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HIV and SARS-CoV-2 Co-infection: Epidemiological, Clinical Features, and Future Implications for Clinical Care and Public Health for People Living with HIV (PLWH) and HIV Most-at-Risk Groups

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Abstract

Purpose of Review The purpose of this review is to use the currently available clinical and epidemiological data, to identify key aspects to improve both the clinical management and public health response to SARS-CoV-2/HIV co-infection among HIV vulnerable populations and people living with HIV (PLWH).

Recent Findings While at the beginning of the COVID-19 pandemic, the lack of robust information on SARS-CoV-2/HIV co-infection, prevented a clear picture of the synergies between them, currently available data strongly support the importance of common structural factors on both the acquisition and clinical impact of these infections and the relevance of age, comorbidities, and detectable HIV viral load as associated worse prognostic factors among PLWH.

Summary Although more information is needed to better understand the biological, clinical, and epidemiological relationship between both infections, a syndemic approach to prevent SARS-CoV-2 among HIV high-risk groups and PLWH, targeting these populations for SARS-CoV-2 vaccines and protocolizing early identification of PLWH with worse COVID-19 prognosis factors, is crucial strategies to decrease the overall impact of SARS-CoV-2 /HIV co-infection.

Keywords HIV · AIDS · SARS-CoV-2 · COVID-19 · Co-infection · Epidemiology · Clinical guidelines · Impact · Synergia · Sindemia

Introduction

As we make efforts to grapple with HIV, the novel COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been an unprecedented threat to global health, challenging the robustness of health systems and the overall economy as a whole. Since the first case was reported in Wuhan, China, in 2019, infections are approaching 200 million and claimed more than 4 million lives as of July 22, 2021 [1]. Older age and the presence of chronic comorbidities like hypertension, diabetes, obesity, chronic respiratory disease, chronic kidney disease, cardiovascular disease, and malignancies are currently linked with a higher risk of severe disease and mortality [2–5]. On the other hand, as it happens with many other transmissible infections, COVID-19 vulnerability is also associated to social and structural determinants like poverty, population density, and lack of access to health services, creating a syndemia of social and health problems [6].

In this context, HIV most-at-risk populations share many structural factors for SARS-CoV-2 acquisition

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amidst the existing controversy regarding the susceptibility of people living with HIV (PLWH) to SARS-CoV-2 infection and severity of the co-infection. PLWH have higher susceptibility to other infections including respiratory infections due to their aberrant humoral and T-cell-meditated immune responses [7]. Moreover, with PLWH aging [8], having higher prevalence of chronic comorbidities [9], and presenting with other risk factors of severe COVID-19 such as smoking [10], this population might have an increased risk of poorer COVID-19 outcomes.

Although there are antecedents of two previous coronavirus epidemics, the severe acute respiratory syndrome (SARS) in 2003 and the Middle East respiratory syndrome (MERS) in 2013 [11], there is little to learn from these experiences regarding the incidence and clinical severity of HIV co-infection with these two coronaviruses. Currently available data do not suggest higher SARS-CoV-2 infection rates among PLWH [12–15] and although initial studies assessing the severity of COVID-19 among PLWH showed no clear evidence of poorer outcomes [16], emerging data are reporting higher risk of morbidity [13] and mortality [17–20] among some HIV-SARS-CoV-2 co-infected patients, particularly those with lower CD4 cell counts and those with unsuppressed HIV viraemia [21–23]. Some researchers have also speculated lower risk of infection and severe outcomes among HIV/SARS-CoV-2 co-infected patients because of the potential protection from some antiretroviral therapy (ART) regimens [12, 24, 25] and have even suggested that immunosuppression could restrict the development of COVID-19-related cytokine storm [26, 27].

Finally, governments across the globe implemented strict measures to reduce mobility of persons and limit social activities in order to control the transmission of SARS-CoV-2. These measures disrupted daily human lives and inadvertently hampered the delivery of key preventive and clinical HIV services [28].

The inconsistency of clinical data regarding the impact of SARS-CoV-2 on HIV and the scarcity of population-based data sources which reports both infections highlights the importance of robust information systems with sociodemographic, biological, and clinical data to respond to the increasing number of questions needed to be answered to better articulate an effective response and to improve both clinical and public health guidelines on HIV-SARS-CoV-2 co-infections.

We have reviewed the association of HIV and SARS-CoV-2 and its implications for HIV services from both a clinical and public health perspective, with a particular emphasis on the European context. Moreover, we explain how the COVID-19 pandemic has disrupted HIV prevention and treatment services, creating huge challenges to the continuity of essential healthcare activities. Finally, we highlighted topics where further research is required such as vaccination.

Epidemiology of HIV and SARS-CoV-2

Estimates from the UNAIDS show that as of the end of 2020, there were 37.6 million (estimate range, 30.2–45.0 million) people were living with HIV with 1.5 million new cases and 690,000 deaths in 2020 only [29]. Since it was identified in 1980s in the World Health Organization (WHO) European Region, the HIV epidemic remains an on-going public health problem in the region with over 2 million people living with the infection by the end of 2019 [30]. In 2019, there were 136,449 reported new cases in the region representing a crude rate of 15.6 per 100,000 persons of newly diagnosed infections [30]. Late diagnosis remains a challenge in the region as 31% of newly diagnosed persons presented with advanced HIV (CD4 < 200 cells/mm^3) [30].

The COVID-19 pandemic first hit Europe on January 24, 2020, with the first three cases reported in France [31]. As of July 22, 2021, the region had reported 33,956,561 cases and 742,847 deaths [32]. France, UK, Italy, Spain, Germany, and Poland have been hugely affected in the European region in terms of number of confirmed cases and deaths [32]. The European monitoring of excess mortality for public health action (EuroMOMO) network reported excess mortality estimates in the initial stages of the COVID-19 pandemic in Europe. By the 18th week after the pandemic commenced in Europe, the cumulative excess mortality in all ages was 185,287 deaths. People aged ≥ 85 years contributed most to the excess mortality (48%) and was least among 15–44 year olds (1%) [33].

Across Europe, the incidence of COVID-19 among PLWH ranges from 0.3 to 5.7% person years [12, 14, 22, 34, 35]. Two studies have assessed the prevalence of HIV among hospitalized COVID-19 patients in Europe being between 0.26 and 1.0% [20, 36]. In a pooled analysis, PLWH were identified to be more susceptible to SARS-CoV-2 infection with a risk ratio (RR) of 1.24 (95% confidence interval [95% CI] 1.05–1.46); the prevalence of HIV among hospitalized COVID-19 patients in this analysis was however not significantly different than the background population (RR = 1.22, 95% CI 0.61–2.65) [37]. Nevertheless, because diagnostic rates are a function of the screening criteria, it is likely that — particularly at the beginning of the pandemic — diagnostic rates among PLWH were overestimated because testing was based on symptoms, age, comorbidities, or epidemiological criteria.

HIV/SARS-CoV-2 co-infected patients in Europe were 38–56 years which is about a decade younger than the reported average age in the general population [20] and predominantly males [12, 14, 20, 22, 34, 35]. COVID-19

diagnosed PLWH were more likely to belong to a low socioeconomic class [17] and likely to be of black ethnicity [17, 20]. Mortality rates among HIV/SARS-CoV-2 co-infected patients in Europe have ranged from 1.9 to 29.0% [12, 14, 20, 21, 34–36, 38–42].

An essential aspect of any infectious disease control and prevention measure is quality epidemiological surveillance, timely and accurate enough to identify cases and patterns of transmission to guide early and effective preventive interventions. Both in the USA [43] and Europe [44], retrospective analysis of influenza monitoring sentinel networks suggested that SARS-CoV-2 was circulating earlier than the first cases were officially recognized and therefore a high percentage of these infections remaining undiagnosed. A study from Wuhan, China, reported that if public health measures had begun 3 weeks earlier, cases could have been reduced by 95% [45].

Robust population-based programmatic and surveillance data, including epidemiological, microbiological, clinical, and syndromic information are crucial to understand the distribution and dynamics of SARS-CoV-2 and its impact in key populations such as PLWH. Unfortunately, at the beginning of the COVID-19 pandemic, many national information systems were not prepared to face an integrated approach of the needs emerged by the SARS-CoV-2 infection. Systematizing the use of microbiological methods to identify SARS-CoV-2 infection among PLWH is imperative not only to have a better picture of the epidemiological pattern of the co-infection, but also to identify individuals at risk of worse clinical outcomes promptly.

Potential Impact of Antiretrovirals on SARS-CoV-2 Infection Risk and Outcomes

Since the beginning of the COVID-19 pandemic, the possibility that some antiretroviral drugs might be active against SARS-CoV2 was considered. However, with the evidence available so far, the antiretroviral treatment should not be modified to treat SARS-CoV-2, since no proven activity of any antiretroviral drug has been consistently documented. Some studies are ongoing to bring light to this issue. The association of tenofovir disoproxil (TDF) use and a potentially lower COVID-19 infection rate has sparked much debate. In studies from Spain [12] and South Africa [18], TDF was associated with lower SARS-CoV2 infection incidence rates.

However, selection biases were present in both studies since it is unlikely to provide TDF to PLWH with known comorbidities such as cardiovascular risk factors or kidney disease, which have been identified as risk factors for COVID-19 and poor outcomes. Therefore, PLWH treated with TDF would probably be preferentially younger and with no known comorbidities, entailing an intrinsic lower risk for SARS-CoV-2 infection. In the South African study, receipt of TDF (vs. zidovudine) was associated with reduced COVID-19 mortality even after adjusting for renal disease, viral suppression, and antiretroviral treatment duration, but again, other non-adjusted factors (prior virologic failure, tuberculosis) could be associated with zidovudine use [18]. A third study in subjects with chronic hepatitis B (without HIV infection) has also reported significantly lower rates of severe COVID-19, intensive care unit (ICU) admission, ventilatory support, and fewer days in the hospital in those receiving TDF vs entecavir [46]. However, again, people taking TDF had significantly lower comorbidity rates. Finally, TDF/FTC PrEP users presented a higher seroprevalence to SARS-CoV-2 than the control group, with no significant differences in clinical manifestations [47]. Similarly, a matched case–control comparison in the PREVENIR-ANRS French study with middle-aged HIV-negative people who did or did not use TDF/FTC PrEP found no evidence that TDF may help ward off SARS-CoV-2 infection [48].

HIV protease-inhibitors (mainly lopinavir/ritonavir) have been used early during the pandemic to treat COVID-19 but, currently, no study supports their use.

Potential Impact of Comorbidities on SARS-CoV-2 Infection

Although some studies have reported HIV infection as a risk factor for poor outcome, there is no clear evidence for a more severe disease course of SARS-CoV-2 infection in PLWH on active ART and with good cellular immunity (CD4 cell count) levels. Among hospitalized COVID-19 patients, most studies reported a younger age of PLWH vs. HIV-negative patients, with higher rates of comorbidity [14, 23, 35]. These comorbidities are consistently associated with poorer outcomes in PLWH with well-controlled HIV infection and constitute the underlying bias in all series reported.

On the other hand, larger cohort studies suggested poorer outcomes for PLWH not only in the presence of comorbidities, but also in those with low CD4 cell count (< 200 cells/mm^3) [18, 23]. This would be consistent with the poorer COVID-19 outcomes seen in other immunocompromised hosts. In addition, severe COVID-19 has been also described in PLWH with concomitant opportunistic infections, such as tuberculosis and/or *Pneumocystis jirovecii* [49].

Thus, PLWH have a higher risk for severe COVID-19 outcomes in two clinical contexts: (i) uncontrolled HIV infection and/or advanced immunodeficiency, or (ii) additional comorbidities.

Outcomes (Hospitalization, Intensive Care Unit, and Mortality) and Determinants

In studies including outpatients, overall rates of ICU admission ranged between 3 and 22% for PLWH [50]. When only hospitalizations were reported, ICU admission for PLWH ranged between 17 and 33% [50]. Severity of COVID-19 illness increases with age and comorbidities, as it does in the general population. Multimorbidities have been reported in nearly two-thirds of patients co-infected with HIV and SARS-CoV-2 [23, 50].

Despite the existing debate, clinical data from 37 countries reported to the WHO Global Clinical Platform for COVID-19 indicate that HIV infection is a significant independent risk factor for severe/critical COVID-19 presentation at hospital admission and in-hospital mortality [19]. Mortality in hospitalized PLWH with COVID in the UK showed an adjusted hazard ratio (aHR) of 1.69 (95% CI 1.15–2.48; $p = 0.008$) [20], whereas, in primary care alone, after adjustment for age, gender, ethnicity, smoking, and obesity among other variables, the aHR was 2.59 (1.74–3.84; $p < 0.0001$). Most deceased PLWH had other comorbidities [17]. Similar results were found in Western Cape, South Africa, in multivariate analysis with PLWH having a risk of death with COVID-19 of 2.14 (1.70–2.70) [18]. However, global mortality varied considerably across studies, depending on the design. Mortality was as high as 24% in the UK series (only hospitalizations) [20], as low as 2% in a series from France [41], and 3.6% in the South African cohort study [18] with a higher number of patients and the inclusion of outpatients, but also a more severely immunosuppressed population.

A recent analysis from the PISCIS Cohort Study in Catalonia (Spain) identified HIV co-infected patients with detectable HIV viral load, lower CD4 cell counts, older age, chronic comorbidities, and migrants as those with higher risks of severe outcomes [22]. Of note, lower CD4 cell counts were a risk factor to severe COVID-19 only among patients with detectable viral load in stratified analysis.

European Guidelines on Clinical Management

Clinical and radiological COVID-19 presentation is no different in PLWH to typical reports in the general population [23, 50].

The European AIDS Clinical Society and several National HIV/AIDS Societies have provided general recommendations for the management of PLWH with COVID-19 [51]. Essentially, the diagnostic approach and overall management should follow those indicated for the general population. Differential diagnosis should include other respiratory diseases such as *Pneumocystis jirovecii* and tuberculosis, particularly in severely immunocompromised PLWH.

However, when treating COVID-19 in PLWH, specific issues must be addressed. The first is to consider and check for drug-drug interactions between COVID-19 treatments and ARV drugs. The second is to consider the potential overlapped toxicities of ARVs and SARS-CoV-2 therapies, such as liver or kidney toxicity of remdesivir with specific ARV drugs.

For PLWH with severe immune depletion and other types of immunosuppressed individuals (solid transplant recipients, onco-hematologic patients), prolonged SARS-CoV-2 replication and shedding have been reported, which may require longer isolation periods. However, no specific recommendation for testing and isolation has been provided yet for PLWH.

Finally, emerging data is showing that long COVID will have a great impact in the burden of disease both in developed and low- and middle-income countries (LMIC) [52]. Given the huge symptomatic spectrum and the lack of knowledge about its pathophysiological mechanism, PLWH exposed to SARS-CoV-2 should be monitored to clarify if they are at higher risk of experiencing some features of long COVID syndrome.

SARS-CoV-2 Vaccination Among PLWH

There is limited information of the immunogenicity and reactogenicity of commercially available COVID-19 vaccines in PLWH. Studies analyzing the response of PLHIV to COVID-19 vaccines are needed to define the potential advantages and disadvantages of some types of vaccines (adenovirus-based vs. mRNA vs. recombinant spike vaccines) or the need for additional vaccine doses to achieve full protective immunity in immunosuppressed HIV-infected patients. The latter is an important point because it is well known that the immune damage to B-cell compartments and antibody generation caused by HIV infection can decrease the humoral response as it has been demonstrated to other vaccines (e.g., influenza or pneumococcal vaccines) [53, 54]. Therefore, dysfunctional B-cell memory lymphocytes and follicular helper T-cell activity could potentially decrease humoral responses to neo-antigens such as SARS-CoV-2 protein spike.

Data on PLWH included in approved phase 2/3 vaccine trials so far is limited. Regarding mRNA vaccines, in the Moderna and Pfizer trials [55, 56], only 0.6% and 0.5% of participants were PLWH respectively. The HIV sub-study

results of these trials have not been published yet. However, in another small study in 12 PLWH (seven women, five men), the Pfizer vaccine induced, between 7 and 17 days after the second vaccine dose, a robust humoral and cellular immune responses comparable to that seen in 17 healthy donors (seven women, 10 men) [57]. Regarding the adenovirus-based vaccines, the safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine [58] were evaluated in 54 individuals in a single-arm open-label vaccination substudy. All participants were men (most white) on ART, with undetectable plasma HIV viral loads (< 50 copies/mL), and CD4 counts of more than 350 cells/mm^3 (median 700 cells/mm^3). No serious adverse events occurred. Anti-spike IgG responses peaked at day 42 and were sustained until day 56 with no correlation with CD4 cell count or age. Compared with HIV-negative participants, the study found no differences in magnitude or persistence of SARS-CoV-2 spike-specific humoral or cellular responses. Finally, using the recombinant spike protein, the NVX-CoV2373 vaccine phase 2b trial [59] performed in South Africa included 6% of PLWH. The vaccine efficacy in PLWH was lower than in non-HIV-individuals (52% vs. 60%).

Immunosuppressed PLWH should be considered a risk group in which early COVID-19 vaccination would be advised as supported by European AIDS Clinical Society (EACS) Guidelines [51]. PLWH with low CD4 counts (below 200 cells/μL or even below 350 cells/μL) are at higher risk of developing severe COVID-19 [22] and could be considered as a priority group for COVID-19 vaccination. Therefore, we urgently need studies that analyze the efficacy and safety of vaccines in these immunosuppressed patients, in patients without ART, in women, and in different races. In addition, we should also know the duration of the immune response since some PLWH may need additional doses of vaccines.

Finally, since there is evidence that HIV adenovirus-based vaccines increased the risk of acquiring HIV [60–62], further information is also needed to better understand the appropriateness of using the adenovirus type 5 vectored vaccines among HIV most-at-risk groups.

Impact of SARS-CoV-2 Pandemic in HIV Most-at-Risk Groups and PLWH

Aside the direct risks to physical health, the psychological impact of COVID-19 could also be detrimental to mental well-being as elevated levels of stress and anxiety are further exacerbated by the ongoing uncertainty of the situation [63]. Key populations among PLWH experience particular forms of exclusion, criminalization, inequality, and discrimination that render them particularly vulnerable to COVID-19 [64]. This burden can affect the physical, emotional, and social well-being of PLWH and interfere with the reception of effective healthcare and access to HIV treatment [65].

A survey of older PLWH in Miami, USA, found that participants reported increased stress associated with their sense of social isolation and fragile economic situation [66]. PLWH who reported higher levels of anxiety and depression also reported losing their jobs during the pandemic [67]. Another study has described that psychological stress might be a predictor of COVID-19 burden (financial and social burden) and COVID-19 risk (health factors associated with an increased risk of severe health outcomes due to COVID-19) [67]. Additionally, COVID-19 burden and COVID-19 risk were predictors of depression and sleep problems [68]. Lesbian, gay, bisexual, transgender, and intersex (LGTBI) people reported an elevated risk of domestic and family violence, increased social isolation, difficulties in accessing crucial HIV treatment, and gender-affirming health services [67, 69].

The impact of COVID-19 on sexual behavior among gay and bisexual men living with HIV has been described in three studies which reported changes in sexual behaviors, including avoiding close physical contact and reducing or ceasing sex with casual partners [70, 71]. There is also a reported increase in recreational drugs such as marijuana and methamphetamine (up to 8%), and alcohol consumption and binge drinking [70–72].

Impact on Health Services, Access to Diagnosis, and Treatment

In addition to the health emergency caused by the COVID-19, the pandemic has threatened the excellence in ART delivery in well-resourced countries which could potentially result in reduction in adherence and decreased healthcare retention [73, 74]. It is estimated that a significant proportion of PLWH could access usual care because many HIV/AIDS prevention and control centers around the world have been converted into COVID-19 treatment centers and the perceived fear of contracting COVID-19 has made this group situation more vulnerable [75].

Vital HIV care resources including healthcare personnel have been channeled into curbing the COVID-19 pandemic [76]. A high percentage of community-based testing services have stopped or dramatically decreased their activity [77] and many HIV care centers worldwide were repurposed for the fight against COVID-19 denying PLWH the possibility of accessing crucial ART. [75]

During these periods, drug guarantee and distribution strategies were adopted by several countries; however, there are still uncertainties regarding the situation of assistance to PLWH in countries where the economy was highly affected. A study evaluating the impact of the pandemic on care for

this population as well as on the provision of treatment found that no country, among the 19 participants, reported the closure of HIV care services; however, the functioning was normal in 6 countries (31.6%) and in 11 of them (57.9%), care was shared between HIV and COVID-19. Furthermore, the rechanneling of health professionals, especially HIV specialists, to the COVID-19 response caused the exhaustion of many HIV care teams [77].

For this reason, recommendations for management and prevention of COVID-19 among PLWH emphasize the need for continuity of HIV care, including uninterrupted access to ART, routine vaccinations, and the use of telehealth means to access care, as long as it follows the general COVID-19 preventive guidelines. Also, continuous monitoring of the impact of the pandemic on this population is encouraged, so that it is possible to systematize evidence to support the reorganization of assisting services for PLWH. Regarding prevention services, the pandemic has challenged the functioning of HIV prevention services such as free access to condoms and HIV pre-exposure prophylaxis (PrEP) and calls for innovative approaches going forward [78].

In Europe, some HIV prevention and diagnosis services have incorporated self-sampling and self-testing approaches [77]; nevertheless, applicability of these strategies may not be easy as they require good information technology and mailing systems, which is not the case in many LMIC. On the other hand, steady access to clinical care may be facilitated by means of telemedicine. But again, in light of the COVID-19 pandemic, as it has been described from an experience in the USA, it is likely that economic, geographic inequities, and the digital divide will prevent some PLWH from accessing care via this route due to lack of necessary technology (e.g., computer, smartphones) or stable internet access, especially among older PLWH [79].

Conclusions

In this review, we have highlighted some aspects of the SARS-CoV-2/HIV co-infection from both a public health and clinical perspective. Although at the beginning of the COVID-19 pandemic the lack of integrated epidemiological surveillance and programmatic data prevented to have a clear picture of the overlapping distribution of both infections and its determinants, from a public health perspective, currently available data confirms the role of common structural determinants in both their acquisitions and clinical impact. Public health weakness, drug use, mental health, stigma, social marginalization, and other structural determinants all disproportionally increase the exposure to both HIV and SARS-CoV-2.

From a clinical perspective, data suggest that PLWH taking effective ARV treatment are not at higher risk of acquiring SARS-CoV-2. Moreover, there is no current evidence suggesting that TDF could reduce the risk of SARS-CoV-2 infection or severe COVID-19 outcomes in PLWH, and both clinical and radiological features of COVID-19 in PLWH are similar to those without HIV infection. Nevertheless, HIV-associated comorbidities, low CD4 (< 200 cells) cell counts, and in particular unsuppressed HIV viraemia are associated with poorer COVID-19 clinical outcomes and death among PLWH. In such a context, PLWH should be considered a priority target group for SARS-CoV-2 vaccinations and further information is needed to identify potential advantages or disadvantages of the different commercially available vaccines and vaccination schedules to be used into this population.

The SARS-CoV-2 pandemic has not only impacted PLWH, particularly disrupting access to ARV treatments, but also HIV most-at-risk groups — including men who have sex with men (MSM), sexual workers (SW), and people using drugs (PUD) — decreasing access to HIV prevention and early diagnosis and linkage programs. Under the current uncertain epidemiological scenario, both clinical services offering medical care to PLWH and community programs offering services to vulnerable groups should be adapted to the evolving COVID-19 pandemic and the corresponding mitigation scenarios to prevent disruption of the HIV continuum of care among these populations. Systematization of SARS-CoV-2 testing among PLWH is basic not only to better understand the epidemiological co-infection pattern, but also to identify PLWH co-infected with SARS-CoV-2 with worse prognostic factors, as soon as possible. Integration of SARS-CoV-2 testing strategies in HIV testing programs should therefore be considered. With this regard, alternative approaches like telemedicine, self-sampling, and self-testing technologies have been used in both developed and LMIC with promising results and they should be scaled up.

Integrated information systems including epidemiological, microbiological, clinical, vaccination and mortality data should be reinforced and maintained to monitor the impact of COVID among PLWH and HIV most-at-risk-groups. The use of longitudinal clinical data from PLWH, population-based SARS-CoV-2 diagnosis data as well as ecological approaches to include structural indicators, seems crucial to increase the knowledge and improve the practices of SARS-CoV-2/HIV co-infection from both a clinical and public health perspective.

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