviation of acute lung injuries. Similar indication is evident in a report of a COVID-19 patient who presented rapid improvement in pulmonary infiltrates upon treatment with imatinib (Morales-Ortega et al., 2020).

Thus, in summary, leukemia patients can serve as long term transmission hosts. Therefore a general recommendation to reduce the risk has been issued—such as—to assent to telemedicine options, to make only essential visits and minimize the time spent in hospitals and infusions sites and treatment tips including indications to reducing or managing therapy-associated immunosuppression (O’Connell et al., 2020; Cengiz Seval et al., 2021). A surveillance mechanism must be attached with every leukemia ward during and postpandemic time for years till SARS-CoV-2 threat is evident.

The treatment of hematological neoplasm and malignancies have to be personalized depending on the disease risk predicted through the type, molecular signatures of disease, respective chemotherapy and its prognosis, the level of immunosuppression and the rate of community transmission of SARS-CoV-2 (i.e., if the patient is in COVID-19 hotspot zones), related healthcare infrastructure and logistics in the area with respect to the availability of HSCT donors, related diagnostics, associated drugs and cryopreservation for HCTs (Ferrara et al., 2020; Hus et al., 2021; Paul et al., 2021). And every patient of leukemia must to treated on emergency basis not only in COVID-19 but in any pandemic. Perhaps in the coming future of around 5 years a general treatment protocol can be drawn from the experience with respect to each type of leukemia and respective targeted or semitargeted chemotherapy and COVID-19 outcome.

Thus, in summary, it is predicted to a great confidence that patients of leukemia are at greater risk for themselves and as well as for others as they can be the reservoir for viral sustenance. Patient feedback mechanisms (such as telemedicine, mobile apps) must be employed to connect and monitor patient remotely and advice for hospital visits in COVID-19 appropriate guidelines to receive therapy for leukemia and also COVID-19 if contracted. Patients under the influence of immune-suppressors post donor HSC transplantations must be advised for COVID-19 appropriate behavior and monitored by RT-PCR on weekly basis. The use of TKI must be employed actively in consultation with the pulmonologist and every protocol for leukemia therapy, including matching healthy bone marrow transfer must be followed without any delay irrespective of local lockdowns to save

and protect as many patients as possible. This will in turn contribute in bringing down the overall mortality during COVID-19 outbreaks in present and future.

As per the European Society for Medical Oncology (EMSO), the prioritization of the cancer patients based on urgency of treatment is determined for hospitalization. As per these guidelines patients are categorized into high priority—when patients are unstable clinically or if situation is life threatening qualifies for this category; medium priority—patient condition may not be critical at the moment but may turn out to be critical after 6 weeks; and low priority—patient condition is stable and can be delayed beyond or for the duration of COVID-19 situation.



### **3 COVID-19 and HIV**

In this section, we present the impact of COVID-19 on patients affected by HIV. We discuss in detail about epidemiology, challenges of diagnosis and management of the HIV-affected patients.

World Health Organization (WHO), have reported 169,597,415 COVID-19–positive cases of which 3,530,582 people lost their lives across the world (WHO COVID-19, accessed on May 30, 2021). Since 1981 from the onset of the HIV/AIDS epidemic, 76 million people were diagnosed with HIV, out of which about 33 million died. Globally, 38 million people were HIV positive by the end of 2019. Approximately, 0.7% of middle-aged adults are living with HIV, although the occurrence and impact has been found to vary as per countries. The African region remains most severely affected, contributing to more than 67% of the People Living with HIV (PLWH) (WHO HIV/AIDS, 2021). Incidentally, it is noted that both COVID-19 and AIDS are due to retro viruses originated from animals. SAR-CoV-2 and HIV virus are distinct in their mode of transmission. Another major difference is in their incubation period. COVID-19 has a shorter incubation period relative to AIDS and spreads at a faster rate within few days (Dawa and Narain, 2021). It was believed initially that HIV positive patients don't have higher risk of getting infected with COVID-19. However, recent studies have observed that PLWH especially diagnosed with depleted CD4<sup>+</sup> T-cells counts or who have not started any treatments for HIV infection might be more severely affected with COVID-19. Lock-down measures taken due to COVID-19 pandemic led to interruption in HIV treatment services worldwide which poses a life-threatening challenge to PLWH. There is not much information on influence of geographical

location on the COVID-19 and HIV co-infections. Some of the observations suggest poor clinical outcomes in PLWH diagnosed with COVID-19, especially with low immunity and deprived of antiretroviral therapy (ART) (Boulle et al., 2020; Geretti et al., 2020; Tesoriero et al., 2021). The aged population and people with chronic disease and poor immune systems have high SARS-CoV-2 infection rate (Johns Hopkins University, accessed on May 30, 2021) (Kalichman et al., 2020; Meyerowitz et al., 2020). Although various parameters that determine the severity of the COVID-19 are still under investigation, compromised immune system and other parallel chronic conditions comprise the predisposing conditions for COVID-19 (Sigel et al., 2020). Additionally, renal disease, which is commonly observed in PLWH can lead to poor COVID-19 outcomes (Center for Disease Control and Prevention, 2021). Furthermore, food insecurity as a consequence of lockdowns can lead to poor nutrition which can impede immune functioning (Shalev et al., 2020).

Apparently, substance use is also predisposing condition for increased COVID-19 morbidity and mortality both in general population and PLWH (Suwanwongse and Shabarek, 2020). Tobacco use and/or smoking, is found to be associated with severity of COVID-19 by interacting with other substances and cause imbalance in the functioning of the immune system (Patel et al., 2020; Vizcarra et al., 2020). Alcohol and other drug use also suppress immune responses (Davies, 2020; Gervasoni et al., 2020; Karmen-Tuohy et al., 2020) particularly among PLWH (Childs et al., 2020). Some studies exhibit that continuous substance use with existing co-morbid conditions extend the complexity of COVID-19 in PLWH (Braunstein et al., 2021; Center for Disease Control and Prevention, 2021).

### 3.1 The epidemiology of COVID-19 in PLWH

Due to lockdown implemented in several countries in 2020, it is believed that the temporary suspension of HIV treatment services might have resulted in increase in mortality in 2020. Research indicates that PLWH represent around 1% of total hospitalized COVID-19 cases (Blanco et al., 2020; Okoh et al., 2020; Bhaskaran et al., 2021). Occurrence of SARS-CoV-2 infection in PLWH is in the range of 0.68%–1.8%, which is close to that in the general population ranging between 0.6% and 0.8% (Cooper et al., 2020; Mirzaei et al., 2021). Considering the clinical representation in PLWH co-infected with COVID-19, it was noted that approximately 67% presented mild signs, 22% showed acute symptoms, and remaining

exhibited serious conditions and were hospitalized (Cooper et al., 2020; Mirzaei et al., 2021). However, there is no evidence of asymptomatic infection rates in PLWH (Cooper et al., 2020). In series of studies in Europe and United States—the clinical outcome was not significantly different, rather similar between PLWH and people without HIV infection (Gervasoni et al., 2020; Härter et al., 2020; Karmen-Tuohy et al., 2020; Patel et al., 2020; Shalev et al., 2020; Sigel et al., 2020; Stoeckle et al., 2020; Vizcarra et al., 2020). In another case study, where more than 95% of the participants were male, not much variation in COVID-19 were found between the HIV positive and the general population (Park et al., 2020). However, in contrast, in other cohort studies with PLWH and COVID-19 in the United Kingdom, United States, and South Africa, showed increased mortality rates (Bouille et al., 2020; Dandachi et al., 2020; Geretti et al., 2020; Bhaskaran et al., 2021; Hoffmann et al., 2021; Tesoriero et al., 2021). The severity of COVID-19 was found to be associated with lower CD4-T lymphocyte cell counts (i.e.,  $<200$  cells/mm<sup>3</sup>) in patients with HIV and COVID-19. High risk was anticipated even in HIV patients who were treated through ART (Dandachi et al., 2020; Hoffmann et al., 2021). Similar observations were made in New York with higher rates of hospitalization and fatality in PLWH and COVID-19 (Tesoriero et al., 2021).

The epidemiology of COVID-19 in PLWH might be impacted in the future by COVID-19 due to different responses to wide range of available vaccines. In spite of presence of COVID-19 in the general population, more investigations need to be performed to study the interactions between SARS-CoV-2 and HIV (Cooper et al., 2020; Prabhu et al., 2020).

### **3.2 Role of interferons in natural defense to SARS-CoV-2 proliferations in PLWH**

Some studies reveal that the clinical behavior of COVID-19 is associated with class-I interferon responses in addition to antibodies that defend cells by neutralizing effect (Park and Iwasaki, 2020). But opposing to this, other investigations observed that, low or delayed immune responses allow rapid spread of virus leading to pneumonia, lung function failure, and even death (Vardhana and Wolchok, 2020). Few reports obtained from patients with severe COVID-19 suggest that cytokine storm is the result of sustained interferon responses coupled with tumor necrosis factor production in lungs (Lee and Shin, 2020). SARS-CoV-2 has evolved to fight or suppress the interferon responses. There can be several reasons for poor COVID-19 outcomes some of which could be low immunity or rare genetic disorders

leading to decreased interferon response, and antiinterferon component release (Bastard et al., 2020). HIV infection in order to control virus multiplication naturally activates interferon responses (Doyle et al., 2015). Some experimental data show that ART treats HIV patients by reducing the damages caused by interferon signaling (Díez-Fuertes et al., 2019). Therefore, immunological response of HIV positive patients to COVID-19 is a matter of concern.

### 3.3 Antibody generation against SARS-CoV-2 and potential threats in PLWH

Patients with COVID-19 might develop ineffective immune responses triggering lymphopenia, high production of cytokines, and fatigue. Lungs also undergo devastating changes leading to pneumonia and death. Cytokine storm also surfaces in acute HIV infection due to virus replication that amplifies immune response (Stacey et al., 2009; Fenwick et al., 2019). In most of the cases, ART restores normal levels of interferons and cytokines. In general, a complete viral suppression with ART ensures drastic immunity improvement in PLWH. However, despite ART, most of the HIV positive patients showed continuous viral replication, associated with low CD4<sup>+</sup> T-cell counts, and elevated concentrations of inflammatory markers, which can lead to rapid COVID-19 disease progression. Additionally, COVID-19 vaccines will not serve the purpose in case of defective B-cell functioning and sufficient number of T-cell counts. It has been observed through few studies that the high survival rates for COVID-19 are associated with early productions of anti-SARS-CoV-2 spike protein-IgG antibodies (Atyeo et al., 2020). Some investigations suggested that both B-cell and T-cell responses which are specific to the antigen help in prevention of COVID-19 development, thereby reducing fatalities (Atyeo et al., 2020). In PLWH, HIV multiplication triggers high production of cytotoxic T-cells which in turn leads to depletion of lymphocytes (Fenwick et al., 2019). In some cases, polyclonal response, abnormalities in B cells and T-cell activity have been reported (Moir and Fauci, 2017). If ART does not restore some of these damages in patients with advanced HIV infection, it can result in poor prognostic outcome with added SARS-CoV-2 infection. A couple of studies identified similarity in the concentration of IgG, IgM, and neutralizing antibodies in response to COVID-19 in PLWH and general population (Alrubayyi et al., 2021; Pallikkuth et al., 2021), however, another study displayed a lower rate of production of antibodies in PLWH (Spinelli et al., 2021). Thus, there

are contradictory reports, perhaps they can be attributed to the background inflammations and other co-morbidity or associated environmental factors.

### 3.4 Challenges of SARS-CoV-2 diagnosis in PLWH

Nasal and throat swab samples are most often collected for diagnosis of COVID-19 (Winichakoon et al., 2020). But SARS-CoV-2 is also identified in other samples such as in blood, stool, and urine (Wang et al., 2020a). In general, the SARS-CoV-2 virus concentration is similar in HIV negative and PLWH. In advanced stages of HIV disease, PLWH might exhibit a longer duration of SARS-CoV-2 expulsion and release of progeny (Aydillo et al., 2020). Not much is known about the COVID-19 disease progression in PLWH receiving ART (Peluso et al., 2020; Hu et al., 2021c). Real-time RT-PCR is currently used for diagnosis of COVID-19 which targets specific genes of the virus. It is a known fact that antibody detection is based on host immune responses to infection but there are chances that antibody response might be impaired in immune-deficient PLWH. There is not much evidence regarding the duration up to which IgG and total antibodies can be detected, virus shedding, and factors affecting antibody response which can include age, comorbidities, and immune-deficient conditions like HIV infection (Hanson et al., 2020).

### 3.5 Management of COVID-19 and HIV co-infections

Antiretroviral drugs have already been used in treatment of COVID-19. There is evidence that drug tenofovir might be active (Ayerdi et al., 2020; Del Amo et al., 2020) as it binds to RNA-dependent RNA polymerase, a critical SARS-CoV-2 enzyme (Elfiky, 2020). However, some clinical trials and research studies could not demonstrate therapeutic and preventive potential of the drug toward COVID-19 (Ayerdi et al., 2020; Del Amo et al., 2020). Protease inhibitors such as lopinavir-ritonavir and darunavir are tested for anti-SARS-CoV-2 activity. It was reported that darunavir did not show anti-SARS-CoV-2 activity at different concentrations and lopinavir-ritonavir failed to demonstrate significant efficacy in reducing mortality (Horby et al., 2020; WHO Solidarity Trial Consortium, 2021). Some investigations identified that remdesivir, an antiviral drug, when used alone or in combination with baricitinib, a JAK inhibitor, improved recovery time period among patients with advanced stages (WHO Solidarity Trial Consortium, 2021; Beigel et al., 2020; Spinner et al., 2020; Stebbing et al., 2020; Wang et al., 2020b; Kalil et al., 2021). However, the WHO Solidarity

trial did not reveal significant survival status after usage of these drugs in patient (WHO Solidarity Trial Consortium, 2021). Thus, these findings oppose the decisions with regard to the emergency use of remdesivir for COVID-19, taken by the Food and Drug Administration (FDA). Also, there is data reporting that the use of plasma from recovered COVID-19 patients and neutralizing antibody prevents disease progression and hospital admission in mild disease compared with placebo (Li et al., 2020b; Chen et al., 2021; Libster et al., 2021; Weinreich et al., 2021). Most of the antiinflammatory drugs, such as systemic corticosteroids, and baricitinib are under studies which show that they might act against inflammation and alleviating cytokine storms in severe COVID-19 (Li et al., 2020a). Dexamethasone when given in low doses consistently for 1–2 weeks has shown promising results in reducing mortality by inducing cytochrome P450 3A4 in critical patients on ventilation (Horby et al., 2020). Dexamethasone administration in PLWH suffering from COVID-19 should be decided in consultation with HIV specialist. There are no indications that drugs used for inflammations, elevated viral infections in PLWH. Hence, COVID-19 treatment for PLWH need not be different than the HIV negative-general population. In addition, anticoagulation therapy is also administered as a precautionary measure and is recommended in all the patients with severe COVID-19 manifestation including PLWH (Nadkarni et al., 2020).

### **3.6 Interrelationship between HIV infection and SARS-CoV-2 vaccines**

The principle behind most of the approved vaccines is based on effective production of neutralizing antibodies against the virus surface proteins. The same concept has been followed to target the spike protein of SARS-CoV-2 in generation of vaccines to mitigate COVID-19 (Krammer, 2020). To enable rapid results on SARS-CoV-2 vaccinology, some of the HIV preventive models under development such as RNA and adenovirus vectors have been used for the Coronavirus vaccines (Krammer, 2020). Very few PLWH were part of phase 3 vaccine trials, therefore their immune response to vaccines remains unclear (Baden et al., 2021). Predictions regarding the effectiveness of COVID-19 vaccine administration to PLWH are based on several parameters like the damages to the T-cell and B-cell compartment thereby consequently leading to diminished antibody generation in turn reducing the total immune responses to the SARS-CoV-2 spike protein. Several studies have showed that PLWH are not much responsive to most of the vaccines against different virus

(Geretti et al., 2020; Doyle et al., 2015). Therefore, specific recommendations are suggested, one of them being repeated vaccine doses (Ceravolo et al., 2013). People living with comorbidities or reduced CD4+ T-cell levels (less than 200 cells per  $\mu\text{L}$ ) are more prone to COVID-19, and hence must be advised for COVID-19 vaccination. Therefore, some of the agencies are in support that HIV positive patients must be administered vaccine without delay. Unfortunately, as mentioned earlier very less HIV positive patients volunteered for COVID-19 vaccine trials in PLWH, which included less than 1% participants for Moderna and Pfizer vaccine trials (Libster et al., 2021) Though there is not enough data obtained for vaccine effects on PLWH; nevertheless, it is suggested that during vaccination, ART should be provided.

### **3.7 Future scope of work in coinfection of SARS-CoV-2 and HIV**

Though there are very few research work done on PLWH infected with COVID-19, most of the reports indicate increased risk of death (Hadi et al., 2020). Majority of the observations revealed the associations of low CD4 counts with poor COVID-19 outcomes. Further investigations need to be conducted comparing COVID-19 prognosis in HIV-positive patients and general population with varied geographical status. The WHO Global COVID-19 Clinical Platform (WHO, 2021) has been collecting relevant information from PLWH and the general population undergoing treatment for COVID-19. Though there were conflicting results of drugs on SARS-CoV-2 infection, preexposure prophylaxis (PrEP) should be given for protecting against HIV-infection. Similarly, no data obtained so far suggests PLWH should be diagnosed or treated by distinct methods in case of COVID-19 progression. Lockdown measures have affected working of HIV clinics in many countries. Accessibility to hospitals and to ART should be a priority for HIV patients in the COVID-19 pandemic. No evidence exists right now to prove that the vaccines approved might vary in response or increase the risk of HIV infection. Therefore, a COVID-19 vaccine should be immediately available to PLWH to protect them from COVID-19. With regards to this, further studies must be conducted to know the immune response to all COVID-19 vaccines and to check how many doses would be sufficient to attain the required immunity for PLWH. Though research on COVID-19 and its relation with AIDS is progressing, there exists knowledge gaps which can be a focus and future scope of work for the scientific community across the world.



Over the past 1 year, statistics show that more than a million of people have succumbed to COVID-19 across the globe. It is also a known fact that HIV is a deadly disease and PLWH have higher risk of COVID-19. PLWH can have adverse effects if co-infected with SARS-CoV-2 which can be fatal. HIV positive patients who are under ART also can develop COVID-19. In whichever countries HIV is prominent, government must make sure that HIV patients have access to hospitals, treatment and ART even if lockdown measures are taken to mitigate COVID-19 spread. It would be better if PLWH are vaccinated at the earliest to prevent severe side effects of COVID-19, if at all they are infected. It is the need of the hour that hospitals treating COVID-19 patients are educated and made aware of guidelines set by WHO, Centers for Disease Control and Prevention (CDC) and National institutes of Health (NIH) on how to manage HIV and COVID-19 co-infections. Though, there is not much evidence and research to suggest which COVID-19 vaccines and treatments would work efficiently on HIV positive patients, it is recommended that PLWH be given same COVID-19 diagnostic procedures, vaccines and treatment as the general population until further scientific investigations leads to new outcomes and developments which have contradictions to current instructions for disease management.

People infected with HIV and patients of leukemia are not only at greater risk but also, they can serve as reservoir for the sustenance of SARS-CoV-2, its evolution and long-term shedding. Therefore, they must be attended and administered with disease and individual specific therapeutics with antiretroviral in combination with management of SARS-CoV-2 infection.

The advanced stages of HIV infected people (AIDS)—if co-infected with SARS-CoV-2, shows prolonged shedding of virus in all body fluids. Therefore, continuous weekly monitoring of virus in all body fluids accompanied with cytokine profile to predict the “cytokine storm,” will be helpful in administration of corticosteroids (antiinflammatory) for managing the window of risk and also the B-cell and T-cell function should be monitored to mark the disease course which will help to treat added infection of SARS-CoV-2 and HIV together. Antiinflammatory corticosteroids, especially dexamethasone treatment for 1–2 weeks should be fruitful to alleviate cytokine storm and thereby limit the cytotoxic effects on lung tissue and delay or cease the induction of fibrosis, which will be beneficial to maintain the capacity of lung function. Anticoagulant is also administered in PLWH under observation to inhibit thrombosis/coagulation effects predicted due to SARS-CoV-2.

The observation of T-cell count in PLWH is an essential parameter, as the maximum benefit of vaccination depends on the number of primed T-cells, which can cross-talk with B-cells to induce them for maturation

and differentiation (plasma and memory B cells) to generate long-term memory cells and thereby leading to the protection. Therefore, the timing of the COVID-19 vaccination for PLWH can be chosen for each patient depending on their total CD4+ T-cell count- which will ensure the optimum signaling between T and B cells.



## **4 Effect of COVID-19 and current treatment or management strategies for mentally ill patients**

In this section, we discuss epidemiology and treatment options for mentally ill patients affected by COVID-19.

The global pandemic caused by SARS-COV2 has not only affected physical health but has severely impacted global market, economy, agriculture, health care, etc. Despite employing all resources to mitigate the aftermath of this pandemic, the failures and uncertainty involved have caused a lot of mental distress among people. In this era of heavy social media users, exposure to unauthentic and misleading information about the pandemic has caused spread of conflict, rumors and negative social behaviors. Most impacted are the infected and sick patients, healthcare workers and their family members since they are directly on the receiving end of the pandemic's consequences. Mental health problems like anxiety, depression, insomnia, and emotional outbursts often interfere with decision making capacity of health workers (Kang et al., 2020). Further, isolation strategies to break the transmission chain has created panic, fear, and acute physiological stress within people. As WHO speculated, isolation has led to an increased use of alcohol, drugs, insomnia, loneliness, anxiety, abusive behavior, and depression (World Health Organization, 2020b). A massive change in regular activities and routine has played a role in increasing stress about workplace factors, livelihood factors making this pandemic a psychological pandemic as well. Apart from acute emotional effects, chronic mental disorders like posttraumatic stress due to loss of a colleague/family and obsessive-compulsive disorders like maladaptive behavior of sanitization are rising. Increasing financial losses, shortage of resources, irregular and conflicting information from authorities, trial and error public health measures and looming uncertainty increases the risk of mental illness, unhealthy behavior like suicidal thoughts and noncompliance with public health directives.

### **4.1 Impact of COVID-19 on mentally ill patients**

The distress, uncertainty, and the unpredictability of the pandemic with no treatment in sight has led to relapse of anxiety, depression, panic, psychosis,

delirium, and suicidality in mentally ill patients. Patients with limited access to treatment will experience a further depletion in attention due to unavailability of resources for care and therapy which may increase their anguish. Patients with serious psychiatric conditions like schizophrenia are already socioeconomically disadvantaged and with the lockdown, isolation, stay at home orders with subsequent reduced access to employment can only aggravate their distress economically as well as socially stressing the patient caregivers as well (Gautam et al., 2020).

Patients with severe mental illness who need treatment and rehabilitation consistently are finding it difficult due to lockdowns as well as limited access to healthcare in psychiatric hospitals and also there is always the risk of exposure with regular hospital visits (Lima et al., 2020; Muruganandam et al., 2020), reported in their study that 72% of the patients with severe mental illness did not know about symptoms and about 64% were not aware of the precautionary measures about COVID-19. 8.3% of the patients were ignorant or not aware of the transmission mode of the SARS-CoV-2. With home isolation being mandatory all over the country, the hardships and burden on the caregivers was higher in this patient category which manifests in the form of very or no social support, increased negative expressed emotions (Nirmala et al., 2011), domestic violence toward patients (Afe et al., 2016) thereby raising the risk of relapse significantly (Altman et al., 2006). Other factors like social isolation, financial strain, negative social interactions, low emotional support, and psychological distress enhances the burden of the caregiver.

Deterioration of the patients who were stable before lockdown was seen in around 30% of them. The cause could be high liability to stress in home isolation, (Altman et al., 2006), major life events (Sam et al., 2019), poor access to psychiatric hospitals and poor treatment compliance (Xiao et al., 2015), disturbed biological rhythm (Karatsoreos, 2014), and upsurge of caregiver burden (Nirmala et al., 2011). Psychiatric doctors who were in regular consultations with the mentally ill patients exhibited more awareness of the recent situation suggesting that regular access to treatment is directly proportional in improving the condition of the patients as well as appraising them to the current ongoing pandemic. Novel set of psychiatric symptoms related to COVID-19 or exacerbation of preexisting psychopathology in patients with SMI can be seen in such pandemic (Fischer et al., 2020). This sector of population with relapse translates to poor hygienic conditions, inability to practice social distancing, delay in seeking and reporting medical attention, aggression, suicidal behavior, increased substance use, poor compliance

for their psychiatric treatment and comorbid medical illness will have a major social impact during the pandemic (Gunnell et al., 2020).

## 4.2 Treatment of mentally ill patients during COVID-19

The consequence of the pandemic on mental health is considered less important than its physical one. The flood of patients and their immediate dismissal on recovery to facilitate admission of more patients often causes neglect in proper psychiatric care. Attention from mental health professionals is required to avoid the psychological risks that occur due to confinement of patients. Facilities like regular follow-up with telemedicine to monitor suicide risk, PTSD risk could be helpful (Chevance et al., 2020). Further, experienced psychiatrists should help governments in framing management plans and create awareness among public like the development of a psychological support plan in France. Self-help manual to deal with stress by the disease are proposed for better management (Zhou, 2020). Health policy makers should show an inclusive approach to accommodate therapeutic needs of different effected groups. Telepsychiatry via online means is an appropriate alternative to deal with the challenges of this pandemic. It has an advantage of providing accessibility to underserved, rural areas, greater flexibility and availability of appointments and reduced costs.

Providing general guidelines to public along with a free 24-h helpline in collaboration with mental health volunteers and coordinated supervision of psychological consultants would be an ideal strategy to support people. To reduce the risk of increasing mental disorders from continuous exposure to temporary symptoms like anxiety, depression, loneliness; communication with family, colleagues and use of professional helplines must be encouraged (Fiorillo and Gorwood, 2020). The sources of stress must be limited, spread of unverified information must be monitored. Asking for professional help to seek emotional aid, dealing with significant repetitive symptoms, such as panic attacks, persistent insomnia must be easily accessible. Health care systems and policymaking should focus on prevention and interventions related to the public mental health to deal with pandemic associated mental health challenges. Regional factors and other parameters should be taken into account to meet the mental health needs of the population. A strong collaborative network for effective therapeutic strategies accessible to public easily could help alleviate the ongoing and to come mental health challenges.

The ongoing pandemic has affected millions of people across the globe mentally, physically, and emotionally. The losses of loved ones, enforced

isolation and reduced healthcare system have seen to be the case in almost every country. We, humans are social animals by nature and due to the contagious nature of the disease we are unable to isolate ourselves for long periods of time and this is having a negative effect on our mental wellbeing. All age groups across the continents have been having adverse effects due to lesser social interactions. Mentally ill patients who already have stress are having an extremely difficult time coping up with the new norms. Regular access to hospital care as well as medication due to lockdowns and fear of spread of the outbreak of COVID-19 has seen to have a relapse of their conditions. The only way moving forward is to have regular telephonic counseling by the doctors.



## 5 COVID-19 and Ayurveda's holistic lifestyle approach

Here, we elaborate the relevance of Ayurveda and Yoga for treating COVID-19 patients.

Much of the human history is littered with epidemics and pandemics apart from history course changing social events. It is been well described about epidemics, pandemics in the ancient book of medicine Charaka samhitha pertaining to Ayurveda branch of medicine. While epidemics are sudden out breaks and confine to particular area, pandemics are global in nature. Epidemics are described as *aupasargika roga* and pandemics *asjanapadodhvansa roga* (Murthy, 2010) in Ayurveda. *Janapadodhvansa* means annihilation of populations.

Due to the hegemony of COVID-19 pandemic, some preventive measure has to be in place until an effective cure is found. Recently the AYUSH ministry of the Indian Government had an initiative to receive proposals from Ayurvedic and homeopathic medicine researchers and received more than 2000 proposals and are under active consideration for funding. As per Ayurveda experts, medicinal plants such as giloy, amla, shilajit, and neem are suggested to be helpful in enhancing the immune systems (Rajput, 2020). As per Dr. Chauhan, director, Jiva ayurveda, a tablespoonful of Chywanprash daily intake boosts the immune system and may prevent the spread of the virus. Many traditional Ayurvedic medicinal such as guduchi/glioy (*Tinospora cordifolia*), kutki (*Picrorhiza kurroa*), Amalaki or amla (*Embolica officinalis*), neem (*Azadirachta indica*), tulsi (basil) are suggested to for daily intake for enhancing the immune system (Mondal et al., 2011; Jamshidi and Cohen, 2017; Girija and Sivan, 2020; Roy and Bhattacharyya, 2020; Mishra et al., 2021). Good digestion plays an important role in fighting

diseases and a regular intake of ginger tea or mint tea or fennel tea are recommended for better digestion. Recent reports indicate that there is 15% hike in the demand of turmeric powder, shilajith, aswagandha in India as people are looking for alternative measures to manage COVID-19 (Jagetiya and Aggarwal, 2007). “Nasya,” a therapeutic intervention for cold, head ache, sour throat, can be alleviated by giving oils such as anu oil and shadabindu oil (Kar et al., 2020; Tomooka et al., 2000; Mittal and Chand, 2020; Rajput, 2020). As per, Baba Ram dev, a famous yoga guru, giloy and tulsi are suggested to be effective for treating COVID-19 (Ozah, 2020; Tillu et al., 2020). Yoga exercises such as pranayama, kapalabhati and anulom vilom are recommended for boosting immunity (Eda et al., 2013). Abhyagana (self-massage) as per Ayurveda, stabilizes nervous system, relieves stress, and supports immune system (Majumdar et al., 2020). Sesame oil can be used to do the massage. In addition, oil pulling and nasya can be tried to boost the immunity (Nagendra, 2020).

Some yoga poses such as Utaanasana (standing forward bend) or sarvangasana helps the lymphatic system to drain pathogens and waste products (Fulambarker et al., 2012; Infante et al., 2014; Lim and Cheong, 2015; Raghuram et al., 2008). Warm bath with Epsom salts, ginger oil, cardamom, rosemary, eucalyptus, cedar, pine, cinnamon, basil, poine helps in keeping the virus at bay. A quality sleep helps in production of cytokines that helps immune system to fight pathogens (Fulambarker et al., 2012; Liu et al., 2014; Lim and Cheong, 2015). Meditation not calms down the mind but also helps in keeping sound mental status so that proper messages can be transmitted through the brain during the vital periods of infections and diseases, reduces oxidative stress there by helping immune system (Donesky-Cuenca et al., 2009; Gupta et al., 2014; Guleria et al., 2015; Kusnanto et al., 2018; Bushell et al., 2020).

It has been found that the general treatments including the Ayurveda and holistic practices are very important to enhance host immune response against RNA viral infection. The AYUSH Ministry of Indian government is actively seeking proposals and boosting funding for establishing the validity of some Ayurveda medicines as viral drugs and improves the immune system. It is highly being encouraged by the government of India for all Ayurveda physicians to collaborate and follow scientific guide lines to support Ayurveda claims. So as of now the best available remedy to combat the Covid-19 is the effective utilization of Ayurveda therapy and holistic management with the adoption of yoga practice, proper diet regimen, and detoxification procedures to bring back the energies (doshas) to balance.

The health care systems were challenged by COVID-19 pandemic across the globe, which in turn has brought the world attention to body's immune system against the pathogenic organisms. COVID-19 pandemic has brought serious psychological and mental distress among the people as the diseased are more vulnerable viral infections in the respiratory tract. As per *Charaka Samhita, the ancient Ayurveda text*, immunity plays a significant role in the prevention and progression of the disease and maintenance of homeostasis in the body. The Ayurveda primarily focuses on building the strong immunity in addition to strengthening the mind by getting rid of stress. Several treatments in Ayurveda including herbal decoctions and immunomodulators (Rasayana) are known to enhance the immune system against the respiratory diseases. As per the Ayurvedic prescription, which are routinely practiced in many households, consumption of hot water and Ayurvedic herb infused water in addition to steam inhalation and gargling with medicated water do wonders in preventing respiratory illness caused by COVID-19. Yoga and Pranayama have positive effect on strengthening the immune system and the respiratory system to maximize the efficient oxygen intake.

In the next section, we present various digital platforms used for contract tracing and managing COVID-19-related information.



## **6 Softwares/web tools/digital platforms used for COVID-19 management**

Unprecedented levels of COVID-19 pandemic necessitated urgent development/usage digital platforms through web tools, social media platforms such as WhatsApp and Facebook. WHO and various health organizations have developed various digital tools for dissemination of COVID-19-related information. GoData ([WHO GoData, 2021](#)) is a web and mobile based digital platform, which is used by World Health organization (WHO). It is used for collecting COVID-19 data from sources like labs, hospitals, etc. It is also used for tracing the contacts of COVID-19-infected persons. It also provides data visualization and a dashboard to have an overall glimpse of the COVID-19 information. Maldives used this software to manage COVID-19 outbreak.

In India, CoWIN portal is used for registration of COVID-19 vaccination ([CoWin, 2021](#)). Using this portal, the citizens can register for COVID-19 vaccination and schedule it at various hospitals. Those who vaccinated

can download the vaccination certificate from the portal. For contact tracing, “Arogya Setu” (meaning-“Health Bridge”) mobile-Bluetooth enabled app is used to know the information of infected people in the vicinity in real-time mode. It alerts if a person using the app comes in contact with the infected person which enables for timely medical treatment. It assesses the possibility of infection through the self-assessment test. It enables the regulatory bodies of the Government of India to identify COVID-19 hotspots and enforce predictive localized lockdown or restricted movement so that the spread of virus can be reduced or quarantined. The Arogya Setu app is primarily used for COVID-19 contact tracing. In other countries, there are many such digital tools are used. Similar contact tracing apps are used in many other countries world-wide with exhaustive list of them available on Wikipedia ([Wikipedia, 2021](#)).



## 7 Concluding remarks

The devastating effects of COVID-19 pandemic created a situation requiring an urgent and war footing efforts to contain the disease. Perhaps, it is for the first time in medical history that a causative agent for the disease and development of vaccines from bench to bed happened within a couple years which itself is a remarkable achievement of human efforts. However the availability and administration of vaccines for billions of people is proving to be a daunting task due to the production and logistics. As the information related to the COVID-19 is still pouring in, researchers and administrations are constantly adopting various strategies to contain the disease. It is anticipated that, as the time progresses, the virus gets weak and probably COVID-19 becomes a short illness like a flu and could be contained with periodic vaccination. It is reassuring that the many vaccines that are available now could work effectively against several variants of the SARS-CoV-2 barring few strains. In future, the management of the COVID-19 would become a routine and well standardized procedure giving a scope for better management of patients suffering from other diseases like cancer, HIV, and mental illness.

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