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REVIEW

Emerging viral diseases in kidney transplant recipients

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SUMMARY

Viruses are the most important cause of infections and a major source of mortality in Kidney Transplant Recipients (KTRs). These patients may acquire viral infections through exogenous routes including community exposure, donor organs, and blood products or by endogenous reactivation of latent viruses. Beside major opportunistic infections due to CMV and EBV and viral hepatitis B and C, several viral diseases have recently emerged in KTRs. New medical practices or technologies, implementation of new diagnostic tools, and improved medical information have contributed to the emergence of these viral diseases in this special population.

The purpose of this review is to summarize the current knowledge on emerging viral diseases and newly discovered viruses in KTRs over the last two decades. We identified viruses in the field of KT that had shown the greatest increase in numbers of citations in the NCBI PubMed database. BKV was the most cited in the literature and linked to an emerging disease that represents a great clinical concern in KTRs. HHV-8, PVB19, WNV, JCV, H1N1 influenza virus A, HEV, and GB virus were the main other emerging viruses. Excluding HHV8, newly discovered viruses have been infrequently linked to clinical diseases in KTRs. Nonetheless, pathogenicity can emerge long after the discovery of the causative agent, as has been the case for BKV. Overall, antiviral treatments are very limited, and reducing immunosuppressive therapy remains the cornerstone of management. Copyright © 2012 John Wiley & Sons, Ltd.

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INTRODUCTION

KT is the treatment of choice for ESRD and results in increases in the duration and quality of life for patients [1]. Worldwide, the number of KTs increases each year. In the USA, among the 571,000 patients treated for ESRD in 2009, 30% (171,000) received a renal allograft compared with 27% (93,000) in 1998 [2,3]. In France, in 2010, the prevalence of ESRD patients treated by KT was 44.4% (29,841 patients) [4]. However, successful transplantation requires the administration of immunosuppressive therapies to prevent allograft rejection, which is inextricably linked to infection. Anti-infective regimens make immunosuppressive therapies safer, but they do not completely prevent the occurrence or increased severity of infectious diseases. Thus, infections remain an important concern and constitute the second-leading cause of mortality among KTRs behind cardiovascular complications [2,5]. Viruses are the most important cause of infections and represent a major source of morbidity and mortality [6–8]. KTRs may acquire viral infections through exogenous routes, including community exposure, the donor organ, and blood products or by endogenous reactivation of latent viruses [6]. Virus-associated diseases may manifest as direct illness or indirect effects mediated by immunomodulation [6], and viruses will more fully display their potential dangerousness in KTRs than in immune-competent

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Abbreviations used
BKV, BK virus; BKVAN, BKV-associated nephropathy; ESRD, end-stage renal disease; JCV, JC virus; KS, Kaposi's sarcoma; KT, kidney transplantation; KTR, kidney transplantation recipient; MCD, multicentric Castleman's disease; PVB19, parvovirus B19; PTLD, post-transplant lymphoproliferative disorder; PEL, primary effusion lymphoma; PML, progressive multifocal leukoencephalopathy; SOTR, solid organ transplant recipient; TTV, torque teno virus; WNV, West Nile virus.

individuals [9]. In KTRs, the most typical viral infections are those caused by *Herpesviridae*, hepatitis viruses, HIV, and *Papillomaviridae* [8,10]. However, several emerging viral diseases have recently been highlighted in this population.

The word "emerging," when applied to a viral disease, can have various meanings [11]. Emerging viral diseases are diseases that newly appear in a population or that have been recognized earlier but whose incidence or geographical range is increasing. Re-emerging viral diseases are diseases that re-appear in a same or different geographical area. Emergence can correspond to the appearance of new viruses or can rely on migrations of people, reservoir, or vectors, on new environmental conditions, new behaviors, or new medical practices. Alternatively, emergence can reflect an improved awareness by clinicians of the disease, which leads to an increase in testing and diagnosis. Finally, emergence can rely on the implementation of new diagnostic tools that reveal levels of incidence and prevalence previously underestimated. Recent decades have been very favorable for the emergence of viral agents and viral diseases. Notably, urbanization and globalization have shown dramatic expansions [12]. Concurrently, new technologies and medical practices have been implemented or their use has been increasing, as is the case for organ transplantation [5], and the tools for scientific and medical information have grown significantly [13,14]. Moreover, the number and performance of viral detection methods have evolved dramatically over the last decades [15]. Particularly, molecular methods have been increasingly implemented in clinical virology and have considerably impacted this field by allowing the rapid detection of viruses, including those that cannot be cultivated in the laboratory.

The purpose of this review is to provide an update on emerging viral diseases and newly discovered viruses in KTRs.

METHODS

We first performed a search in the NCBI PubMed database by using as keywords "virus" OR "viral infection" AND "kidney transplantation", limiting the search to humans and to the last 20 years. We obtained 3444 references. We then checked these references by identifying the name of the virus or family of viruses in the title or abstract of the reference, we confirmed that the viruses occurring in most publications in the field of KT were CMV (723 references, 20% of the total number of references), HCV (656 references, 18%), EBV (478 references, 13%), HBV (280 references, 8%), HIV (168 references, 5%), and human papillomavirus (109 references, 3%) (Figure 1).

We focused on other viruses and the yearly evolution of the number of articles that quoted them if more than 10 papers were available over the last 20 years (Figure 2). The virus for which the number of citations showed the greatest increase over this period was BKV, followed by HHV-8, GB virus, PVB19, WNV, JCV, H1N1 influenza virus A, and HEV (Figure 3).

Finally, to possibly relate emerging diseases in KTRs to newly discovered viruses, we searched the NCBI PubMed database for each virus

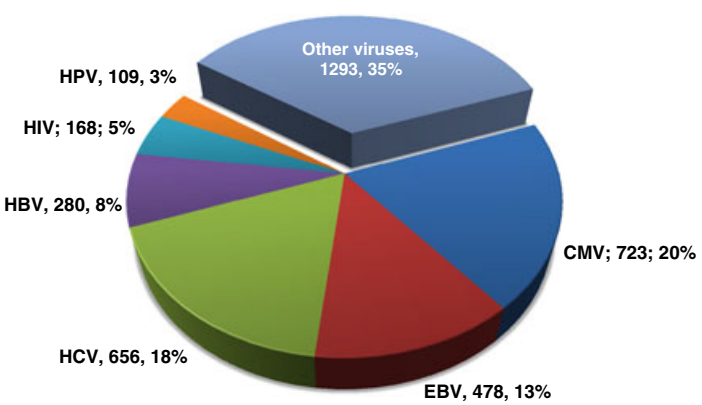

Figure 1. Viruses cited in publications related to KT over the last 20 years. The viruses the most frequently cited were CMV (723 references, 20% of the total number of references), HCV (656 references, 18%), EBV (478 references, 13%), HBV (280 references, 8%), HIV (168 references, 5%), and human papillomavirus (HPV) (109 references, 3%). Other viruses including emerging viruses represented 35% of the publications

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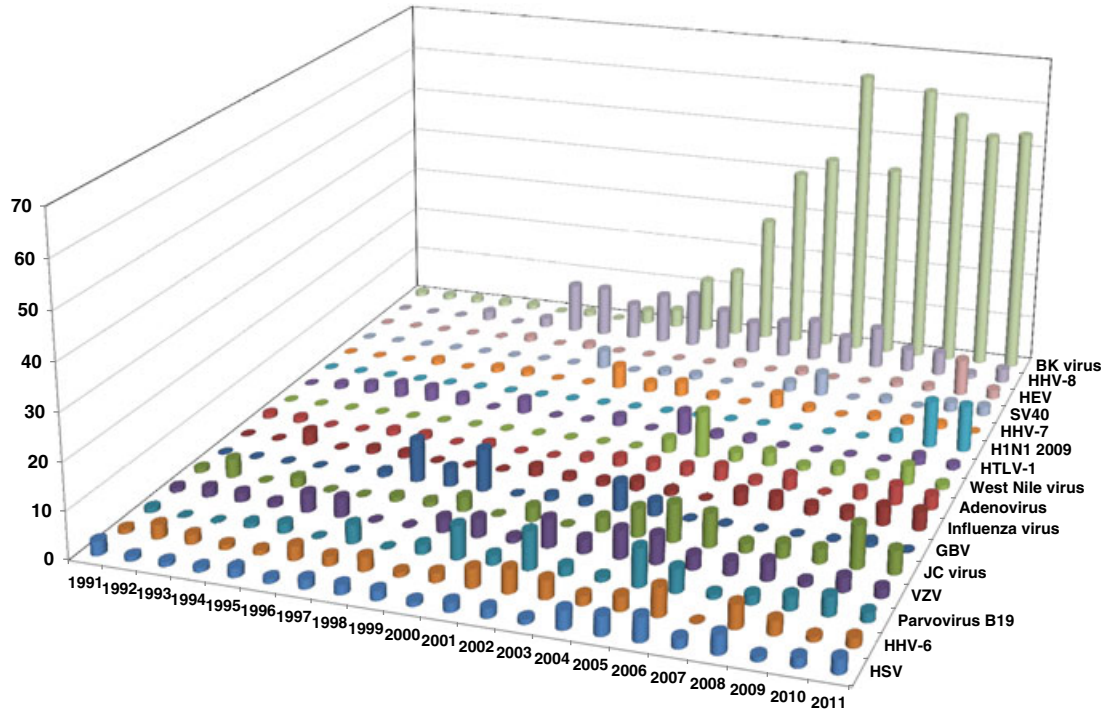

Figure 2. Yearly number of publications (if more than 10 were referenced over the last 20 years) about viruses other than the major opportunistic viruses and the hepatitis viruses. The virus for which the number of citations showed the greatest increase over the study period was BKV. The vertical axis represents the yearly number of publications for each virus. SV40: Simian virus 40, GBV: GB virus

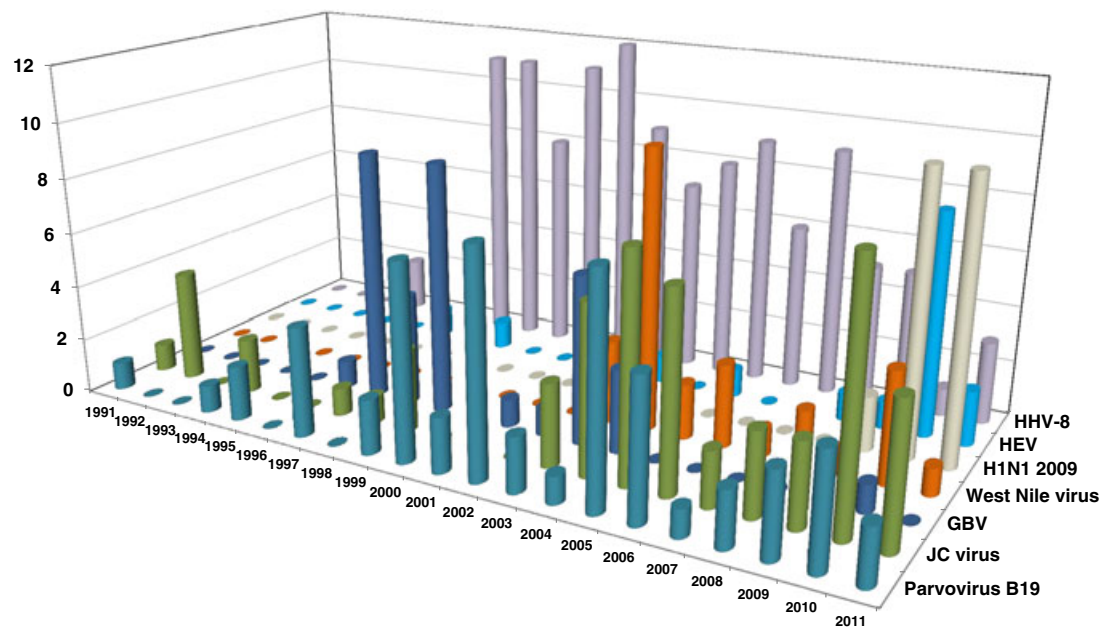

Figure 3. Yearly number of publications about HHV-8, GB virus (GBV), PVB19, West Nile Virus, JC virus, H1N1 2009 influenza virus A, and HEV. These viruses were those for which the number of citations showed the greatest increase over the last 20 years, apart from BK virus. The vertical axis represents the yearly number of publications for each virus

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discovered over the last 20 years and concurrently searched for keywords "renal transplant," "renal transplantation," "kidney transplant," or "kidney transplantation".

EMERGING VIRAL DISEASES IN KTRS

Polyomavirus-associated nephropathy

The human polyomaviruses BK and JC have both been recognized as causative agents of polyomavirus-associated nephropathy, but BK is the major etiologic agent [16]. BKV was first isolated in 1970 from a KTR who presented with a ureteral stenosis [17]. The virus was named BKV after the initials of this patient (Table 1). BKV was discovered well before the clinical consequences of infection could be appreciated in KTRs. In 1993, the first case of BKV interstitial nephritis was diagnosed by a renal allograft biopsy in a patient with acute renal failure [18,19]. Infections with BKV and JCV occur early in life and are benign [20]. In blood donors, the IgG seroprevalence was 82% and 58% for BKV and JCV, respectively, whereas viruria rates were 7% and 19%. Neither BKV nor JCV was detected in plasma [21]. The distribution of latent viruses in different tissues is thought to occur during the primary viremia. The best-known site of BKV and JCV latency is the urogenital tract, and BK viral sequences can be detected in the bladder, in prostate tissues, and in kidneys (in up to 57%) procured from asymptomatic individuals [22–24]. After KT, the incidence of viruria increased to 35% for JCV and 16% for BKV, and infection by one polyomavirus was negatively associated with reactivation of the other [16]. BKV reactivation most likely occurs in the cells of the donor kidney [20].

The emergence of BKVAN over the last two decades is well documented [25] and coincides with the extensive use of potent immunosuppressive drugs such as tacrolimus, mycophenolate mofetil, and sirolimus that began in the late 1990s. Pathologists retrospectively reviewed all renal allograft biopsies performed between 1985 and 1995 in Basel, Switzerland but could not authenticate any cases [26]. Thus, it is unlikely that the increase in the incidence of BKVAN is merely the result of increased awareness. The prevalence of BKVAN in recent studies is between 1% and 10% [25,27]. A large retrospective KTR cohort analysis revealed that the rates of treatment of BKV continued to increase in the time period from 2003 to 2006 [28]. The different

Table 1. Characteristics of viruses involved in emerging diseases in KTRs

Species	Family, subfamily, genus	Genome	Capsid	Diameter of particle (nm)	Year of discovery, reference
BKV	*Polyomaviridae*, —, *Polyomavirus*	Circular, dsDNA, 5 kb	Icosahedral	45	1971, [17]
JCV	*Polyomaviridae*, —, *Polyomavirus*	Circular, dsDNA, 5 kb	Icosahedral	45	1971, [33]
HHV-8	*Herpesviridae*, *Gammaherpesvirinae*, *Rhadinovirus*	Linear, dsDNA, 165 kb	Icosahedral	110–150	1994, [45]
HEV	*Hepeviridae*, —, *Hepevirus*	Linear, ssRNA, 7.2 kb	Icosahedral	27–34	1983, [62]
PVB19	*Parvoviridae*, *Parvovirinae*, *Erythrovirus*	Linear, ssDNA, 5.4 kb	Icosahedral	20–25	1975, [74]
Influenza virus A Subtype H1N1 A/California/04/2009	*Orthomyxoviridae*, —, influenza virus A	Linear, 8 ssRNA segments, 14 kb	Helicoidal	80–120	2009, [86,87]
WNV	*Flaviviridae*, —, *Flavivirus*	Linear, ssRNA, 10 kb	Icosahedral	40–50	1940, [91]

ds: double-stranded; kb: kilobase; ss: single-stranded.

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prevalence rates in different geographical areas most likely reflect local immunosuppression protocols and diagnostic approaches rather than true differences in BKV epidemiology. Risk factors for BKV infection may be donor, recipient, allograft, or virus related. The intensity of immunosuppression is the greatest risk factor for BKV infection and thus BKVAN, and the immunosuppressive therapy is the most modifiable factor [29]. BKVAN may affect SOTRs other than KTRs, but the preferential development in the renal allograft may be due to a microenvironment permissive for BKV replication [16].

BKVAN is usually described in the first year post-transplant, but approximately 25% of cases are diagnosed later [25]. BKVAN presents as renal dysfunction without other clinical manifestations [25,29]. The diagnosis of BKVAN requires a renal allograft biopsy and is demonstrated by presence of intranuclear viral inclusions in tubular epithelial (Figure 4) and/or glomerular parietal cells, which is often associated with epithelial cell necrosis and acute tubular injury [25]. Histological studies indicate that BKVAN progresses schematically through three histologic patterns [25]. Viral cytopathic changes initially predominate (pattern A). A cytopathic-inflammatory stage without significant fibrosis (pattern B) and a late stage with predominant tubular atrophy and fibrosis (pattern C) follow them. Patterns B and C were significantly associated with allograft loss [25]. Viral-induced tubular inflammation is morphologically indistinguishable from acute cellular allograft rejection, and in the early

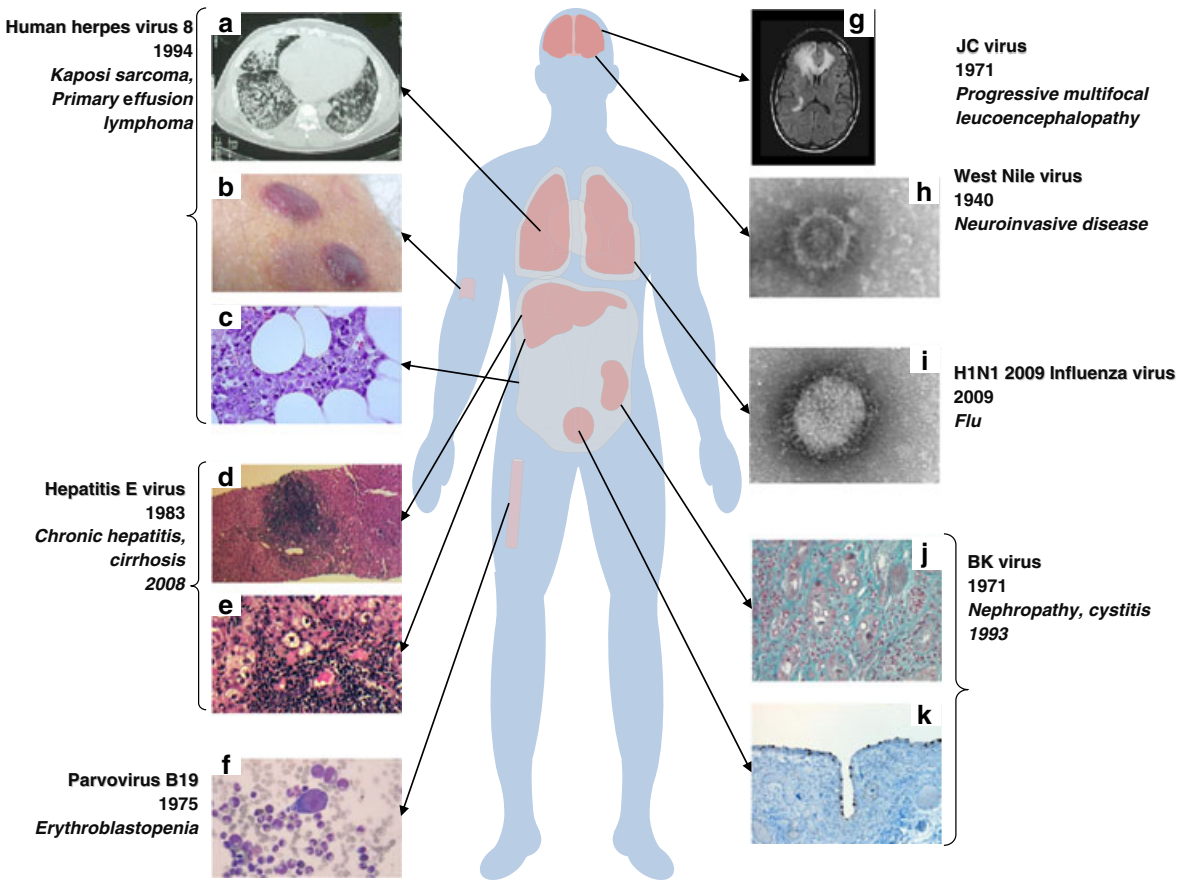

Figure 4. Schematic of the emerging viral diseases and related viruses in KTRs. For each disease, the name and discovery date of the virus are indicated. (a) KS lung lesions observed by computed tomography. (b) Typical KS skin lesion. (c) Peritoneum biopsy, PEL (Hematoxylin Erythrosine Saffron (HES) staining, X400). (d) Liver biopsy, chronic hepatitis E (HES, X200). (e) Liver biopsy, chronic hepatitis E (HES, X400). (f) Bone marrow examination, PVB19 erythroblastopenia (May-Grünwald Giemsa staining, ×40). (g) Hyperintense lesions of PML on fluid-attenuated inversion recovery sequences observed on magnetic resonance imaging. (h) Electron micrograph of flavivirus in a culture supernatant. (i) Electron micrograph of influenza virus in a culture supernatant. (j) Renal transplant biopsy, BKVAN (Masson trichrome, ×400). (k) Bladder biopsy, BKV cystitis (Immunohistochemistry anti-polyomavirus, ×200)

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years of BKVAN emergence, misdiagnosis of acute cellular rejection instead of viral nephritis likely resulted in unnecessary antirejection treatment that could inflate rates of allograft loss of 50%–100% recorded in earlier studies. A proactive approach to accurate and early diagnosis has decreased the incidence of BKVAN-related graft loss to less than 10% [27]. Reactivation of BKV in the ureter can manifest as a ureteric stenosis, and in the bladder, it can manifest as a hemorrhagic cystitis [30]. Renal cell carcinoma of the graft and carcinoma of the bladder are increasingly considered complications of BKV's oncogenic properties [27,31].

Routine screening is presently the most important tool used to identify patients at increased risk for BKVAN [32]. Detection of viremia is required in KTRs with high level of urinary BKV replication (decoy cells or BKV loads $> 10^7$ copies/ml) because 30%–50% of them progress to BK viremia and BKVAN [20]. Screening is especially recommended during the first year of KT and whenever unexplained serum creatinine rise occurs [32].

JCV-associated PML

JCV was isolated from the brain of a patient suffering from Hodgkin's disease and PML in 1971 [33]. The virus was named JCV after the initials of this patient (Table 1). JCV is the causative agent of PML in immunodeficient patients, but it has not been established if PML results from primary infection or reactivation of the latent virus. The normal brain may be a site of JCV latency, and the reactivation of the virus can lead to lytic infection of glial cells and to the onset of PML in the case of failure of immunosurveillance [34]. However, PML occurs rarely in KTRs. In a retrospective study, there were nine cases of PML identified among 32,757 adult KTRs, which corresponded to an incidence of 8.8 cases/100,000 person-years [35]. Since the review of the literature by Crowder *et al*. in 2005 that listed 13 cases of PML in KTRs, only three new cases have been reported [36], two cases in children [37,38] and a third in an adult following rituximab treatment for a PTLD [39]. The prevalence of PML does not seem to be increasing in KTRs, despite increasing use of mycophenolate mofetil and rituximab (a mAb directed against CD20 in B cells), which have been the objects of safety alerts regarding potential associations with PML [40,41].

PML is a demyelinating disease of the CNS, and the pathological lesions are typically demyelinated plaque areas with irregular borders surrounded by macrophages and bizarre-appearing glial cells that have enlarged nuclei with typical polyomavirus inclusions [36]. The PML symptoms appear at a median time of 37 months after KT (range 5–120 months) [36]. The most common symptoms are hemiparesis, cognitive impairments, visual disturbances, ataxia, cranial nerve deficits, and seizures [36]. On magnetic resonance imaging, PML lesions typically appear hyperintense on T2-weighted and fluid-attenuated inversion recovery sequences (Figure 4) and hypointense on T1-weighted sequences. The lesions are located in subcortical and deep white matter and are usually multiple and bilaterally distributed [42]. PML is definitively diagnosed by detecting JCV DNA in the CSF or on cerebral biopsy [43]. The clinical course of PML is progressive and nearly always fatal. Nine of the 13 KTRs with PML died, eight within 5 months of the diagnosis [36].

HHV-8-associated diseases

HHV-8 is the causative agent of KS, which was described in 1872 by Moritz Kaposi [44]. Kaposi described the sporadic or classic subtype. The iatrogenic subtype has subsequently been described in immunocompromised patients, particularly KTRs. HHV-8 was discovered using RDA between healthy skin and KS tumor obtained in an AIDS patient [45] (Table 1). Primary HHV-8 infection in immune-competent individuals is associated with mild, nonspecific symptoms of fatigue, diarrhea, rash, and lymphadenopathy [46]. Following primary infection, HHV-8 establishes latency mainly in B lymphocytes and spindle cells [46]. HHV-8 is a geographically restricted virus, and its incidence varies from low incidence (<5%) in North America to very high incidence (>50%) in Africa and the Amazon basin [46]. Contrarily to HHV-7, the pathogenic potential of HHV-8 in KTRs is clear. HHV-8-associated diseases are most often neoplastic: KS, MCD, and PEL [46].

In France, the prevalence of HHV-8 infection among organ donors is low (1.08%), whereas KTRs are more frequently HHV-8 seropositive (3.2%) [47]. The prevalence of KS ranges from 0.5% in KTRs from northern Canada and Europe to 4.1% in KTRs from Saudi Arabia, reflecting the north-to-south gradient of seroprevalence of HHV-8 [48]. KS is the most common tumor in KTRs from Saudi Arabia, representing 87.5% of all malignancies [49]. Active HHV-8 infection after solid organ transplantation

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may occur either as primary infection in HHV-8 seronegative recipients of allografts or blood transfusion from HHV-8 seropositive donors [50,51] or as secondary reactivation of the latent endogenous virus [47]. In a prospective study, KS was due to HHV-8 reactivation in 87% of the cases and was due to primary infection in 13% of cases, in which seronegative KTRs received a kidney from a seropositive donor [47]. In seropositive KTRs, independent risk factors for KS were age and black skin [47]. Screening of donors and recipients for HHV-8 is recommended to assess the risk in geographic regions with high rates of infection and to monitor HHV-8 viremia after KT to determine the risk of disease in HHV-8 seropositive recipients or in those who receive a kidney from an HHV-8 seropositive donor [46].

The mean time between KT and KS onset is 20 months, with a range from a few weeks to 18 years [48]. Skin lesions are seen in >90% of all cases with KS. The lesions have a dark blue or purplish color on white skin (Figure 4) and often appear pigmented on black skin. Initially macular, they are subsequently infiltrated and sometimes nodular. Most cutaneous lesions occur at the extremities. Visceral involvement is observed in 40% of the cases with KS [52]. Oral lesions consist predominantly of purple stains on the palate and are associated with visceral involvement of the gastrointestinal tract, which is typically detected as red spots during endoscopic examination of asymptomatic patients. Other visceral sites of KS are the lymph nodes and the lungs (Figure 4). Regardless of the localization, the diagnosis of KS can be based on its histological features [48]. Typical lesions exhibit a network of spindle-shaped cells and large vascular spaces surrounded by an endothelial cell layer. Immunochemistry using mAb directed against HHV-8 antigens is useful for the pathological diagnosis, as is PCR to detect viral replication [46].

Other HHV-8-associated diseases include the body cavity-based PEL [53,54], MCD [55–57], and PTLDs [55,58–60]. These occur rarely in KTRs, and the cases reported in the literature are summarized in Table 2. Besides, primary HHV-8 infection resulted in nonmalignant diseases with a potentially lethal acute syndrome characterized by fever, hemophagocytic syndrome, and bone marrow failure [61]. The risk factors for these less common clinical manifestations of HHV-8 infection have not been defined.

Chronic hepatitis E

HEV was discovered after an outbreak of unexplained hepatitis occurring in Soviet soldiers in Afghanistan (Table 1). Balayan presented with hepatitis after ingestion of a pooled stool extract of patients and detected the virus in his stool by EM [62]. HEV is a leading cause of acute hepatitis in adults in developing countries, where it is hyperendemic, of genotype 1 or 2, and principally water borne [63]. In developed countries, hepatitis E was first considered imported from HEV hyperendemic geographical areas but is currently an emerging autochthonous (i.e. locally acquired) disease and a porcine zoonosis caused by HEV genotype 3 or 4 [63]. Hepatitis E typically causes an acute and self-limiting infection in immune-competent individuals. However, fulminant hepatitis and high mortality are described, reaching 25% in cases involving pregnancy in developing countries and 70% in cases involving underlying liver disease [63]. The first case of HEV infection in a KTR was reported in 2003 in India [64]. The patient died of severe acute pancreatitis attributed to HEV infection with elevated serum alanine aminotransferase and bilirubin levels, positive anti-HEV IgM, and a surprisingly normal serum amylase level. European autochthonous acute HEV infections in KTRs were first described in Toulouse, France [65]. The incidence of HEV infections has been estimated to be 2.7 cases/100 person-years after KT in southwestern France [63]. The only independent predictive factor for HEV infection in SOTRs is the consumption of game meat [63]. In KTRs, acute hepatitis E is mostly asymptomatic [66]. Liver enzyme levels are lower, and histological lesions are less severe than those seen in immune-competent individuals [67]. Various extrahepatic manifestations have been described in KTRs in association with HEV infections, including transient cryoglobulinemia, glomerulonephritis [63], and neurological symptoms involving both the peripheral and CNS [63].

HEV infection emerged as a clinical concern among KTRs in Europe when chronic infections associated with autochthonous genotype 3 HEV were described in 2008 [67,68]. Chronic hepatitis E is defined as hepatitis and persistent infection documented by PCR, lasting for more than 6 months. The incidence of chronic evolution after HEV infection has been estimated to be 51% in KTRs [66]. Clinical studies suggest that the occurrence and persistence of chronic hepatitis E are related to the immunological status of

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Table 2. Case reports of HHV-8-associated PEL, MCD, and PTLDs in KTRs

Disease	Sex, age at diagnosis (yrs), geographical origin	Clinical presentation, time to KT for onset	Outcome	Year, reference
KS/PEL	Male, 57, Mali	KS at 5 M, pleural effusion at 35 M, PEL diagnosed at 44 M	Death 8 M after PEL diagnosis and 17 M after first pleural effusion	2008, [53] 2010, [54]
KS/PEL	Male, 41, Kossovo	KS at 19 M, pleural effusions at 48 M, pleural effusion, ascites, and pericarditis at 66 M, PEL diagnosed at 66 M	Death 1 M after PEL diagnosis and 9 M after first pleural effusion	2010, [54]
PEL	Male, 63 Senegal	Ascites at 28 M, pleural effusion, ascites, and pericarditis at 54 M, PEL diagnosed at 54 M	Death 8 D after PEL diagnosis and 26 M after first pleural effusion	2008, [53]
PTLD/MCD*	Male, 35, Italy	Cervical lymphadenopathy at 16 M	Alive 12 M after PTLD/MCD diagnosis	2003, [55]
MCD	Male, 30, Turkey	Generalized lymphadenopathy, splenomegaly at 17 M	Death 2 M from sepsis after MCD diagnosis	1997, [56]
MCD/KS	Male, 55, Italy	Fever, generalized lymphadenopathy, splenomegaly at 48 M, MCD diagnosed at 69 M	Death 21 M after MCD diagnosis	1993, [57]
PTLD*	Female, 48, origin ?	Redness, swelling, and warmth in lower extremity at 120 M, PTLD diagnosis	Alive 32 M after PTLD diagnosis	2005, [60]
PTLD/KS	Male, 17, Israel	Fever, splenomegaly, generalized lymphadenopathy, haemolysis at 9 M, PTLD/KS diagnosis	Alive 22 M after PTLD/KS diagnosis	2001, [58]
KS/PTLD	Male, 26, Hispanic	KS at 24 M, "shortly after KS" generalized lymphadenopathy, hepatosplenomegaly, PTLD diagnosis	Death from PTLD after an unknown duration	1999, [59]

KS, Kaposi sarcoma; yrs, years; M, month; D, day.
*Also EBV-associated.

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Table 3. Case reports of WNV infections transmitted to KTRs through transplantation or blood product transfusion

Patient, country	Route of transmission, time to KT for onset of symptoms	Clinical manifestations due to viral infection	Outcome	Ref
Organ donor 1, USA	BT	None	Death not related to WNV	[96]
KTR 1, USA	14 D after KT	Fever, rash, upper respiratory tract symptoms, backache, diarrhea, meningitis, coma, mechanical ventilation	Alive	
KTR 2, USA	17 D after KT	Fever, headache, myalgia, arthralgia, anorexia, diarrhea, meningitis, encephalitis, mechanical ventilation	Death related to WNV	
Organ donor 2, USA	Mosquito bite	Felt febrile before fatal trauma injury	Death not related to WNV	[97]
KTR 3, USA	After KT	Asymptomatic viremia	Alive	
KTR 4, USA	After KT	No infection on D16 and D27	Alive	
KTR 5, USA	10 D after BT	Meningoencephalitis	Death related to WNV	[98]
KTR 6, USA	10 D after KT, 10–11 D after fresh frozen plasmapheresis	Fever, chills, diplopia, tremor, hallucinations, coma, mechanical ventilation	Death related to WNV	[99]

BT, blood transfusion; D, day; Ref, reference.

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Table 4. Viruses discovered after 1990 and associated with human diseases

Virus	Settings of discovery, date and localization of discovery, reference	Reservoir
Sin nombre virus	Outbreak of Hantavirus Pulmonary Syndrome, 1993, USA, [120]	Rodents
Sabiá virus	Two cases of Brazilian hemorrhagic fever, 1994, Brazil, [121]	Presumed South American rodent
Hendra virus	Outbreak of fatal respiratory disease in horses and humans, 1995, Australia, [122]	Fruit bats
H5N1 influenza virus	Outbreak in chickens and of fatal respiratory disease in humans, 1997, Hong Kong, [123]	Birds
Nipah virus	Outbreak of fatal encephalitis, 1999, Malaysia, [124]	Fruit bats
SARS coronavirus	Outbreak of Severe Acute Respiratory Syndrome, 2003, China, [125–127]	Bats

SARS, severe acute respiratory syndrome.

patients. Indeed, this form of hepatitis E is described only in severely immunocompromised patients, especially SOTRs, HIV-infected patients, and individuals with hematological diseases [63]. In pooled SOTRs, the occurrence of chronic hepatitis E has been related to the dose of immunosuppressants [66,69]. As in the acute form, chronic hepatitis E is often subclinical in KTRs, with mild liver abnormalities (Figure 4). Twenty-seven chronic hepatitis E cases have been reported in Western Europe since 2008 [66,68,70–72]. Evolution to cirrhosis may occur rapidly after HEV infection [68,73]. Three of the four reported cases of HEV-related cirrhosis have died from decompensated cirrhosis [66,68,71].

PVB19-associated anemia

PVB19 was discovered in 1975 during systematic screening of hepatitis B in nine healthy blood donors, a patient with acute hepatitis, and a patient who received a renal allograft 1 week earlier, without a specific illness having been associated with PVB19 at that time (Table 1) [74]. Primary PVB19 infection most often occurs early in life [75]. In immune-competent individuals, PVB19 infection is generally asymptomatic but may manifest in children as a mild rash called erythema infectiosum or fifth disease and in adults as a polyarthritis [75]. The first description of hypoplastic crisis during PVB19 infection dates to 1981 in patients with sickle-cell anemia [76]. The clearance of the virus is usually complete, but some studies have demonstrated ongoing viral replication in the blood and suggested that PVB19 could establish a persistent infection in the kidney [23,77]. The mechanisms of infection after KT are either primary infection or reactivation of a latent infection [75,78,79]. PVB19 transmission most commonly occurs through the respiratory tract. Moreover, nosocomial outbreaks in transplant units have been reported [79]. The persistence of viral replication in the blood and kidneys could result in transmission of PVB19 in KTRs from the renal allograft or blood products [23,77]. The prevalence of PVB19 infection is estimated to be between 2% and 30% in KTRs [80,81]. The difference in incidence between the early and late 2000s may be explained by the increased use of molecular techniques in diagnosis and surveillance in the late 2000s [82,83]. Eid *et al*. reviewed 98 cases of PVB19 infection after transplantation in 2006 [75]. Among these cases, 53 have occurred after KT. The median time to infection was 1.25 months. The most common manifestation was anemia (in 98.1% of KTRs), whereas the most frequent clinical symptom was fever (23.9%) [75]. Anemia results from the viral replication in erythroid progenitors, leading to their apoptosis, and is typically refractory and severe. More rarely, leukopenia (34%) and thrombocytopenia (19.1%) were present. Renal graft dysfunction and hepatitis existed in 15.6% and 6.5% of the KTRs, respectively [75]. Collapsing glomerulopathy and thrombotic microangiopathy have been reported in renal allografts [79]. Other manifestations were seldom reported, including pneumonitis, encephalitis,

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Table 5. Human viruses discovered after 1990 with new diagnostic methods and systematic screening of samples

Virus	Origin of sample; date and localization of discovery; reference	Clinical significance
Human metapneumovirus	28 NPAs from epidemiologically unrelated children with unidentifiable viruses URTIs and LRTIs between 1981 and 2000; 2001, Netherlands; [128]	RTIs
Human coronavirus HKU1	One NPA in a case index of pneumonia and retrospectively detected in 1/400 NPAs; 2004, China; [129]	RTIs
Human coronavirus NL or NL63	One nose swab sample in a case index of pneumonia in 1988 and retrospective detection in 4/139 nasal aspirate; 2004, Netherlands; [130] One NPA in a case index of bronchiolitis and retrospective detection in 7/406 respiratory specimens (NPAs, OPAs, and BALs) of hospitalized and outpatient individuals with URTIs and LRTIs (co-infection with *Pneumocystis jiroveci* in an HIV-infected patient and co-infection with RSV in another case) between December 2002 and August 2003; 2004, Netherlands; [131]	RTIs
HTLV-3	One DNA sample from the 240 plasma tested for HTLV-1 and/or HTLV-2 antibodies, during a campaign of HIV-1 screening; 2005, Cameroon; [132]	Unresolved
HTLV-3 and -4	One DNA sample for each virus from 930 persons with infrequent primate exposure risks during a campaign of HIV-1 screening; 2005, Cameroon; [133]	Unresolved
Human bocavirus	Large-scale molecular virus screening of respiratory tract samples, 7/378 being positive and retrospective detection in 17 of the 540 additional children; 2006, Sweden; [134]	Unresolved
KI polyomavirus	Large-scale molecular virus screening of clinical samples submitted for diagnosis of viral infections: 6/ 637 NPAs and 1/192 fecal samples were positive; 2007, Sweden; [135]	Unresolved
WU polyomavirus	High throughput sequencing of respiratory secretions from a patient with acute respiratory disease of unknown etiology, Australia, 2007, and retrospective detection in 5/410 upper respiratory specimens and in 1/480 BAL samples from severe acute respiratory illness of unknown etiology; 2007, USA; [136]	Unresolved
Human rhinovirus C	Molecular human rhinovirus screening in NPAs prospectively collected from hospitalized children with acute respiratory tract infections and negative for common respiratory viruses (co-infection with human bocavirus in 12 cases), during a	Unresolved

Continues

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Table 5. (Continued)

Virus	Origin of sample; date and localization of discovery; reference	Clinical significance
	1-year period: 21/203 were of new genotype; 2007, Hong Kong; [137]	
MC polyomavirus	Digital transcriptome subtraction: detected in 8/10 Merkel Cell Carcinoma tumors; 2008, USA; [138]	Unresolved

HTLV, human T lymphotropic virus; NPAs, nasopharyngeal aspirates; OPAs, oropharyngeal aspirates; BALs, bronchoalveolar lavages; URTIs, upper respiratory tract infections; LRTIs, lower respiratory tract infections; RTIs, respiratory tract infections; RSV, respiratory syncytial virus.

myocarditis, and hemophagocytic syndrome [79]. Bone marrow examination typically reveals red cell aplasia (Figure 4). Diagnosis of PVB19 infection is based on serological tests, blood/bone marrow PCR, and bone marrow examination [79]. The persistence of viral replication in the blood has been demonstrated in KTRs several months after the correction of the hematologic abnormalities [79]. Chronic infection can manifest as chronic anemia or relapses of anemia [78,84,85]. The relapses of anemia are more frequent after primary infection [84]. Recurrences of PVB19 infections occur in 34% of the KTRs [75].

H1N1 flu

A new strain of influenza A H1N1 was first recognized in 2009 and resulted in a worldwide pandemic (Table 1) [86]. This pandemic H1N1 has been characterized as a reassortant virus with genes from swine, avian, and human influenza viruses [87]. Severe disease has been noted in children, pregnant women, and people with comorbid disorders including chronic lung or heart disease, diabetes, and obesity [88]. In SOTRs, pandemic H1N1 resulted in a spectrum of illness ranging from mild and self-limiting to severe disease. The largest study reported data on 237 SOTRs from North America; of which, the majority (37%) was KTRs [89]. The most common presenting symptoms were cough, fever, myalgias, rhinorrhoea, sore throat, and headache. Lung imaging showed pneumonia in 32% of patients. H1N1 was diagnosed by PCR on nasopharyngeal swabs (Figure 4). The incidence of hospitalization was 71%, and the rate of admission to the intensive care unit was 16%. Of these patients, 21 needed mechanical ventilation. Two adults and one child received extracorporeal membrane oxygenation. The type of transplant in these patients was not specified, but it did not seem to affect the outcomes. Ten adults died (7%). The overall mortality rate was 4%. Different studies showed that morbidity and mortality observed in KTRs and non-immunocompromised patients infected with pandemic H1N1 were similar [90].

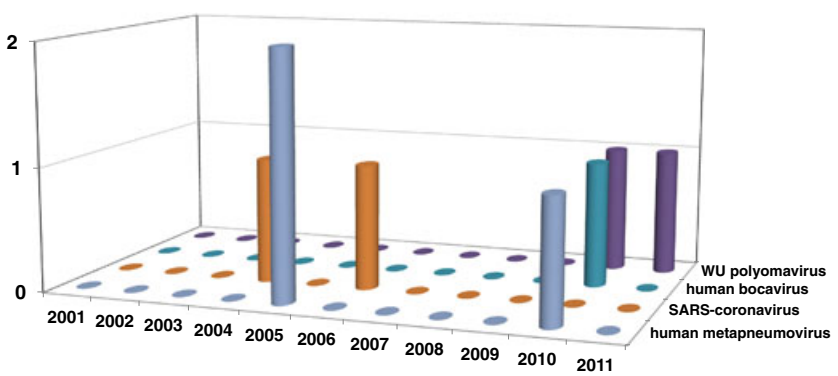

Figure 5. Yearly number of publications about newly discovered respiratory viruses in KTRs. Very few publications about KTRs involved respiratory viruses discovered over the last 20 years. The vertical axis represents the yearly number of publications for each virus

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Table 6. New respiratory viruses in KTRs

New respiratory virus	Studies in KTRs
Human metapneumovirus	Severe pneumonia requiring 5 days of mechanical ventilation in a 43-year-old male KTR. Immunofluorescence on BAL and NPA was strongly positive for human metapneumovirus and negative for the other viruses. Clinical recovery was obtained under supportive treatment [139] Retrospective analysis of respiratory tract samples from hospitalized patients, including KTRs, has identified human metapneumovirus, but the clinical syndrome was not defined [140]
Coronavirus NL63/HKU1	One 15-year-old KTR with pneumonia had coronavirus retrospectively detected in nasal wash by RT-PCR as the only respiratory pathogen. Subtype NL63 or HKU1 was not specified [141]
Polyomavirus KI/WU	Prevalence of WU and KI polyomaviruses was established in plasma (3.6%), urine (14%), and upper respiratory tract specimens (10%) in KTRs. All the patients with a positive respiratory specimen had acute upper respiratory tract infection, but none of these samples were tested for any acute respiratory virus [142] Prevalence of WU and KI polyomaviruses was determined in immunocompromized patients. KI polyomavirus was detected in 16 of the 200 patients by RT-PCR. One of them was a 72-year-old KTR that presented with an acute upper respiratory tract infection and was co-infected with human rhinovirus. The sample positive for the viruses was a NPA [143]

NPA, nasopharyngeal aspirate; BAL, bronchoalveolar lavage.

WNV disease

WNV is an example of a previously known pathogen whose emergence is related to epidemiological factors that favored its spread. The appearance of WNV in New York in 1999 and the panzootic that followed have drawn attention to this virus, which was isolated for the first time in 1937 in a woman suffering from fever in the province of West Nile in Uganda (Table 1) [91]. Whereas WNV fever may be a real emerging disease in the Americas with a peak of activity in 2003 that affected 9862 persons, including 2866 cases of neuroinvasive disease and 264 deaths [92], in the Old World, less than 200 human deaths have been recorded over the past decade [93]. Birds are the primary reservoir of WNV (Figure 4), and mosquitoes are the vectors, acquiring the infection by feeding on a viremic bird and transmitting it to humans from bites. In immune-competent individuals, 80% of the infections are asymptomatic, whereas 20% have a self-limited febrile illness that may be accompanied by a maculopapular rash [94]. The estimated rate of neurological involvement is less than 1% [94,95].

KTRs may acquire WNV by three primary mechanisms: from an infected organ donor, an infected blood product, and community-acquired exposure. To date, WNV infections after KTs and blood product transfusions have been reported in six KTRs [96–99] (Table 3). The majority of reports of WNV infections in KTRs describe infections acquired by mosquito exposure occurring from 2 months to 8 years post-transplant [94,95,100–103]. The incubation period seems to be longer among SOTRs than among the general population. A study conducted in >800 SOTRs after an epidemic of WNV in Canada found that seroprevalence was low (0.25%) and the risk of neurological disease was 40%, much higher than for the general population [104]. SOTRs had a 40 times greater risk of symptomatic infection than normal hosts [94].

NEWLY DISCOVERED VIRUSES IN KTRs

New viruses were discovered after 1990 in two different settings: in well-characterized human diseases, for example during outbreaks (Table 4), or

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Table 7. Treatments for emerging viral diseases in KTRs

Viral disease	Curative treatment
Influenza A H1N1	Consider KTRs at increased risk for complications. Treat KTRs promptly empirically with NA inhibitors (oseltamivir or zanamivir) when H1N1 is confirmed or suspected regardless of the duration of symptoms. Starting antiviral treatment within 48 h of symptom onset was associated with decreases in admission to the hospital and the intensive care unit, need for mechanical ventilation, and risk of death [89]. Reduce immunosuppressive therapy in case of significant disease [144]
Polyomavirus-associated nephropathy	No specific antiviral drug. Reduce immunosuppressive therapy in case of BKVAN or sustained BK viremia [20,27,29,32]. No definitive data confirming the effectiveness of cidofovir, leflunomide, and ciprofloxacin for either treatment or prevention of BKVAN [27,29,32]
JCV-associated PML	No specific antiviral drug. Reduce or discontinue immunosuppressive therapy. Treatment is mainly supportive [36].
Kaposi Sarcoma	Reduce or discontinue immunosuppressive therapy [46]. KS disappeared in 17% of the patients with mucocutaneous involvement and 16% with visceral involvement after reduction of immunosuppressive therapy [52]. Complementary surgical excision, radiation therapy, or cytotoxic chemotherapy can be useful [46]
Chronic hepatitis E	Reduce immunosuppressive therapy [63]. However, this response is not sufficient to cure all cases and can be dangerous, through increasing the risk of acute allograft rejection. The use of IFN is currently contraindicated in KTRs. Ribavirin has an anti-HEV effect and has been used in KTRs [63]
PVB19-associated anemia	No specific antiviral drug [75,79]. Reduce immunosuppressive therapy [75,79]. Iv Ig infusions are given [75,79]. The clinical response is a reticulocytosis and correction of the anemia. Erythrocyte transfusion could be required [79].
WNV disease	No specific antiviral drug. Reduce or discontinue immunosuppressive therapy. Treatment is mainly supportive [94,102]

due to systematic screening of samples (Table 5). In the latter case, the viruses were found from human samples collected during authenticated infectious syndromes or from laboratories but without clinical data. The clinical significance of newly discovered viruses without accompanying clinical data is often unknown. In contrast, new viruses that have been discovered in human outbreaks are clearly pathogens, and 66% are zoonotic (Table 4).

Among viruses discovered after 1990, HHV-8 is the only virus to clearly cause an emerging disease in KTRs. Very few new respiratory viruses have been studied in KTRs (Figure 5), and we have summarized these studies in Table 6. However, community exposure of KTRs to respiratory viruses is important. The consequences of respiratory viral infections include higher rates of viral pneumonia in KTRs than in immune-competent individuals and increased risk of superinfection with bacterial and fungal pathogens [8]. Nevertheless, identification of viruses in respiratory infections in KTRs is difficult. In a prospective study of respiratory viral infections, detection of a respiratory virus was positive only in 17 of the 68 (25%) cases [105]. Large

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Table 8. Prevention of emerging viral diseases in KTRs

Viral disease	Prevention	Organ procurement/donation
Influenza A H1N1	Vaccinate KTRs and KT candidates with at least one dose of H1N1 vaccine [144]. The H1N1-adjuvanted vaccine was of limited efficacy with a seroconversion rate around only 50% but was safe in KTRs [145].	During an influenza pandemic [144]: screen all donors and KTRs for recent flu-like symptoms. Recommend a treatment of 5–10 days at therapeutic doses for the KTR if the donor did not complete a course of treatment. Defer KT with living donor having H1N1 until the donor has been treated and is clinically well.
Hepatitis E	KTRs should avoid eating insufficiently cooked game meat or pork products [63]. Two manufactured recombinant hepatitis E vaccines showed promising results in preventing of hepatitis E cases in humans, one of them being now available on the Chinese market [63].	
WNV disease	Infection prevention is essential and includes education regarding the transmission of WNV in areas of high WNV activity. KTRs should be counseled on the use of insect repellant when outdoors during the late summer and fall, on potentially avoiding outdoors activities at dawn and dusk, and on removing any stagnant water collections [10,94]	All USA and Canada blood bank products are today tested for WNV to reduce the risk of transmission. Concerning the organ donors, in North America, all living donors are prospectively tested close to the time of transplant and deceased donors with any form of encephalitis are avoided. Concerning transplant recipients living or traveling in areas where WNV is endemic, the transplant teams must have a high index of suspicion for the illness when dealing with fever in transplant recipient [10,94,102]. Outside areas of viral traffic, the transplant teams must also be informed about any history of recent stay in North America of the donor.

prospective controlled studies in KTRs with comprehensive viral testing are needed to establish the epidemiology and to determine whether newly discovered respiratory viruses cause respiratory diseases in this population.

Finally, several reports have been published on GB virus C and TTV in KTRs, peaking in 1997 and 2003, respectively, and then decreasing. Despite the fact that GB virus C and TTV were first found in serum samples of patients with unexplained hepatitis [106–108], most papers have dismissed significant roles for these viruses as etiologic agents of diseases in immune-competent individuals [106,108–110] and in KTRs [111–115] (Supplementary Table).

TREATMENT

Except for H1N1 flu and hepatitis E, there is no available antiviral intervention. Reduced immunosuppressive therapy and supportive treatment are the main recommendations for the treatment of emerging viral diseases that are presented here.

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Treatment options and measures to prevent infection are compiled in Tables 7 and 8.

CONCLUSION

This review summarized the current knowledge on viruses that had shown the greatest increase over the last two decades in the field of KT according to the number of citations. The viral diseases that were discussed result from endogenous reactivation or from community exposure. They were most often the first and only described in immunosuppressed populations, and their clinical expression has become apparent several years after the discovery of the virus. Apart from HHV8, the viruses that have been discovered over the last two decades are infrequently involved in clinical diseases in KTRs. Nonetheless, in favorable circumstances, the pathogenicity of a newly discovered virus can fully express itself long after its discovery.

Virology remains a very fast-moving field because of the implementation of new technologies. These technologies are helpful in detecting new or old pathogens in undiagnosed infections [116] and are also influential in conducting technology-based research [117]. Viruses are suspected to be the most abundant inhabitants of our biosphere and to number approximately 3×10^{12} in the human body [118]. Metagenomics now allows us to characterize the virome in clinical samples, which has revealed the presence of expected and unexpected viruses and a large number of viral coinfections [119]. The increased use of these tools in special populations, such as KTRs, that are particularly concerned with infectious diseases might lead to breakthroughs in the knowledge of the biology and clinical impact of viruses.

CONFLICT OF INTEREST

The authors have no competing interest.

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