Research Article
Volume 12:5, 2021

Journal of AIDS & Clinical Research

ISSN: 2155-6113 **Open Access**

Epidemiology of Infections Caused by Seasonal Human Coronavirus in Hospitalized Adults with HIV Over a 5-year Period in Mexico City

Becerril-Vargas Eduardo, Delgado-Cueva Andrea*, Mújica-Sánchez Mario Alberto, García-Colín María del Carmen, Valencia-Trujillo Daniel, Erazo-Pérez Luzvi, Mireles-Dávalos Christian, Flores-Pérez Elia, Martínez-Orozco José Arturo, Becherano-Razon Gastón, and Cojuc-Konigsberg Gabriel

Laboratorio de Microbiología clínica, Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico

Abstract

Although the incidence of HIV-associated lung infections has changed due to the use of antiretrovirals, and the knowledge of the contributions of respiratory viruses, including subtypes of seasonal human coronavirus (HCoV) has increased, studies to analyze and compare prognosis and risk factors between HIV-positive and negative individuals with HCoV respiratory infections are scarce. Patients with HIV are at a higher risk of getting infected with various pathogens, including viruses, therefore, it is important to comprehend the epidemiology of these infections. This study aimed to expose the epidemiological aspects of HCoV infections, comparing HIV-positive and negative patients. This study used a retrospective design and the data analyzed were collected from November 2013 to March 2018, a comparison of characteristics between patients with HIV and without HIV infected with HVoC using $\chi 2$, Student's T or Mann-Whitney U tests was performed. The detection of coronavirus species by the Luminex system in patients with HIV showed that HCoV-NL63 was the most frequent, with a prevalence of 45.5%, followed by HCoV-OC43 and HCoV-22E9, with 36% and 18.2%, respectively. Overall, the HCoV-OC43 species was detected more frequently and winter was the season when more cases occurred. Pneumonia was the most frequent clinical manifestation and the main coinfection was due to *Pneumocystis jirovecii*. Seasonal human coronaviruses are an important cause of infection in HIV-infected patients, resulting in several clinical repercussions. Further studies are necessary to determine the implications of HCoV in these patients, as well as the epidemiological significance of HCoV infections in HIV-positive individuals in Mexico and throughout the globe.

Keywords: Pneumonia • Virus • Epidemiology • HCoV • HIV

Introduction

Human coronaviruses (HCoVs) belong to the order of *Nidovirales*, of the *Coronaviridae* family, with a positive-chain RNA and the largest genome of all RNA viruses (≥27 Kb). Genomic RNA is limited by nucleocapsid protein inside an enveloped virion. The viral envelope consists of a spiculated surface glycoprotein cover which gives the virus its crowned appearance. Human infecting coronaviruses are the cause of up to a third of the upper respiratory tract infections in adults and some are the cause of diarrheas in newborns and infants [1].

In Mexico during the winter season viral respiratory infections are very common and the most prevalent in vulnerable groups, such as children younger than 5 years old and adults over 60. Coronaviruses have been described as an important cause of both upper and lower respiratory infections. Currently there are 7 known species capable of infecting humans. Before 2002 only HCoV-229E and HCoV-OC43 were known for infecting humans. However, since the identification of the Severe Acute Respiratory Syndrome (SARS) CoV two more human infecting coronaviruses have been identified, HCoV-NL63 and HCoV-HKU1, followed by the Middle East Respiratory Syndrome (MERS) and more recently in 2019, SARS-CoV-2. Respiratory infections by HCoVs are more frequent in temperate climates in winter and spring [2-4]. These coronaviruses are responsible for approximately 5–10% of all upper and lower respiratory tract infections [5]. In the United States HCoV-OC43 and HCoV-229E have demonstrated a periodicity of extensive epidemics with intervals of 2 to 3 years, and are the most relevant localized outbreak and the second most important epidemic of that country [1]. The epidemiology of infection caused by HCoVs in people living with HIV is unknown.

Several studies have found that the lung is the most frequently affected site in patients with HIV/AIDS. Because of the immunocompromised state in these patients' infections are commonly seen. In the existing literature there is no consensus on a diagnostic algorithm with regard to pulmonary infections in HIV patients because of the lack of information about this topic. Diagnostic and treatment options depend on the epidemiological features in a specific geographical area. The incidence of HIV-associated pulmonary infections has changed because of the use of antiretrovirals; bacterial pneumonia replaced *Pneumocystis jirovecii* pneumonia as the most frequent cause of these infections. In Mexico and in the world in general, epidemiological and descriptive studies about respiratory viruses are limited and there are no studies about common human coronavirus infection in HIV patients [3].

The advances in molecular diagnosis have provided powerful tools for the precise detection of pathogens. Traditionally, respiratory viral infections have been diagnosed by culture, rapid antigen test and immunofluorescence. However, many studies have demonstrated that molecular diagnostic assays show greater benefits and are now becoming acceptable as the new gold standard. Methods based on PCR in particular offer significant advantages in terms of sensitivity, specificity and rapid turnaround time [6-8]. The Luminex xTAG Respiratory Viral Panel (RVP) Fast v2 (Luminex Molecular Diagnostics, Toronto, ON, Canada) is a qualitative multiplex molecular assay for the simultaneous detection of 19 viral types and subtypes in a single reaction [9]. Previous reports have shown that the sensitivity and specificity of this assay

Address for Correspondence: Delgado-Cueva Andrea, Laboratorio de Microbiología clínica, Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico. Tel: +525516996524; E-mail: a.idc1910@gmail.com

Received 20 April 2021; **Accepted** 17 May 2021; **Published** 24 May 2021

are consistently high [10-14]. Additionally, this assay has the benefit of broad viral detection in a short period of time using a limited amount of material, providing a fast and accurate diagnosis, which is directly reflected in the clinical management of patients.

The clinical characteristics of HIV-positive patients infected with any human coronavirus, as well as the HCoV subtypes, are directly related to the morbidity and mortality rates. It is therefore highly important to keep updating epidemiological profiles in order to identify any increase in respiratory infections in humans. Moreover, it is essential to observe and recognize any behavior in the Mexican population that may be similar to reports from other countries, defining clinical and laboratorial profiles that allow for the obtaining of an early diagnosis, treatment, and the establishment of preventive measures to avoid transmission and contagion [15].

The lack of studies pertaining to viral infections in people infected with HIV brought forward the need of this study, which was conducted within Mexico's National Institute for Respiratory Diseases (INER) with the objective of generating new knowledge about the main epidemiological characteristics of the HCoV infections in Mexico, and its distinctiveness in HIV patients. Therefore, this study aimed to describe the epidemiological, clinical, and paraclinical characteristics of HCoV infections in patients with and without HIV who received care at the Mexican National Institute for Respiratory Diseases.

Materials and Methods

Study design and population

A retrospective cohort study was conducted With respect to the sample, the inclusion criteria were: Patients between 18 and 99 years of age; having a diagnosis of confirmed HCoV by a positive RT-PCR; and having received medical attention at the National Institute of Respiratory Diseases between November of 2013 and March 2018. The exclusion criteria were: Patients who did not receive treatment at the National Institute of Respiratory Diseases; and those who did not complete medical records.

The clinical and sociodemographic data collection were obtained through clinical records reviews of patients who had a positive PCR for HCoV from different clinical samples (i.e. bronchoalveolar lavage, bronchial aspiration, biopsy, and Nasopharyngeal swab). After obtaining the clinical (i.e. coughing, fever, dyspnea, hemoptysis, pleuritic pain, asthenia, adynamia) and sociodemographic (i.e. age, sex) data, they were recorded in an Excel database. Then, statistical analysis was performed using IBM SPSS 21.

RNA extraction

Nucleic acids extraction was performed by using the QIAamp® MinElute® Virus Spin Kit (Qiagen, Hilden, Germany) and the QIAcube platform (Qiagen) through a semiautomatic method according to the manufacturer's protocol. A sample input volume of 200 µl and an output volume of 55 µl was used.

Detection of HCoV species by the luminex system

Detection of HCoV subtypes was performed using de xTAG RVP Fast v2 assay. The Luminex assay includes reagents to detect 19 viral types and subtypes, including four species of HCoV (HKU1, 229E, OC43 and NL63). Bacteriophage lambda was included in every run to control amplification and assay performance. The assay comprised a reverse transcription followed by a multiplex PCR amplification and a microspheres hybridization step, the process was performed according to manufacturer's instructions. Signal acquisition presented as MFI (median fluorescence intensity) was done on the Luminex 200 platform through flow cytometry.

Ethical considerations

This study followed the established ethical guidelines for the use of patient information and was approved by the institutional ethical committee at the National Institute of Respiratory Diseases under the number C31-17.

Statistical analysis

Results are thus presented through descriptive statistics. Medians with ranges and/or means with standard deviations were used for quantitative variables, whereas qualitative variables were expressed through frequencies and percentages. A bivariate analysis was performed for the quantitative variables. Patients were divided into two groups: Patients with positive PCR for HCoV with HIV and patients with positive PCR for HCoV without HIV. The corresponding results were compared through an X2 test or Fisher's Exact Test. Student's T-test and/or Mann-White U tests were performed for the qualitative variables (i.e. parametric or non-parametric variables). A p-value <0.05 was considered as statistically significant. Data was presented along with the p-value and odds ratio with a confidence interval of 95%.

Results

Socio-demographic data and patient characteristics

A total of 36 patients that had clinical records and were treated at INER were found. Their mean age was 47.8 years (± 14.36). Only 11 (31%) had a history of HIV infection. The HIV patients were younger than those without HIV. A higher number of cases were observed in male patients, with a male/female ratio of 5:1. A high proportion of comorbidities were observed; however they were HIV-uninfected (Table 1).

Amongst HIV cases, 8/11 cases had a CD4 count below 200 when the diagnosis was made. Average CD4 and viral load (CV) was 19.5 cell/mm^3 (interquartile range [IQR] 6,75-126.75) and 5331.5 copies (IQR 6286.5-757739.25), respectively.

Prevalence of HCoV species and coinfection

A total of 7,668 tests for respiratory viruses molecular detection were received at the Laboratory of Clinical Microbiology of the National Institute for Respiratory Diseases (INER) in the established study period (November 2013 - march 2018) from patients with respiratory tract infection symptoms. Of these, 3,617 samples tested positive for one or more of the nineteen viruses. 1,952 (53.96%) positive samples correspond to the adult population (>18 years old, media 47.04%). Finally, there were a total of 87 (4.4%) positive samples for any of the four seasonal HCoV species, distributed as shown in Figure 1.

27 (31%) samples showed coinfection with other respiratory viruses (including 24 double and 3 triple coinfection). The most frequently observed co-pathogens were human rhinovirus (n=11; 12.46%), influenza AH1N1pdm and human parainfluenza virus (n=6; 6.89%). Three triple combinations of coinfections were detected: HCoV-HKU1/InfAH1N1pdm/HRhV, HCoV-229E/InfAH1N1pdm/HRhV, and HCoV-229E/InfAH3/HPiV (Table 2).

Seasonal distribution

A higher viral circulation was observed during the winter months, with a prevalence of 69% with respect to the rest of the year where a lower one is observed (31%) (Figure 2). OC43 and HKU1 species had a higher seasonal prevalence with a biannual predominance, while 229E and NL63 species co-circulated in low prevalence annually. In the seasons in which OC43 circulated, a greater number of infections were observed compared to the seasons in which the circulation of HKU1 was predominant (Figure 3).

Clinical manifestations

The most common symptom was cough in 80.6% of all patients, also more common in patients who were HIV-infected (100%) (Table 3). Dyspnea, fever and cough were the most common symptoms in patients with HIV. The frequencies of the main signs and symptoms can be found in Table 3. 83.3% of the HIV-infected patients had a fever, in contrast with 60% in the HIV-uninfected group (Table 3).

Pneumonia was present in all (11/11) of the HIV-infected group; 81% (9/11) had mixed-etiology pneumonia; 52% (13/25) of the HIV-uninfected

Table 1. Socio-demographic data in patients.

Variables	Total (N=36)	HIV-infected (N=11)	HIV-uninfected (N=25)	P-value	OR	95% CI
Men	83% (30/36)	100% (11/11)	76% (19/25)	P=0.79	0.63	0.44-0.80
Median Age	47.72 (±14.54)	43.75 (6,59)	49.71 (16,99)	P=0.01		
Comorbidities	44% (16/36)	9.09% (1/11)	60% (15/25)	P=0.01	0.06	0.73-60.52
Diabetes Mellitus	5.6% (2/36)	9.09% (1/11)	4% (1/25)	P=0.56	2.09	0.11-36.63
Hypertension	22.2% (8/36)	0	32% (8/25)	P=0.03	1.6	1.22-2.21
Asthma	19.4% (7/36)	0	28% (7/25)	P=0.07	1.7	1.25-2.31
Interstitial Lung Disease	5.6% (2/36)	0	8% (2/25)	P=0.47	1,4	1.17-1.86

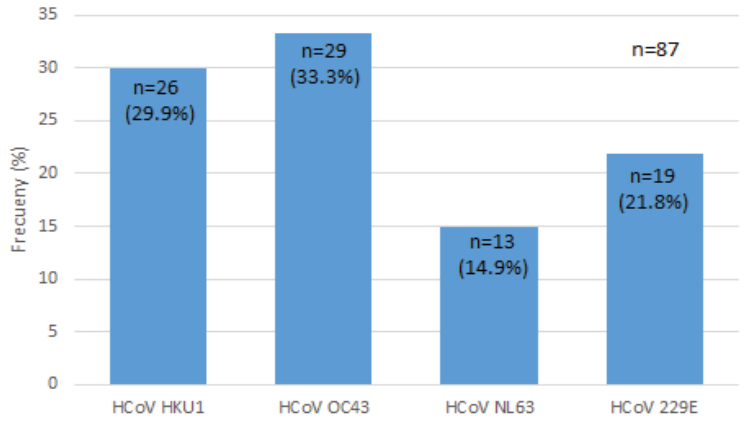

Figure 1. Frequency of HCoV species detected in adult patients attended at INER between November 2013 and March 2018. HCoV-OC43 is the most predominant species (33.3%, 1.48% of total virus), followed by HCoV-HKU1 (29.9%; 1.33% of total virus), HCoV-229E (21.8%; 0.97% of total virus) and finally, HCoV-NL63 (14.9%; 0.66% of total virus).

Table 2. Co-pathogen detection in HCoV´s-positive patients.

Co-pathogen	229E	NL63	OC43	HKU1	HCoV´s
Inf. A H1N1pdm	4	/	1	1	6
Inf. A H3	1	/	1	/	2
Inf. B	/	/	1	/	1
HRV	2	2	2	5	11
HMPV	/	/	/	/	/
HAdV	/	/	1	/	1
RSV	/	/	/	1	1
HBoV	/	/	2	/	2
HPIV	3	/	/	3	6

A total of 27 samples showed coinfection with at least one more respiratory virus; HRV=Human Rhinovirus, HMPV=Human Metapneumovirus, HAdV=Human Adenovirus, RSV=Respiratory Syncytial Virus, HBoV=Human Bocavirus, HPIV=Human Parainfluenza Virus. 3 of the 27 samples show coinfection with three viruses: HCoV-HKU1/InfAH1N1pdm/HRV, HCoV-229E/InfAH1N1pdm/HRV, and HCoV-229E/InfAH3/HPIV.

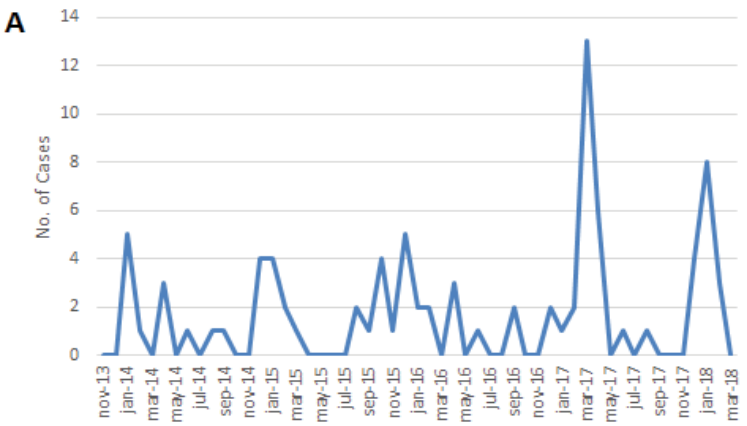

Figure 2. Seasonal distribution of HCoVs detected in adults that were attended at INER between November 2013 and March 2018. A higher number of cases appeared during the winter season.

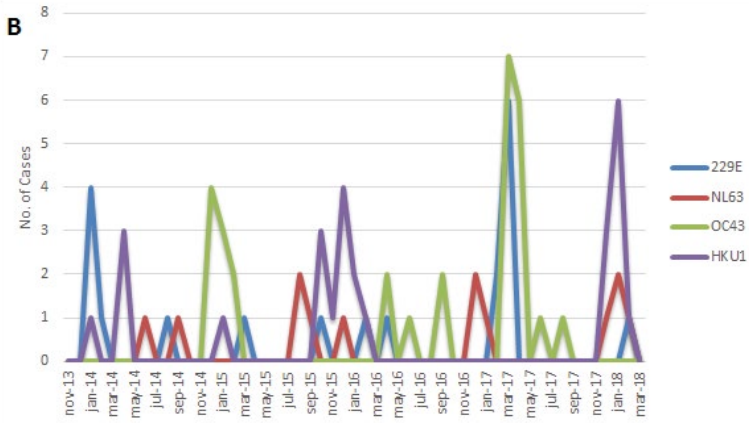

Figure 3. Seasonal distribution of HCoVs species detected in adults that were attended at INER between November 2013 and March 2018. A higher number of cases appeared during the winter season, being HCoV-OC43 the most predominant species.

Table 3. Signs and symptoms in HIV-infected and HIV-uninfected patients.

Variables	Total (N=36)	HIV-infected (N=11)	HIV-uninfected (N=25)	P-value	OR	95% CI
Headache	30.6% (11/36)	45.4% (5/11)	24% (6/25)	P=0.44	1.46	0.32-6.63
Rhinorrhea	30.6% (11/36)	18.1% (2/11)	36% (9/25)	P=0.26	0.33	0.5-1.74
Odynophagia	16.7% (6/36)	18.1% (2/11)	16% (4/25)	P=0.10	1	0.156-6.42
Fever	69.4% (25/36)	83.3% (10/11)	60% (15/25)	P=0.26	3	0.53-16.89
Dyspnoea	75% (27/36)	90.9% (10/11)	68% (17/25)	P=0.68	2.05	0.35-11.90
Cough	80.6% (29/36)	100% (11/11)	75% (18/25)	P=0.23	3.66	0.33-34.64
Sputum	25% (9/36)	18.1% (2/11)	28% (7/25)	P =0.35	0.48	0.08-2.80
Asthenia	63,9% (23/36)	63.6% (7/11)	64% (16/25)	P=0.34	0.7	0.16-2.91
Myalgias	25% (9/36)	18.2% (2/11)	28% (7/25)	P=0.42	0.35	0.08-2.80
Arthralgias	16.7% (6/36)	9.0% (1/11)	20% (5/25)	P=0.34	0.34	0.03-3.35
Impaired Consciousness	11.1% (4/36)	9.0% (1/11)	12% (3/25)	P=0.59	0.63	0.05-6.86
Gastrointestinal Symptoms	13.9% (5/36)	9.0% (1/11)	16% (4/25)	P=0.45	0.45	0.04-4.58
Duration of Symptoms (Days).	14 (±6.97)	17.92 (±7.58)	9.54 (±4,70)	P=0.20		

patients had pneumonia. This difference was statistically significant (Table 4). In 48% of the HIV-uninfected individuals, HCoVs caused the exacerbation of chronic lung diseases. Median symptom duration before diagnosis was 14 (±6.97). This was lower amongst HIV-uninfected patients: 9.54 (±4.70), compared to patients with HIV infection, 17.92 (±7.58); the difference was not statistically significant (p=0.17).

Distribution of serotypes in HIV-infected patients

Table 5 shows the frequencies of the various serotypes of causal agents for infections in HIV-infected patients and HIV-uninfected patients. The most common was OC43, identified in 50% (18/36) of the patients, of whom 11 had pneumonia, followed by NL63 which was found in 9 patients (25%), and 229E in 8 patients (22.2%). The frequency of the HCoVs subtypes was different in HIV-infected patients. The most common in HIV infected patients was NL63, which was identified in 45.5% (5/11), followed by OC43 and 229E.

Distribution of associations between the various causes

The most common co-infection in HIV-infected patients was *Pneumocystis jirovecii*. We found this co-infection in 40% of HIV infected patients (Table 6). The coinfections with other respiratory viruses were more common in HIV uninfected patients.

Diagnostic methods and laboratory findings

The principal laboratory findings were; presence of anemia in the HIV-infected patients, among which the average hemoglobin was 11.97 (± 2.59), and lymphocytopenia. 72% of the HIV-infected patients had a CD4+ count below 200, although the average lymphocyte count remained within the normal parameters (Table 7).

Table 4. Clinical manifestations.

Variables	Total (N=36)	HIV-infected (N=11)	HIV-uninfected (N=25)	P-value	OR	95% CI
Pneumonia	66.6% (24/36)	100% (11/11)	52% (13/25)	P=0.04	1.84	1.27-2.66
Exacerbation of COPD and asthma	33.3% (12/36)	0%	48% (12/25)			
Coinfections	41.6% (15/36)	81% (9/11)	24% (6/25)	P < 0.05	2.14	1.12-4.08

Discussion

Seasonal human coronaviruses (HCoV) represent an important burden of disease. They make up approximately 10% of all viral respiratory tract infections [16] and although they have been set aside for the past few years, their clinical impact has proven to be much larger than estimated. Coronaviruses are not only a cause of common cold; they can also provoke pneumonia and trigger exacerbations of various pulmonary and systemic diseases. It has been demonstrated as well that seasonal human coronaviruses can be fatal in immunosuppressed patients [17]. However, information on these viruses, especially affecting HIV-infected patients, is hard to come by, and the evidence regarding the epidemiology and clinical practice is limited.

There is a strong belief that coronaviruses are predominantly seasonal infections, particularly in autumn and winter. Our study shows that there is a

Table 5. The frequencies of the various serotypes of causal agents for infections in HIV-infected patients and HIV-uninfected patients.

Distribution of HCoV serotypes			
Variables	**Total**	**HIV-infected**	**HIV-uninfected**
	(N=36)	**(N=11)**	**(N=25)**
OC43	50% (18/36)	36% (4/11)	56% (14/25)
NL63	25% (9/36)	45.5% (5/11)	16% (4/25)
229E	22.2% (8/36)	18.2% (2/11)	24% (6/25)
HKU1	2.8% (1/36)	0	4% (8/25)
Distribution of serotypes causing clinical syndromes			
	Total	**HIV-infected**	**HIV-uninfected**
	(N=24)	**(N=11)**	**(N=13)**
Pneumonia			
OC43	45.8% (11/24)	35.6% (4/11)	53.8% (7/13)
NL63	29.2% (7/24)	45.5% (4/11)	15.4% (2/13)
229E	20.8% (5/24)	18.2 (2/11)	23.1% (3/13)
HKU1	4.2% (1/24)	0	7.7% (1/13)
Exacerbation of COPD and asthma			
OC43	25 % (3/12)	0	25 % (3/12)
NL63	16.7% (2/12)	0	16.7% (2/12)
229E	58.3% (7/12)	0	58.3% (7/12)

Table 6. Distribution of associations between the various causes in HIV-infected and HIV-uninfected patients.

Distribution of associations between the various causes in HIV-infected				
Variables	**Enterovirus/ Rhinovirus**	**Histoplasma**	**Tuberculosis**	**Pneumocystis**
OC43	0	13% (1/11)	13% (1/11)	13% (1/11)
NL63	13% (1/11)	0	0	27% (3/11)
229E	0	13% (1/11)	0	0
Distribution of associations between the various causes in HIV-uninfected				
	Enterovirus/ Rhinovirus	**Influenza A**	**Pseudomonas**	**Bocavirus**
OC43	0	33% (2/6)	0	17%(1/6)
NL63	0	0	17% (1/6)	0
229E	17% (1/6)	0	0	0
HKU1	0	17% (1/6)	0	0

Table 7. The principal laboratory findings in the HIV-infected and HIV- uninfected patients.

Laboratory Findings				
Variables	**Total**	**HIV-infected**	**HIV-uninfected**	**P-value**
	(N=36)	**(N=11)**	**(N=25)**	
Leukocytes (10^3/mm^3)	10.11 (± 5.10)	7,36 (± 4.54)	11,48 (± 4.89)	P=0.32
Neutrophiles (10^3/mm^3)	8.07 (± 14.54)	5,09 (± 2,34)	9.56 (± 4,58)	P=0.04
Lymphocytes (10^3/mm^3)	1.22 (±1.14)	1.01 (± 0.55)	1.32 (± 1.35)	P=0.04
Hemoglobin (G/DL)	13.62 (± 2.35)	11.97 (± 2.59)	14.54(± 1.75)	P=0.06
Platelets (mcL)	236,388 (±114,251)	235,000 (± 80,987)	237,083 (±129327)	P=0.41
Creatinine (MG/DL)	0.90 (± 0.34)	1.03 (± 0.51)	0.84 (± 0.22)	P=0.02

significant seasonal predilection, since the appearance of 69% of the OC43 and HKU1 species occurred during the winter months. This data equates to the work published by Masse et al. [18], which shows that seasonal coronaviruses were more prevalent in the winter.

Nevertheless, comparing the HKU1 positive tests with a study conducted in Israel, the seasonal prevalence is different. Friedman et al. described a higher incidence for the HCoV-HKU1 during the spring-summer period [19]. In terms of HIV-infected patients, most infections occurred in the winter, both in our study and the one reported by Garbino et al. [20].

The study revealed that the vast majority of the HCoV infections were caused by HCoV-OC43 (50%), HCoV-NL63 (25%) and HCoV-229E (22.2%). Nevertheless, in our study the frequency in HIV-infected patients varied, being NL63 the most common HCoV present, followed by OC43 and 229E.

Most seasonal HCoV infections are due to the OC43 species [19], with a phylogenetic analysis showing two frequent genotypes [21], followed by HCoV-229E [4]. It is thought that the clinical impact of OC43 is considerably larger than the 229E species [22]. Nonetheless, in immunosuppressed patients HCoV-229E could have a relevant clinical significance [3]. 70% of all immunocompromised individuals in Gaunt's et al. study were infected by HCoV-229E, whereas in otherwise healthy patients this species had no clinical repercussions.

In the study conducted by Garbino et al. [20] between 2003 and 2006,

18.6% of HIV-infected patients presented a viral respiratory infection, HCoV-OC43 being the most prevalent, followed by parainfluenza and influenza. HIV-infected patients are more susceptible to a number of important infections, and the limited existing evidence points toward HCoV as a dominant microbiologic agent in these cases.

Approximately 31% of the patients present a pattern of viral coinfection, mainly with influenza and parainfluenza viruses. Masse et al. [18] identified two common coinfection strains in HCoV-infected patients, HCoV-229E/NL63 and HCoV-HKU1/OC43. An estimate of a third of all respiratory infections of viral etiology are caused by more than one viral species, with no preponderant causality [18,23].

Two fifths of the HIV-infected patients were also infected by *Pneumocystis jirovecii*. The aforementioned coinfections were more frequent in HIV-unaffected individuals. There is an important difference in both HCoV species and coinfections when it comes to HIV-infected patients. Immunosuppressed patients are more susceptible to diverse community-acquired infections, and are exposed daily to many respiratory viruses [20].

Moreover, almost half of the HIV-patients both in our study and Garbino's et al. [20] had a concomitant opportunistic infection. Seemingly, the superposed HCoV exposure might exacerbate the clinical characteristics of either the *Pneumocystis jirovecii*, fungal or mycobacterial pneumonia [20].

Pneumonia was the commonest form of disease in HIV-infected individuals, present in the entirety of the group. Nonetheless, 73% of these patients had mixed-etiology pneumonia, compared to only 50% in HIV-uninfected subjects. This difference is statistically significant, and should be taken into consideration when evaluating incidental viral infections in HIV-infected patients.

Dyspnea, fever and cough were the prevailing symptoms. These clinical features present as a wide spectrum and are not specific for HCoV disease. It is suggested that HCoV-OC43 is more closely associated with bronchoalveolar infections, compared to other coronaviruses [24]. In Israel, HCoV clinical symptoms were more severe than those of RSV infections but milder than influenza symptoms [19].

The existing evidence indicates that because of the little clinical specificity of HCoV infections in immunosuppressed subjects, many alternative diagnoses must be considered before establishing the viral etiology of the disease [3].

In patients with Chronic Obstructive Pulmonary Disease (COPD), the impression is that HCoV infection is a substantial source of exacerbation. Also, comorbidities such as hypertension, asthma and opportunistic pneumonia were important findings in our study.

As Gorse et al. [4] explained, in older adults with COPD, concomitant HCoV infection worsened the spirometric results and predisposed to exacerbations, mostly in patients with the NL63 species. Additionally, a study conducted in Lebanon demonstrated that HCoV infection increased ICU risk, as well as the need for assisted ventilation [23]. In addition, in one of the few other Mexican HCoV studies, Moreno et al. (2) found an intimate association between viral respiratory infections and respiratory distress. Extrapolating this information to our study, the presence of an HCoV-NL63 infection could have clinical relevance, and increase the risk for both COPD exacerbation and hospitalization in HIV-infected patients. However, HCoVs have not proven to be a direct cause of mortality in HIV-affected individuals [20].

In our eleven-patient sample, 72% had a CD4+ lymphocyte count below 200, this being the most relevant laboratory finding. The percentage of cases of lymphocytopenia is equivalent to the data presented by Garbino et al. [20].

Acute respiratory illness supposes a complex and diverse gamut of disease [17]. Further studies are required to ascertain the epidemiological relevance of these infections in HIV-positive patients. As the COVID-19 pandemic is navigated, other HCoVs are set aside, and their relevance is undermined. Yet the concomitant respiratory pathogens will need to be monitored with proximity and differentiated from epidemic-causing species [16]. Despite the recent development of RVP assays and molecular virological advances, which have very accurate sensibilities and specificities [24,25], in Mexico the accessibility to these diagnostic methods is limited, thereby skewing the possibilities and reducing the viral-detection precision.

One of the limitations of our study was not following-up on mortality and survival rates in the population, since that data would have provided relevant results to complement the presented information. The inexact evaluation of comorbidities in HIV-infected patients is another challenge to consider, to further pinpoint causes and consequences of HCoV infections in a more detailed manner.

Conclusion

In conclusion, seasonal human coronaviruses are an important cause of respiratory tract infections in HIV-infected patients, especially during the winter months. The HCoV-NL63, HCoV-OC43 and HCoV-229E are the most prevalent species, evaluated through a Luminex assay. All of the HIV-affected individuals who tested positive for HCoV, displayed pneumonia, with the majority having concomitant infections and low CD4+ counts. The presence of HCoV in HIV-positive patients has not been analyzed to a great extent. Our study shows that in Mexico, over a 5-year period, these pathogens were the cause of a considerable number of infections. There is a need for further investigation regarding seasonal human coronavirus presence in HIV-affected individuals, other than SARS-CoV-2, since the retrieved evidence questions the often-believed impact of these infections, pointing to a more transcendent burden of disease.

References

1. McIntosh, Kenneth, and Stanley Perlman. "Coronavirus, incluido el coronavirus asociado a síndrome respiratorio agudo grave (SRAG). In: Enfermedades Infecciosas; Principios y Práctica." *7th ed. España: Elsevier* 2012.
2. Benito, Natividad, Moreno A, José M Miró, and Antonio Torres. "Pulmonary infections in HIV-infected patients: an update in the 21st century." *Euro Respir J* 39 (2011): 730-745.
3 Gaunt, Eleanor, Alison Hardie, Claas ECJ, and Simmonds P, et al. "Epidemiology and clinical presentations of the four human coronaviruses detected over 3 years using a novel multiplex real-time PCR method." *J Clin Microbiol* 48 (2010): 2940-2947.
4. Gorse, Geoffrey J., Theresa Z. O'Connor, Susan L. Hall, and Joseph N. Vitale, et al. "Human coronavirus and acute respiratory illness in older adults with chronic obstructive pulmonary disease." *J Infect Dis* 199 (2009): 847-857.
5. Jonsdottir, Hulda R., and Ronald Dijkman. "Coronaviruses and the human airway: a universal system for virus-host interaction studies." *Virol J* 13 (2016): 1-9.
6. Boeckh, Michael, Jane Kuypers, Anne Cent, and Campbell AP, et al. "Comparison of conventional and molecular detection of respiratory viruses in hematopoietic cell transplant recipients." *Transpl Infect Dis* 11 (2009): 298-303.
7. Hodinka, Richard L. "Point: is the era of viral culture over in the clinical microbiology laboratory?" *J Clin Microbiol* 51 (2013): 2-4.
8. Gharabaghi, Farhad, Ali Abdullah Hawan, Steven J Drews, and Susan E Richardson. "Evaluation of multiple commercial molecular and conventional diagnostic assays for the detection of respiratory viruses in children." *Clin Microbiol Infect* 17 (2011): 1900-1906.
9. Mahony, James, Sylvia Chong, Merante F, and Sevana Yaghoubian, et al. "Development of a respiratory virus panel test for detection of twenty human respiratory viruses by use of multiplex PCR and a fluid microbead-based assay." *J Clin Microbiol* 45 (2007): 2965-2970.
10. Hang, Vu, Nguyen Thi Han Ny, Tran My Phuc, and Pham Thi Thanh Tam, et al. "Evaluation of the Luminex xTAG Respiratory Viral Panel FAST v2 assay for detection of multiple respiratory viral pathogens in nasal and throat swabs in Vietnam." *Wellcome Open Res* 2 (2017): 80.
11. Gadsby, Naomi, Alison Hardie, Claas EC, and Kate E Templeton. "Comparison of the Luminex Respiratory virus Panel fast assay with in-house real-time PCR for respiratory viral infection diagnosis." *J Clin Microbiol* 48 (2010): 2213-2216.
12. Salez, Nicolas, Astrid Vabret, Marianne Leruez-Ville, and Laurent Andreoletti, et

al. "Evaluation of Four Commercial Multiplex Molecular Tests for the Diagnosis of Acute Respiratory Infections." *Plos One* 10 (2015): e0130378.

13. Choudhary, Manohar, Siddharth P. Anand, Shamal A. Tikhe, and Atul M. Walimbe, et al. "Comparison of the conventional multiplex RT-PCR, real time RT-PCR and Luminex xTAG® RVP fast assay for the detection of respiratory viruses." *J Med Virol* 88 (2016): 51-57.
14. Luchsinger, Vivian, Yara Prades, Mauricio Ruiz, and Rolando Pizarro, et al. "Comparison of Luminex xTAG® RVP fast assay and real time RT-PCR for the detection of respiratory viruses in adults with community-acquired pneumonia. *J Med Virol* 88 (2016): 1173-1179.
15. Tran, Nguyen, Quang Trinh, Ngan Thi Kim Pham, and Vu Minh Phuc, et al. "Clinical and epidemiological characteristics of acute respiratory virus infections in Vietnamese children." *Epidemiol Infect* 144 (2016): 527-536.
16. Nickbakhsh, Sema, Antonia Ho, Diogo F.P. Marques, and Jim McMenamin, et al. "Epidemiology of Seasonal Coronaviruses: Establishing the Context for the Emergence of Coronavirus Disease 2019." *J Infect Dis* 222 (2020): 17-25.
17. Liu, Wen, Qian Liu, De Hui Chen, and Huan Xi Liang, et al. "Epidemiology of acute respiratory infections in children in Guangzhou: a three-year study." *Plos One* 9 (2014): e96674.
18. Masse, Shirley, Lisandru Capai, Natacha Villechenaud, and Thierry Blanchon, et al. "Epidemiology and clinical symptoms related to seasonal coronavirus identified in patients with acute respiratory infections consulting in primary care over six influenza seasons (2014-2020) in France." *Viruses* 12 (2020): 630.
19. Friedman, Nehemya, Hadar Alter, Musa Hindiyeh, and Ella Mendelson, et al. "Human Coronavirus Infections in Israel: Epidemiology, Clinical Symptoms and Summer Seasonality of HCoV-HKU1." *Viruses* 10 (2018): 515.
20. Garbino, Jorge, Sarra Inoubli, Erik Mossdorf, and Rainer Weber, et al. "Respiratory viruses in HIV-infected patients with suspected respiratory opportunistic infection." *AIDS* 22 (2008): 701-705.
21. Zhang, Su-fen, Jiu-ling Tuo, Xu-bin Huang, and Xun Zhu, et al. "Epidemiology characteristics of human coronaviruses in patients with respiratory infection symptoms and phylogenetic analysis of HCoV-OC43 during 2010-2015 in Guangzhou." *Plos One* 13 (2018): e0191789.
22. Walsh, Edward, Jae Hyun Shin, and Ann R Falsey. "Clinical Impact of Human Coronaviruses 229E and OC43 Infection in Diverse Adult Populations." *J Infect Dis* 208 (2013): 1634-1642.
23. Finianos, Mayda, Randi Issa, Martin D. Curran, and Claude Afif, et al. "Etiology, seasonality, and clinical characterization of viral respiratory infections among hospitalized children in Beirut, Lebanon." *J Med Virol* 88 (2016): 1874-1881.
24. Zeng, Zhi-Qi, De-Hui Chen, Wei-Ping Tan, and Shu-Yan Qiu, et al. "Epidemiology and clinical characteristics of human coronaviruses OC43, 229E, NL63, and HKU1: a study of hospitalized children with acute respiratory tract infection in Guangzhou, China." *Eur J Clin Microbiol Infect Dis* 37 (2018): 363-369.
25. Debiaggi, Maurizia, Filippo Canducci, Elisa Rita Ceresola, and Massimo Clementi. "The role of infections and coinfections with newly identified and emerging respiratory viruses in children." *Virol J* 9 (2012): 247.

How to cite this article: Eduardo Becerril V, Delgado-Cueva Andrea, Mújica-Sánchez Mario Alberto, and García-Colín María del Carmen, et al. "Epidemiology of Infections Caused by Seasonal Human Coronavirus in Hospitalized Adults with HIV Over a 5-year Period in Mexico City." J AIDS Clin Res 12 (2021): 842.