Original Article

Clinical profile and disease progression of HIV in adolescents and young adults in Vadodara, India

Geetika Madan-Patel, Vihang Mazumdar[1]
Department of Preventive and Social Medicine, Parul Institute of Medical Sciences and Research, Parul University,
[1]Department of Preventive and Social Medicine, Medical College Baroda, Vadodara, Gujarat, India

Address for correspondence:
Dr. Geetika Madan-Patel, Department of Preventive and Social Medicine, Parul Institute of Medical Sciences and Research, Parul University, P.O. Limda, Taluka Waghodia, Vadodara - 391 760, Gujarat, India. E-mail: medicaldirector@paruluniversity.ac.in

Abstract

Introduction: Adolescents are vulnerable to HIV for many reasons. Unfortunately, there are little data available on adolescents and young adults who have contracted HIV. Only few studies have been conducted in India with an aim to assess the clinical presentation, disease progression, and clinical profile of HIV in adolescents. **Materials and Methods:** There was a cohort study conducted at the antiretroviral therapy (ART) center at a teaching hospital in Western India. The study participants were kept under observation for 1 year. The end point of the cohort analysis was HIV disease progression. Patient details such as sociodemographic profile, CD4 counts at presentation, date of initiation of ART, WHO clinical stage of HIV at presentation, episodes of opportunistic infections, and laboratory investigations were recorded. Descriptive statistics and survival analysis were used for analyzing disease progression, improvement in health conditions, and factors affecting the same. **Results:** Of 155 participants, 100 were followed up till the end of the study. Seventy-two percent participants were adolescents and 53% were female. The mean age at presentation was 16.7 years, and the common modes of transmission were mother-to-child transmission (MTCT) (48%), heterosexual relationships (23%), and blood transfusion (12%). CD4 counts at presentation were <350 cells/mm^3 among 70 participants. Among those infected through MTCT, the median survival duration was 15 years (95% confidence interval: 12.98–17.07). The risk of progression of the disease among young adults was thrice than that of adolescents ($P < 0.05$). **Conclusion:** HIV/AIDS screening and health services shall be tailored to address the special needs of adolescents and young adults. Teaching hospitals shall explore opportunities for student-involved longitudinal research studies to better understand the source of HIV infection, treatment seeking behavior, disease progression and outcome in a comprehensive manner.

Key words: HIV in adolescents, HIV in young adults, HIV profile, HIV progression

INTRODUCTION

As per recent estimates, 37.9 million (32.7–44.0 million) people are living with HIV globally, of which 2.12 million (1.71–2.65 million) are in India. Globally, 4.49% children, <15 years of age, accounted for all people living with HIV compared to higher proportion of 6.54% in India.[1,2] There are about five million youth, in the age group of 15–25 years, living with HIV, and about 30% of new HIV infections are estimated to occur among this group.[3] Adolescents are vulnerable to HIV for many reasons, including lack of support they need to go

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through sexual development during this lifecycle stage, as well as limited access to information about HIV and prevention services.[4] Differences in infection levels between men and women are most obvious among young people – young women in some countries are three times more likely to be infected than young men of the same age.[5] Young people (aged between 10 and 24 years) comprise 30% of India's total population, and it has been estimated that they account for 35% of the country's AIDS burden, with prevalence in the age group being 0.3%.[4,6]

Unfortunately, the differences in pathogenesis and response to treatment in adolescents have not been extensively studied. It is generally believed that adolescents who are infected through sexual behaviors or needle-sharing experience a course of disease similar to that of adults. This has resulted in less information available on progression of disease in adolescents and difference in response to medications administered for HIV.[7] A study carried out on profile of HIV-infected adolescents in the USA concluded that HIV-infected youth appears to enter care with considerable immunosuppression. Clinical profiles and treatment patterns appear to differ by transmission mode, but further study was recommended on adolescent HIV disease progression and determinants of access to care and treatment.[7] Identification of disease progression will also help in contextualizing counseling needs and strengthening protocol for treatment and follow-up.

There is dearth of studies carried out on adolescents and young adults infected with HIV (local as well as national). Very few studies in India have been carried out to study the disease progression and clinical profile of HIV in adolescents. During the last decade, Adolescent Reproductive and Sexual Health and HIV/AIDS among young people have occupied prominent place among India's health agenda. A number of organizations and experts have been working in these areas for long, but the research work carried out by these agencies have not been documented properly; nor many research findings and publications are available in the public domain with regard to their program and achievements.[4] Further, the National AIDS Control Organization (NACO) as well as the Gujarat State AIDS Control Society statistics and annual reports do not provide the data (prevalence, annual deaths, mode of transmission etc.) for HIV-positive adolescents.

An antiretroviral therapy (ART) center was established at a medical college affiliated district hospital in Vadodara, India, in January 2009. With the availability of Integrated Counselling and Testing Centre (ICTC), ELISA, and CD4 testing, it offered better scope for research in HIV. The present study attempted to explore an insight into the progression and common modes of presentation of HIV in adolescents and young adults.

MATERIALS AND METHODS

Objectives

1. To study the clinical presentation and modes of transmission of HIV in adolescents and young adults attending ART center in a medical college affiliated district hospital
2. To study the factors and time of progression of HIV in adolescents and young adults.

Study design

Cohort study (combined retrospective and prospective follow-up).

Study population and sample size

All the adolescents and young adults (10–24 years) registered at ART center at a teaching medical hospital between January 1, 2009, and June 30, 2010, were enrolled. This, being an exploratory study restricted to one teaching hospital, all samples in a given period were included [Figure 1].

Methodology

The study was carried out at ART center of the teaching medical hospital over a period of 1½ years. This ART center recorded inflow of patients from the surrounding localities and neighboring districts as all ART centers were not providing ART. Written informed consent was obtained from all the participants before they were enrolled in the study. The study participants were followed retrospectively from the records in ART center for the respective periods till their registrations and prospectively for 1 year. The end point of the cohort analysis was HIV disease progression (defined below). At progression to first

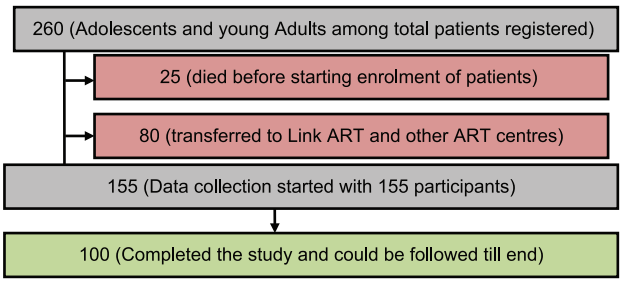

Figure 1: Flowchart summarizing the selection of study participants

occurrence to the end point, persons were censored for further follow-up. Patients on ART were also assessed for improvement in their conditions (disease regression; defined below) following commencement of treatment.

Ethical considerations

The process of data collection did not pose any potential risk or harm to the participants as it did not interfere or intervene with the medical treatment provided to the participants. The questionnaire did not involve any confidential details, and privacy was ensured while conducting their interviews. Privacy and confidentiality of their details were given due consideration. The file containing identities of the participants was kept password protected and the filled-in pro forma was kept under lock and key with key available only in the custody of the researcher. Requisite clearances and permissions were obtained from concerned authorities including the State AIDS Control Society, Institutional Ethics Committee for Human Research, and Hospital Superintendent.

Data collection and analysis

The study instrument was designed keeping in mind the objectives of the study and was pilot tested in 10 patients. The patient cards in the ART center were used for tracking (obtaining) the required details of the patients which included registration date and number, sociodemographic profile, CD4 counts at presentation, date of initiation of ART, WHO clinical stage of HIV at presentation, episodes of opportunistic infections, and laboratory investigations (hemoglobin, TC, DC, hepatitis B surface antigen, venereal disease research laboratory, Liver Function Test (LFT), chest X-ray, ultrasonography, and computed tomography scan).

The participants were also interviewed every 2 months during their scheduled visits to ART center using a pretested semi-structured questionnaire. The qualitative inquiries elucidated information regarding symptoms for which HIV testing was done, duration of such symptoms which persisted before diagnosis, mode and time of acquisition of HIV infection (as per testimony of the patients and cross-verification with ART patient card), admission to hospitals after being diagnosed with HIV (if any), associated substance abuse, and compliance to medication.

Study protocol and finalized study instrument were then peer reviewed in the department. Data were entered in IBM SPSS Statistics for Windows, Version 19.0 (Armonk, NY: IBM Corp.) for statistical analysis. Descriptive statistics was used for analysing demographic and clinical profile. Disease progression and improvement (disease regression) were defined using the change in WHO clinical stage and CD4 counts cut-off of 350 cells/mm^3 as per the WHO treatment guidelines, 2010. Survival analysis (Kaplan–Meir and Cox proportional hazards model) was used for analyzing disease progression, improvement, and factors affecting the same. In all the survival curves, the median has been used for interpretation of the data (rather than mean) because the survival curve is a positively skewed curve and median estimation is more appropriate. Disease progression was analyzed separately for patients infected perinatally and for those infected through other modes (sexually, blood transfusion, and intravenous drugs). This is because for perinatally infected participants, the time of exposure (i.e., birth) is known; however, for those infected through other modes, exact time of exposure cannot be estimated. Hence, the period between acquisition and diagnosis has to be left censored for Kaplan–Meier analysis. Cox proportional hazards model was used to study factors associated with the disease progression.

RESULTS

Out of 155 eligible adolescents and young adults during the study period, only 100 HIV-positive participants were followed up till end. Seventy-two percent of participants were adolescents and all participants required schooling according to their age. Male (47%) and female (53%) participants were almost equally enrolled. About 65% were unmarried and 29% were unemployed. Mother-to-child transmission (MTCT) accounted for 48% of cases in the study sample, followed by heterosexual relationships (23%), blood transfusion (12%), and intravenous drugs (5%). Mode of transmission was not known for 11% of cases. The mean age at presentation was 16.7 years, and perinatally infected adolescents presented at a younger age (14.3 years) as compared to those infected through other modes of transmission (20.5 years). About 45 patients were asymptomatic at presentation and the median duration was 5.5 months among those presented with any symptoms. Of 55 patients, who presented with single/multiple symptoms, 35 patients were found to be suffering from symptoms suggestive of HIV within 6 months. Parent/sibling being HIV positive (31.9%) and prevention of parent-to-child transmission (21.7%) were the most common reasons for which HIV screening was performed.

Gender-wise analysis revealed more females were infected through heterosexual behavior (17/24; 71%) than males in a given cohort. About 46% of the

Table 1: Distribution of patients by mode of transmission and WHO Clinical Stage for disease progression

WHO clinical stage	MTCT, *n* (%)	Hetero/homo-sexual, *n* (%)	BT, *n* (%)	IV drug use, *n* (%)	Unknown, *n* (%)	Total, *n* (%)
I	10 (20.8)	11 (47.8)	3 (25.0)	1 (20.0)	4 (36.4)	29
II	15 (31.25)	4 (17.4)	1 (8.3)	1 (20.0)	3 (27.3)	24
III	22 (45.8)	7 (30.4)	7 (58.3)	0	3 (27.3)	39
IV	1 (2.1)	2 (04.3)	1 (8.3)	3 (60.0)	1 (9.1)	8
Total						100

MTCT: Mother-to-child transmission, IV: Intravenous, BT: Blood transfusion

patients presented when their disease progressed to WHO Clinical Stage III and IV, while 29% and 24% presented during Stage I and II [Table 1]. CD4 counts at presentation were <350 cells/mm^3 among 70 patients, between 350 and 500 cells/mm^3 among 18 patients, and >500 cells/mm^3 among 12 patients. Median CD4 count among patients infected with blood transfusion, MTCT, and heterosexuality was 175, 192, and 270 cells/mm^3.

About 48 patients were identified suffering from single/mixed opportunistic infections during the follow-up period, and tuberculosis (TB) was the most common infection [Table 2]. Extra-pulmonary TB (commonly abdominal and lymph node) was almost as common as pulmonary TB. Among multiple infections also, TB was associated in most (80%) of the cases. The most common multiple infections seen were TB and candidiasis.

Among patients infected through MTCT, the median survival duration was 15 years (95% confidence interval: 12.98–17.07), which meant that, by this age, 50% of patients would progress. Survival curve showed that, by the age of 22 years, most of the patients would progress [Figure 2]. Survival curve for patients infected through other modes of transmission showed that, by 7.8 time periods (within 3.9 years of diagnosis), 50% of patients would progress [Figure 3].

Analysis of Cox proportional hazards model showed that young adults (20–24 years of age) were at about 3 times ($P < 0.05$) higher risk of progressing as compared to adolescents (10–19 years). Further, those who were symptomatic at the time of diagnosis or who presented with TB as a co-infection or multiple co-infections were at greater risk of progression of disease. Other factors such as CD4 counts, WHO stage at presentation, gender, presentation of the clinical features, and number of hospital admissions did not show any association with disease progression.

Table 2: Opportunistic infections among study participants after diagnosis

	n (%)
Patients identified with opportunistic infections (*n*=48)	
Single infections	34 (71)
Mixed infections	14 (29)
Single opportunistic infection	
TB	24 (70.6)
Pulmonary TB	9
Extra-pulmonary TB	9
P/H of pulmonary TB	5
P/H of extra-pulmonary TB	1
Candidiasis	4 (11.9)
Herpes	2 (5.9)
Diarrhea	1 (2.9)
Skin infections	1 (2.9)
ARI other than TB	1 (2.9)
PCP	1 (2.9)
Mixed opportunistic infection	
TB and candidiasis	4 (28.6)
P/H of TB and TB	2 (14.4)
Diarrhea and candidiasis	2 (14.4)
TB and herpes zoster	1 (7.1)
TB and diarrhea	1 (7.1)
TB and ARI	1 (7.1)
P/H of TB and herpes and diarrhea	1 (7.1)
Extra-pulmonary TB and candidiasis	1 (7.1)
PCP and MAC	1 (7.1)

TB: Tuberculosis, P/H: Pulmonary hypertension, PCP: Pneumocystis carinii pneumonia, MAC: *Mycobacterium avium* complex, ARI: Acute respiratory infection

DISCUSSION

Our study identified MTCT (vertical transmission) as the most common mode of transmission (around 50% of cases) in a given cohort compared to only 5.4% in the NACO report.[2] Data on modes of transmission in adolescents and young adults have not been publicly shared by the NACO or any other national/state official report. Sexual transmission has been stated to be the most common mode of transmission of HIV in youth worldwide.[6] Statistics from Centers for Disease Control (CDC, 2001) have also stated sexual route as the most common mode of transmission in the age group of 13–19 years.[8] In the previous study carried out on 32 adolescents at the same teaching hospital, vertical transmission was reported to be the most common mode of

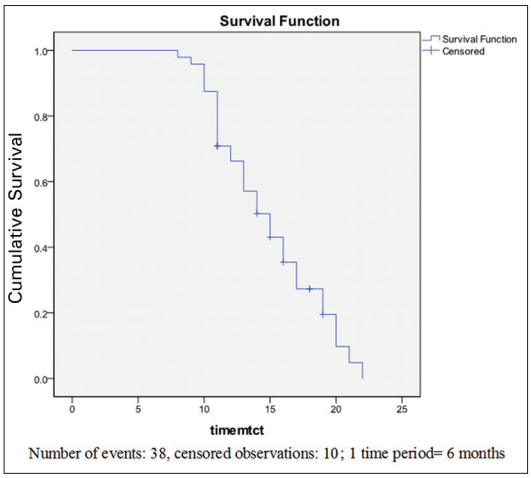

Figure 2: Survival curve for patients infected through mother-to-child transmission (*n* = 48)

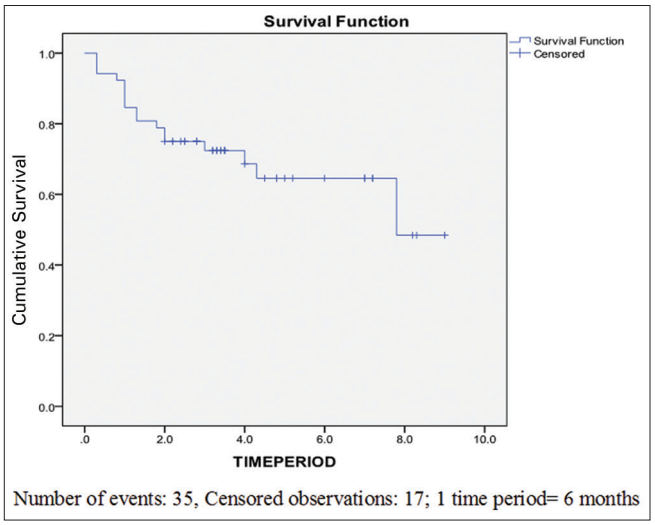

Figure 3: Survival curve for patients infected through modes of transmission other than mother-to-child transmission (*n* = 52)

transmission (64%).[9] Another study on clinical manifestations of adolescents with HIV also reported similar findings, wherein 73% of the patients were infected vertically.[10]

Around 20% of the patients had been suffering from symptoms, suggestive of HIV for more than 6 months, which is indicative of lack of HIV screening practices at various private and government health setups. This may lead to delay in diagnosis as well as initiation of ART, resulting in faster progression and poor outcome of the disease. A further delay occurs in some of the cases when patients do not report to the ART center even after they were tested and declared positive. This delay may be because of the lack of proper communication with the patients or unavailability of an ART center in the vicinity.

A previous research at the same teaching hospital reported that fever/cough/diarrhea and HIV-positive parents were the reasons for HIV testing among 45% and 24% of study participants.[9] It is the index of suspicion of the doctor only, by which the patients are referred to ICTC for getting tested for HIV. Another study had reported lymphadenopathy (82%), dermatitis (72%), hepatomegaly (48%), splenomegaly (30%), and mucocutaneous candidiasis (23%) as the most frequent clinical manifestations.[10]

A study from Zimbabwe on HIV infection in older children and adolescents found that 63% of cases presented with stunting and all were in WHO Clinical Stage III or IV.[11] In another study from Western India, 21 of 33 cases sought treatment when they had already developed AIDS.[9] These findings were in concurrence with the study from Jamaica, where most perinatally infected adolescents were CDC Category C, i.e., AIDS indicator conditions (50%), whereas the majority of nonperinatally infected adolescents were classified CDC Category A (asymptomatic HIV).[10] Many adolescents living with HIV are in WHO Clinical Stage I or II and may not yet feel unwell or need treatment and therefore have no reason to visit the health center. In our study, not even one-third of the patients were diagnosed during the WHO Clinical Stage I, which stresses upon the need for measures to be taken for early detection through screening. Hence, it is important that asymptomatic adolescents living with HIV attend health services so that they can receive care and support as well as education in prevention and treatment.[6]

Median CD4 was lowest among the participants infected through blood transfusion which could be attributed to the increased viral load. Median CD4 count at diagnosis was 101 cells/mm^3 in the study from Zimbabwe.[11] A study on HIV disease progression assessment of adult patients in Thailand found that the median CD4 count at baseline was 318 cells/mm^3 for ART-naïve patients and 110 cells/mm^3 for ART-experienced patients.[12] Lower CD4 counts are associated with greater risk of disease progression.[13] Use of the CD4 count as a means of monitoring ART efficacy is well established. In particular, measurement of the early response in the first 6 months of therapy has strong predictive value for future immunological progression.[12] Immunological recovery is largely dependent on baseline CD4 count, and thus, the timing of ART initiation is important to maximize the CD4 T-cell response to therapy.[14]

Our study found TB to be the most common single opportunistic infection (71%), followed by

candidiasis, herpes, and others (pneumocystis carinii pneumonia, acute respiratory infection (ARI), diarrhea). A study from Thailand also reported similar findings, where TB was the most common AIDS defining illness followed by oropharyngeal candidiasis, *Mycobacterium avium* complex, and *Cytomegalovirus* retinitis.[12] A Zimbabwean study found recurrent urinary tract infections and chronic diarrhea as the most common presenting infections followed by TB, skin infections, and oral candidiasis.[11]

In the present study, there has been no event till the age of 8 years, survival probability (probability of nonprogression in our study) starts falling as shown by the flattening of the curve after the age of 8. The curve also suggests that almost all perinatally infected adolescents (not undergoing any intervention in the form of ART) progressed by the age of 22 years. A previous research from the same study site reported a mean duration of 12.5 years for disease progression in vertically transmitted cases.[9] The results of a research from rural Uganda, on disease progression in adults, showed median duration of 25.4 months from seroconversion to WHO Clinical Stage II and 45.5 months to Stage III.[15] A Thailand-based study reported rate of progression to AIDS at 1.4/100 person years and the median duration of 13.9 months (interquartile range, 6.0–22.3) from trial entry to the occurrence (first AIDS defining disease, CDC Category C). TB was the most common AIDS defining illness that defined disease progression.[12] Rate of progression to AIDS is very low in the first 2 years after infection and shoots up thereafter. Although patients infected by transfusion, especially infants may develop AIDS in the 1st year following infection, progression to clinical AIDS in healthy adults is rare within 2 years of seroconversion.[16]

Study limitations

As the study is a hospital-based, all the patients who did not visit the ART center regularly on scheduled dates or months could not be traced and the process of obtaining data for these patients could not be completed. These patients had to be excluded from final analysis. Medication compliance, which is an important predictor of disease progression, could not be assessed accurately as interviews conducted (which was used as the study tool for in-depth interviews) could not serve the purpose of acquiring complete details regarding patients' adherence to treatment. As this was a time-bound study, the patients enrolled were followed-up prospectively for 1½ year only (depending upon the time of recruitment in the study). A further follow-up of the same patients as a continued long-term institutional research might have provided detailed information regarding disease progression.

CONCLUSION

Given the high prevalence of HIV/AIDS among adolescents and young adults, it is important that concerned stakeholders shall devote resources for directed research for understanding prevention, transmission, onset of disease, progression, and adherence to treatment among the said population. Teaching hospitals shall explore opportunities for student-involved longitudinal research studies to better understand the source of HIV infection, treatment seeking behavior, disease progression and outcome in a comprehensive manner. Reductions in the cost of smartphones, mobile internet, and advances in mobile health technologies shall be leveraged for future research and improving public health outcomes among adolescents and young adults infected with HIV.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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SEXUAL TRASMISSION OF EMERGING INFECTIONS

ZIKA VIRUS[1]

Zika can be passed through vaginal, anal and oral sex and the sharing of sex toys from a person with Zika to his or her partners. Transmission can occur in asymptomatic and in the pre-symptomatic stage.

Zika virus can remain in seminal fluid for a longer period as compared to other body fluids and hence the time range that men and women can pass Zika through sex are different. The mechanism(s) of intrauterine transmission of Zika virus and the cell types involved remain largely unknown.[2]

Zika infection during pregnancy has been associated with fetal malformations, particularly abnormalities in central nervous system (CNS) development and microcephaly in newborns. Chances of sexual transmission of Zika virus can be minimized by the use of male and female condoms and dental dams.

(1) CDCMay 21, 2019 *Sexual Transmission and Prevention*May 01,2020. Available from: https://www.cdc.gov/zika/prevention/sexual-transmission-prevention.html

(2) Maternal-fetal transmission of the zika virus: An intriguing interplay CamilaZanluca a,† , Lucia de Noronhab,† , and Claudia Nunes Duarte dos Santosa a Laboratorio de Virologia Molecular, Instituto Carlos Chagas/Fiocruz-PR, Curitiba, PR, Brazil; b Laboratorio de Patologia Experimental, PontificiaUniversidadeCatolica do Parana, Curitiba, PR, Brazil

Compiled By:

1. Dr. Navnee Jain, Post Graduate Resident, SBKS Medical Institute
2. Dr. Apexa Jain, Post Graduate Resident, SBKS Medical Institute

EBOLA VIRUS

Studies have shown that Ebola virus can be isolated from semen for up to 82 days after symptom onset and recent virus-persistence studies identified genetic material (RNA) from semen, 406 days (13.5 months) after symptom onset. Live virus has never been isolated from vaginal fluids. With such limited data, it is not known for how long virus typically persists in vaginal fluids, or whether it can be sexually transmitted from females to males.

Safe sex should be practiced by male survivors of Ebola virus diseases for 12 months following the onset of symptoms or until their semen tests negative twice for Ebola virus.[1]

(1) Surani A, Marfatia YS, Pal A, Shah R. Ebola virus: An emerging sexually transmissible infection pathogen. Indian journal of sexually transmitted diseases and AIDS. 2018 Jan;39(1):65.

Compiled By:

1. Dr. Navnee Jain, Post Graduate Resident, SBKS Medical Institute
2. Dr. Apexa Jain, Post Graduate Resident, SBKS Medical Institute

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2):

Evidence suggests that saliva and faeces both carry the virus. Virus uses angiotensin-converting enzyme II (ACE2) as a receptor to enter the cells. ACE2 is expressed both in the glandular cells of rectal epithelia as well as oral mucosa. It is likely that oral and anal contacts directly transmit the virus and exposure of the rectal mucosa to saliva can indirectly transmit the virus.(1)

(1) Patrì A, Gallo L, Guarino M, Fabbrocini G. Sexual transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): A new possible route of infection?. Journal of the American Academy of Dermatology. 2020 Jun 1.

Compiled By:

1. Dr. Navnee Jain, Post Graduate Resident, SBKS Medical Institute
2. Dr. Apexa Jain, Post Graduate Resident, SBKS Medical Institute