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Review

Viral infections of the central nervous system in Africa

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ABSTRACT

Viral infections are a major cause of human central nervous system infection, and may be associated with significant mortality, and long-term sequelae. In Africa, the lack of effective therapies, limited diagnostic and human resource facilities are especially in dire need. Most viruses that affect the central nervous system are opportunistic or accidental pathogens. Some of these viruses were initially considered harmless, however they have now evolved to penetrate the nervous system efficiently and exploit neuronal cell biology thus resulting in severe illness. A number of potentially lethal neurotropic viruses have been discovered in Africa and over the course of time shown their ability to spread wider afield involving other continents leaving a devastating impact in their trail. In this review we discuss key viruses involved in central nervous system disease and of major public health concern with respect to Africa. These arise from the families of Flaviviridae, Filoviridae, Retroviridae, Bunyaviridae, Rhabdoviridae and Herpesviridae. In terms of the number of cases affected by these viruses, HIV (Retroviridae) tops the list for morbidity, mortality and long term disability, while the Rift Valley Fever virus (Bunyaviridae) is at the bottom of the list. The most deadly are the Ebola and Marburg viruses (Filoviridae). This review describes their epidemiology and key neurological manifestations as regards the central nervous system such as meningoencephalitis and Guillain-Barré syndrome. The potential pathogenic mechanisms adopted by these viruses are debated and research perspectives suggested.

1. Introduction

Viral infections comprise one of the most important causes of neurological illness with major impact on the global burden of human disease. The estimated incidence of central nervous system (CNS) viral infections is 20–30/100,000 per year (Michos et al., 2007), roughly three times as common as bacterial infections. In resource-limited countries, especially Africa, CNS viral infections are a significant cause of long term neurological dysfunction, mortality and economic burden. On the whole, the prevalence of CNS viral infections in Africa is not known and most likely underestimated, due in part to the limitations in diagnostic tools and poor demographic censuses.

A diverse spectrum of viruses with the capacity to invade the CNS cause devastating acute to chronic neurological disease, sometimes associated with severe disability and/or mortality. Despite the CNS having a highly complex barrier system, a wide variety of viruses elude it, gaining access and inducing disease. The routes of viral entry as well as the specificity of the virus for a particular host tissue and the associated immune responses influence the disease outcome. Based on the distinct anatomic site of the inflammation and the entry site of viral pathogens, infection results in meningitis, encephalitis, myelitis, or a combination of these pathologic features. In the case of multiple site involvement, the terms meningoencephalitis or encephalomyelitis are used (Swanson and McGavern, 2015). Paradoxically, the host's immune system initially mobilized to defend the CNS from the viral invader, can sometimes turn traitor by contributing to the devastating pathological reactions and subsequent neurological sequelae affecting mobility, sensory organs, and cognitive functions.

The data and relevant information for this review was obtained through an electronic search of the PubMed database using free text and Medical Subject Headings terms for articles on the selected viruses with respect to Africa, and published in English from January 1980 to August 2018. We used the search term "viral infections" AND

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"central nervous system" OR "Zika virus", OR "West Nile virus", OR "Chikungunya virus", OR "Ebola virus" OR "Marburg virus" OR "Human immunodeficiency virus" OR "Rift Valley virus" OR "Rabies virus" OR "Herpes Simplex virus". Additional materials were found by manual searches of the reference lists of selected articles, textbooks, and relevant disease-specific guidelines.

This review does not cover several other viruses of relevance to the pathogenesis of nervous system disease and global burden of disease such as but not limited to measles virus, Human-T-Lymphotropic virus type I (HTLV-I), and enteroviruses (poliovirus), extensively reviewed elsewhere (Buchanan and Bonthius, 2012; Khan et al., 2017; Huang and Shih, 2015).The aim of this review is to provide an overview of key viruses involved in CNS infection that are of major public health concern with respect to Africa. These include Flaviviruses- Zika, West Nile and Chikungunya viruses, Filoviruses- Ebola and Marburg viruses, Lentivirus-Human immunodeficiency virus (HIV), Phlebovirus- Rift Valley virus, Lyssavirus-Rabies and the Herpes Simplex viruses. We highlight their epidemiology, key neurological features, different mechanisms involved in the pathogenesis and perspectives for future research.

2. Epidemiology

2.1. Flaviviridae: Zika virus and West Nile virus infections

Zika virus (ZIKV) is a *flavivirus* that can cause disease similar to Dengue and Yellow fever. It is a single strand enveloped RNA enclosed by a capsid protein that encodes structural and non-structural proteins. The first reporting of the virus occurred in the Zika Forest of Uganda using a sentinel monkey in 1947 (Dick et al., 1952).

Transmission of ZIKV to humans is primarily through mosquito-bites of the *Aedes* genus including: *A. aegypti* and *A. albopictus*, which usually bite during the daytime and are widely distributed throughout the tropical and subtropical world. Non-mosquito transmission through mother-to-child during pregnancy (Jouannic et al., 2016; Oliveira Melo et al., 2016) and sexual contact (Hills et al., 2016) also contribute. There are no reports of infants getting ZIKV virus through breastfeeding, therefore mothers are encouraged to continue breastfeeding even in active ZIKV areas. In Brazil, transmission of ZIKV via blood transfusion has been confirmed (Motta et al., 2016).

In the early 1970s, ZIKV appeared in other African countries, notably with infected people showing fever, headache, joint pains, and rash, but with little note of neurological disease. The *Aedes Egypti* mosquito was hypothesized to be a likely carrier, with a high number of young adults showing evidence of infection (Fagbami, 1979). The virus continued to be observed in many African countries and in Asia; in 2007 an outbreak of ZIKV infections occurred in Yap Island, a part of Micronesia (Hayes, 2009). This was the first sign that the virus was capable of spreading outside of Africa and Asia. In 2013, an outbreak of ZIKV occurred in French Polynesia with the first evidence of neurotropism, as many infected persons developed Guillain-Barré syndrome (Cao-Lormeau et al., 2016), a polyneuropathy, which mainly occurs in adults. Since then, cases have been found in South America, Central America, the Caribbean, and North America, with the first case of microcephaly observed in Brazil (Fauci and Morens, 2016).

It was however the explosion of the cases of ZIKV infection in the Americas from late 2014 (Fauci and Morens, 2016) coupled with the severity of associated birth defects, the significant rise in cases of Guillain-Barré syndrome and microcephaly in affected regions (Schuler-Faccini and Feitosa, 2016), that caught the world's attention. This prompted the World Health Organisation (WHO) to declare ZIKV infection a "Public Health Emergency of International Concern" on 1st February 2016, stressing the importance of aggressive measures to curb infection, especially among pregnant women and women of childbearing age (Anon., 2016). As the ZIKV situation continues to evolve, the actual burden of this viral infection in Africa is still unknown despite many countries having been identified to be at risk of continuing ZIKV transmission (see Table 1); the WHO now considers ZIKV infection a "significant enduring public health challenge". The ZIKV epidemic is currently global and poses grave medical, ethical, and economic implications especially in many low income countries in Africa where the resources for early diagnosis are lacking.

The West Nile virus (WNV) is an enveloped virion containing a single-stranded, positive-sense RNA genome of about 11 kb that encodes a single polyprotein (Kilpatrick, 2011). WNV belongs to the "Japanese Encephalitis Virus" complex that comprises several arboviruses (Japanese Encephalitis virus, St. Louis encephalitis virus, and Murray Valley encephalitis virus) whose infection results into encephalitic syndromes. WNV, however, is historically considered among the least virulent members of this serogroup complex (Murphy et al., 1995). This mosquito-borne flavivirus was initially isolated from the blood of a woman presenting with a febrile illness in the West Nile district of Uganda in 1937 (Smithburn et al., 1940). It was later discovered in an ecology study conducted in Egypt and the southern Sudan that in addition to humans, the WNV also caused disease in susceptible birds and other animals (horses) (Taylor et al., 1956). The virus is sustained through a mosquito-bird-mosquito cycle with wild birds serving as amplifying hosts, and humans and domestic animals such as horses, serving as dead end hosts. The *Culex* species of mosquitoes are considered to be the primary global transmission vector of the WNV and in Africa, the *Cx. univittatus* symbolises the principal vector (Taylor et al., 1956; Hubalek and Halouzka, 1999). The other modes of transmission in humans include transmission through blood transfusion, organ transplants, sporadic transmission by breast-feeding and mother to child transmission (Granwehr et al., 2004).

Following its discovery, the WNV was not considered to be a significant human pathogen being noted to cause a minor arbovirus infection manifesting mainly as a non-symptomatic disease or a mild influenza-like illness whose diagnosis was often missed. In the last decade, however, WNV infection became a major public health concern due to the numerous human outbreaks reported with fatal cases and severe neurological diseases such as meningitis, encephalitis, and meningoencephalitis largely observed among the elderly population (Klein et al., 2002; Platonov et al., 2008; Petersen and Hayes, 2008; Sirbu et al., 2011). Furthermore, in Africa with many countries at risk (see Table 1) and limited diagnostic facilities, it is highly likely that the diagnosis and management of WNV encephalitis or meningitis is often compromised since it cannot be clinically distinguished from other viral CNS infections (Campbell et al., 2002). Currently the WNV has a widespread geographical distribution throughout the tropical and temperate regions of the world and is a vector-borne pathogen of global importance. The WNV was responsible for significant human epidemics in South Africa (1974, 2008–2009) (Zaayman and Venter, 2012).

2.2. Togaviridae: Chikungunya virus

Chikungunya virus (CHIKV) is a single stranded RNA alphavirus in the family *Togaviridae* that contains an RNA genome of approximately 11.8 kB. CHIKV is transmitted by mosquitoes of the genus *Aedes*– (mainly *Aedes aegypti* and *Aedes albopictus*) but may also be transmitted

Table 1
The Families of Selected Neurotrophic Viruses, Modes of Transmission and Geographical distribution within Africa.

Taxonomic Family	Genus	Virus	Vector/Mode of Transmission	African countries with reported isolations, outbreaks, and sporadic or serologic cases
Flaviviridae	Flavivirus	Zika virus	Mosquito (Aedes), Sexual Transmission, Mother to child transmission.	Burundi, Burkina Faso, Egypt, Eritrea, Ethiopia, Kenya, Senegal, Somalia, Angola, Zambia, Nigeria, Cabo Verde, Cameroon, CAR, Cote d'Ivoire, Nigeria, Gabon, Uganda.
	Flavivirus	West Nile virus	Mosquito (Culex), Breast feeding, Blood transfusion, Organ transplant, Mother to child transmission.	Algeria, Tunisia, Morocco, Egypt, Senegal, Cote d'Ivoire, Nigeria, CAR, DRC, Chad, Uganda, Kenya, Ethiopia, Namibia, Mozambique, South Africa, Gabon, Madagascar
Togaviridae	Alphavirus	Chikungunya virus	Mosquito (Aedes), Mother to child transmission.	Sudan, Uganda, Tanzania, Congo, DRC, Gabon, CAR, Cameroon, Nigeria, Senegal, Sierra Leone, Zimbabwe, South Africa, Malawi, Madagascar
Bunyaviridae	Phlebovirus	Rift Valley Fever virus	Mosquito (Culex, Aedes, Anopheles, Eretmapoites, Mansonia), contact or aerosol exposure produced during slaughter of infected sheep, goats, and cattle, ingestion of the unpasteurized or uncooked milk of infected animals	Kenya, Zimbabwe, Egypt, CAR, Madagascar, Burkina Faso, Mali, Chad, Ethiopia, Somalia, Guinea, Nigeria, Cameroon, Mauritania, South Africa, Senegal, the Gambia, Sudan, South Sudan, Kenya, Uganda, Tanzania, Zambia, Zimbabwe, Mozambique, Madagascar, Namibia, Gabon, Republic of Congo, Angola, Botswana, Niger, DRC
Filoviridae	Ebolaviruses	EBOV BDBV SUDV TAFV.	Transmission to man from wild animals (fruit bats) and spreads in the human population through human-to-human transmission via direct contact with blood and/or secretions of an infected person	Senegal, Mali, Guinea, Sierra Leone, Liberia, Nigeria, Cote d'Ivoire, Congo, Gabon, DRC, Uganda, Kenya. Sudan, Angola, Zimbabwe, South Africa.
	Marburg viruses	Marburg virus and Ravn virus	Contact with infected nonhuman primates and bats. Transmission via close personal contact with an infected individual or their body fluids. Mother to child transmission.	Uganda, Kenya, DRC, Angola, South Africa
Rhabdoviridae	Lyssavirus	Rabies virus	Transmission through the saliva of infected animals or bite from any infected animal. Transmission between humans is extremely rare, but may occur through aerosolized virus that enters the respiratory tract, corneal and organ transplants.	Endemic to the whole of Africa
Retroviridae	Lentivirus	HIV-1 HIV-2	Transmission by sexual contact across mucosal surfaces, by contact with or transfer of HIV-infected body fluids, by maternal-infant exposure during pregnancy or childbirth, through breast milk, by blood transfusion, and percutaneous inoculation with a contaminated needle.	HIV-1 endemic to the whole of Africa. HIV-2 mostly found in West Africa reported in Guinea-Bissau, The Gambia, Senegal, Cape Verde, Cote d'Ivoire, Mali, Sierra Leone, and Nigeria.
Herpesviridae	Simplexvirus	HSV-1 HSV-2	HSV-1 transmission by contact with infected body fluids or mucosal surfaces and via sexual contact. HSV- 2 primarily via sexual contact	Endemic and is widespread throughout Africa which has the highest prevalence in all the regions of the world.

Abbreviation List: **BDBV** = Bundibugyo ebolavirus; **CAR** =Central African Republic, **DRC**=Democratic Republic of Congo; **EBOV** = Zaire ebolavirus, **HSV**= Herpes simplex virus; **HIV**= Human Immunodeficiency virus; **SUDV** = Sudan ebolavirus; **TAFV**= Taï Forest ebolavirus (also known as Cote d'Ivoire ebolavirus).

via mother-to-child transmission although this is a rare event (Fritel et al., 2010). CHIKV was first isolated in 1953 at the Entebbe virus research institute in Uganda from samples obtained during an epidemic in Tanzania among the Makonde tribe (Ross, 1956). The term Chikungunya derives from the Makonde dialect, that translates to "that which bends up" referring to the posture acquired by many of those infected with CHIKV as a result of the severe joint pain experienced during infection (Ng and Hapuarachchi, 2010).

Since its discovery up to December 2013, CHIKV infection was largely restricted to East Africa and the Indian Ocean (see Table 1). By the first half of 2014, however, an accelerating incidence of CHIKV occurred in the Caribbean and Southern United States, with over 1 million suspected cases (www.cdc.gov/chikungunya). While CHIKV infection is usually self-limiting and seldom fatal, the arthralgia it causes can be extremely painful and debilitating, typically lasting for 1 week or longer. Prior to its re-emergence in the Indian Ocean in 2004 and its subsequent spread worldwide, CHIKV infections rarely involved the CNS. Currently, infection with CHIKV is viewed as a re-emerging alphavirus that can cause severe and fatal disease with CNS involvement in both adults and neonates (Lemant et al., 2008; Gerardin et al., 2008; Lebrun et al., 2009). The recent major outbreaks of CHIKV in La Reunion Island and the Caribbean, attest to this finding by reporting cases of encephalitis that are substantially higher among infants compared to adults (Gerardin et al., 2016).

2.3. Bunyaviridae: Rift Valley Fever virus

The Rift Valley fever virus (RVFV) is a negative-sense, single-stranded RNA virus that belongs to the genus Phlebovirus. RVFV is predominantly transmitted by a range of mosquito species (see Table 1) but is transmitted by other vectors e.g. sandflies and ticks (Fontenille et al., 1998; Moutailler et al., 2008). The virus was first identified in 1931 during an investigation into an epidemic among sheep on a farm in the Rift Valley of Kenya (Daubney et al., 1931). Since then, several outbreaks were reported in sub-Saharan Africa (see Table 1). Recurrent epidemics have since killed hundreds of thousands of animals and more than a thousand humans with mortality rates up to 45% (LaBeaud et al., 2008; Centers for Disease Control, Prevention, 2007). The major means of transmission of RVFV to humans occurs during close contact with infected animals (Wilson et al., 1994) however to date, no human-to-human transmission has been documented. Rift Valley fever can manifest with symptoms ranging from uncomplicated acute febrile illness to its severe form which may present with meningoencephalitis, severe hemorrhagic disease, and death (Bird et al., 2009). Rift Valley fever is a viral zoonosis that primarily affects animals, nevertheless, the severity of RVFV zoonosis, and its capability to cause major epidemics among livestock and humans, coupled with the lack of cost–effective prophylactic and therapeutic measures prevalent in endemic and developing countries (as in Africa), makes it a serious emerging pathogen of public health concern and a potential biological weapon (Borio et al., 2002).

2.4. Filoviridae: Ebola virus and Marburg virus infections

Filoviruses Ebolavirus and Marburgvirus are among the deadliest pathogens known to man, with a mortality rate of 25–90% depending on the species (Lever and Whitty, 2016; Feldmann and Klenk, 1996; Lefebvre et al., 2014). Five distinct species of Ebolavirus genus named after the location of first-related outbreaks are known as the Zaire ebolavirus (EBOV) (Zaire is, currently known as the Democratic Republic of Congo, DRC), Sudan ebolavirus (SUDV) (Sudan), Taï Forest ebolavirus (TAFV) (Taï Forest, Ivory Coast), Reston ebolavirus (RESTV) (in Reston, Virginia, USA) and Bundibugyo ebolavirus (BDBV) (in Bundibugyo, Uganda).

Recently, scientists for the United States collaborating with teams from the government and universities of Sierra Leone have discovered a new addition to the Ebolavirus species called the 'Bombali virus' (Goldstein et al., 2018). The Bombali EBV was isolated from bats and has the potential to infect human cells. It remains to be discovered whether this virus has already caused human infections or is harmful to humans (Goldstein et al., 2018). Bats are suspected to play a role in sustaining filoviruses in nature, but the exact mechanisms of the virus spill over into human populations remain unknown (Leroy et al., 2005). Transmission of the viruses to man occurs through contacts with bodily fluids of an infected animal or infected individual whether alive or dead (Leroy et al., 2005; Muyembe-Tamfum et al., 2012) (see Table 1).

Marburg Marburgvirus, the single species in the Marburgvirus genus, contains two members, Marburg virus (MARV) and Ravn virus (RAVV) (Kuhn et al., 2010). In early August 1967, as a consequence of laboratory technicians handling the viscera, body fluids, and/or kidney tissue cultures from African green monkeys (*Cercopithecus aethiops*) imported from Uganda, concurrent outbreaks of acute haemorrhagic fever occurred in Marburg, Frankfurt (Germany), and Belgrade (former Yugoslavia, now Serbia) (Smith et al., 1967; Siegert et al., 1968). Since the initial occurrence of Marburg haemorrhagic fever in Europe, subsequent outbreaks have been primarily limited to countries in sub-Saharan Africa (see Table 1).

MARV, RAVV, BDBV, SUDV and EBOV triggered deadly outbreaks of hemorrhagic fever in human populations in Central and West Africa (recently in Guinea, Liberia, and Sierra Leone) with more than 28,000 cases and ˜ 11,000 deaths during the 2013-outbreak (Chippaux, 2014; Rougeron et al., 2015; Nyakarahuka et al., 2016). TAFV has been associated with only one non-lethal human case whereas RESTV is known to be non-pathogenic to humans (Burk et al., 2016).

In May 2018, the WHO declared an outbreak of EBV in the Equateur Province of DRC along the DRC's western border with Republic of the Congo. During this outbreak, the most deadly strain EBOV was identified, similar to the one that affected West Africa during the 2014–2016 outbreak (WHO, 2018b). Approximately one week after the end of this outbreak, on the 1st August 2018, a new outbreak of EBV was declared in North Kivu and Ituri provinces of the DRC which neighbour Rwanda and Uganda, making this the 10th EBV outbreak in DRC since the initial discovery in 1976. Although the EBV species associated with the most recent outbreak is similar to that caused in the earlier outbreak (May 2018), genetic differences between the viruses suggest the two outbreaks are not linked (WHO, 2018c).

2.5. Rhabdoviridae: Rabies virus

The rabies virus (RABV), is a bullet shaped enveloped infectious particle, having 12 Kb negative sense single-stranded RNA genome that belongs to the *Lyssavirus* genus of the *Rhabdoviridae* family (Leung et al., 2007).

Today, Africa is the second leading continent most affected by rabies, following Asia (Digafe et al., 2015), the estimates of burden however are unclear due to the absence of reliable data. There are tens of thousands of deaths reported annually due to this disease; Africa and Asia account for more than 95% of rabies deaths in the developing world (WHO, 2018d) with RABV constituting a big chapter of neuroscience (Fooks et al., 2017).The origins and evolution of the disease in Western and Central Africa, have been traced back to the advent and the spread of the rabies virus that coincided with the beginning of

European colonization and urbanization (Talbi et al., 2009). The first confirmed outbreak of rabies in Africa, occurred following the importation of an infected dog to the Eastern Cape Province of South Africa from England in 1892 (Swanepoel et al., 1993). Rabies control in Africa continues to be a problematic issue especially in countries such as South Africa, Zambia, Tanzania, and Angola among others (see Table 1).

Rabies is an infectious viral disease, almost invariably fatal following the onset of clinical symptoms due to the involvement of the CNS. In Africa, maximum mortality rates are documented in children and in the poor farming and vulnerable populations who live in remote rural locations. The most important reason for transmission of rabies in Africa is the rising dog population and urbanization (Chomel and Sun, 2011). Among the other risk factors for the epidemiology of rabies in Africa include trans-boundary spread of the RABV through trading and slaughtering of dogs (Nguyen et al., 2011; De Benedictis et al., 2010)and poor environmental hygiene in most neglected rural communities especially in densely populated areas, which heightens the risk of bidirectional transmission of rabies in dogs and humans (Atuman et al., 2014).

More than 99% of RABV infection in humans occurs in the developing world where the disease poses a great challenge, since rabies is endemic in domestic dog populations. The spread to humans is through bites or scratches, usually via saliva as well as other rarer methods (see Table 1). Whereas domestic dogs are the principal reservoir of rabies throughout most of Africa (WHO, 2018d), wild animal populations in Africa can support rabies cycles (Bingham et al., 1999), with most outbreaks in the domestic dog population activating the wild animal population (Rhodes et al., 1998).

Rabies in Africa is an important infection from a public health perspective first because the virus is unique in that it can affect a wide range of victims including all warm-blooded animals. Second a number of countries do not have the ability to perform confirmatory laboratory tests for rabies cases, and third, most suspected rabies victims do not die in hospital, implying the magnitude of rabies is underreported and finally, canine rabies can be effectively controlled and human deaths eliminated through mass vaccination of domestic dogs and the use of effective human vaccines and immunoglobulins (WHO, 2018d; Wilde and Lumlertdacha, 2011). Nevertheless even with the availability of safe, effective, and inexpensive tools for the control of rabies in domestic dog populations (Kayali et al., 2006) the disease has been neglected across much of Africa where the problem increases (Knobel et al., 2005). According to the WHO, children below the age of 15 are the frequent victims of rabies death and yet most of the affected families either have no access to the rabies post-exposure prophylaxis (PEP), or the cost of treatment is prohibitive. Advocacy for the mass vaccination of dogs in Africa is proposed as the most cost effective way to fight and eliminate this fatal CNS viral infection from the animal source, in order to disconnect the infectious cycle of the disease from other species to humans (WHO, 2018d).

2.6. Retroviridae: Human immunodeficiency virus infection

The human immunodeficiency virus (HIV), is a *lentivirus* (a subgroup of *retrovirus*-RNA viruses that replicate via a DNA intermediate) which damages and weakens the body's immune response to fight against disease and infection, resulting in the condition Acquired Immunodeficiency Syndrome (AIDS). Being a slow-acting virus, HIV may take several years to manifest as an illness in an affected person depending on their prevailing health and nutritional status during the time of the infection as well as the timely administration of anti-retroviral (ARVs) medications and their long term continuation.

There are nine open reading frames that the HIV-1 genome encodes: gag, pol, env, tat, rev, nef, vpr, vif, and vpu (Feinberg Mark and Greene Warner, 1992). The major differences in these genes enable HIV to be categorized at a number of levels, beginning with distinctions between the types of HIV-1 and HIV-2. HIV-1 and HIV-2 are all transmitted in the course of direct contact with HIV-infected body fluids, such as blood, semen, and genital secretions, or from an HIV-infected mother to her child during pregnancy, birth, or breastfeeding (through breast milk) (see Table 1).Earlier studies done in the west African countries of Senegal, Ivory Coast and the Gambia established that HIV-2 is less infectious, has a much lower mother-to-child transmission rate, and a much longer progression time to AIDS than HIV-1 (Kanki et al., 1994). Unfortunately, the clinical and neurological manifestations of HIV-2 are largely unstudied, therefore for the purposes of this review on HIV, we will focus on infections related to HIV-1.

HIV-1 comprises a number of major groups that include group M (Major), as well as groups O (Outlier) and N (non-M, non-O). HIV-1 group M is more prevalent worldwide (accounts for > 90% of reported HIV/AIDS cases), and is responsible for most of the global infections with those infected by it progressing faster and contracting AIDS. Due to the great diversity of the HIV envelope protein, the M group has been further sub-classified into nine major clades or subtypes denoted with numerals. HIV-1 subtypes/clades, include: A1, A2, A3, A4, B, C, D, F1, F2, G, H, J, and K (Taylor et al., 2008). There are also circulating recombinant forms (CRFs) A/E and A/G, many other circulating unique and non-unique recombinant forms (LANL, 2010). Within Africa, the recombinant form CRF02_AG is responsible for the bulk of infections in West Africa, subtype C in Southern Africa as well as Northeastern areas such as Ethiopia and subtypes A and D widespread in East Africa (Hemelaar et al., 2006). The HIV subtype has an impact on HIV disease progression in that those with subtype A have a longer AIDS-free survival than non-A (Kanki et al., 1999); subtype D have a shorter time to death and AIDS than subtype A, C, or the recombinant forms (Vasan et al., 2006). In addition, with respect to pathogenesis, subtype D has been linked to increased risk of dementia (Sacktor et al., 2009).

From the start of the epidemic, over 78 million persons have been infected with HIV/AIDS (UNAIDS Global AIDS update, 2016). By the end of 2016, worldwide, 36.7 million [30.8–42.9 million] people were living with HIV. Over half of all new HIV infections worldwide and nearly two-thirds of the total infections occur in sub-Saharan Africa, with adolescent girls and young women accounting for 25% of new HIV infections among adults (WHO, 2018e). Scientists postulate that the HIV epidemic arose in Africa at about the same time (1981) as in the Western world, however based on information from molecular phylogenetic studies, HIV was probably present in localized populations in central Africa from the early 1900s (Worobey et al., 2008). Rapid urbanization, enhanced transport networks as well as transformations within communities' most likely lead to the current pandemic (Faria et al., 2014). The commonest means of transmission in sub-Saharan Africa is almost exclusively heterosexual, with a parallel epidemic in children through vertical transmission. This implies that women are unduly affected accounting for 58% of the total number of people living with HIV as well as having the largest number of AIDS related deaths.

Over recent decades, great advances for developing HIV therapies permit viral suppression and reduce its effects on the body, hence shifting HIV from being an acute fatal illness to being considered chronic but manageable. Furthermore, major breakthroughs have been achieved in the prevention of HIV including: use of ARVs for the prevention of mother to child transmission (Guay et al., 1999), as pre-exposure prophylaxis (Hurt et al., 2011) and the effects of voluntary

Table 2
Clinical Manifestations of Selected Neurotrophic Viruses and their Management.

Virus	Systemic manifestations	Neurological manifestations	Treatment	References
Zika virus	Flulike febrile illness with rash, arthralgia, myalgia, headache and conjunctivitis	Meningoencephalitis, ADEM, GBS, IUGR, Spontaneous abortions, Microcephaly, Congenital brain anomalies e.g. brain atrophy, hydranencephaly Congenital Zika Syndrome	There are no specific treatment options for Zika virus infection. Neither is there prophylactic treatment or vaccine available for the prevention of Zika virus infection, although phase I human trials of the Zika Purified Inactivated Virus (ZPIV) vaccine have begun.	Dick et al. (1952), Duffy et al. (2009), Fernandez et al. (2017), Sarno et al. (2016), Li et al. (2016), Saad et al. (2018), National Institutes of Health (2016)
West Nile virus	Flu-like illness, backache and muscle aches; fever and phyarngitis, excessive sweating; diarrhoea, nausea, vomiting, drowsiness, headache, skin rash, lymphadenopathy	Meningitis, acute flaccid paralysis, encephalitis, Myelitis, Seizures, Microcephaly, Movement disorders e.g tremors, myoclonus, or parkinsonism. Neurocognitive impairment	Treatment is mainly supportive, there is no specific treatment. Majority of people recover without treatment. The severe cases require supportive therapy in a hospital with intravenous fluids and pain medication.	Solomon (2004), Hayes et al. (2005), Wang et al. (2013)
Chikungunya virus	Fever, rash, headache, arthralgias, myalgias, retinitis, myocarditis, hepatitis, nephritis, haemorrhage.	Rare encephalitis, ADEM, GBS, headache, cranial nerve palsies, vertigo, seizures, altered sensorium, stroke, myelitis,	Currently, there is no specific antiviral treatment nor prophylactic treatment or vaccine available for the prevention of chikungunya virus infection. There is however a phase 2 clinical trial of a chikungunya vaccine underway. Most commonly used analgesics are dipyrone and paracetamol. In cases of allergy to dipyrone, tramadol hydrochloride may be used. In severe neuropathic pain, antidepressants-amitriptyline, or anticonvulsants-gabapentin or pregabalin may be used. If pain complaints persist, corticosteroids should be prescribed at an anti-inflammatory dose.	Lemant et al. (2008), Gerardin et al. (2008), Lebrun et al. (2009), Gerardin et al. (2016), Schilte et al. (2013), Anand et al. (2017)
Rift Valley Fever virus	Flu-like fever, muscle pain, joint pain and headache, hepatitis, hemorrhagic fever syndrome- e.g.(epistaxis, haematemesis)	Meningoencephalitis, headache, hallucinations, seizures, residual neurological deficits, loss of memory, retinitis-blindness	Supportive therapy and treatment with ribavirin	Ikegami and Makino (2011), van Velden et al. (1977)
Ebola Viruses	Fever, headache, myalgia, diarrhoea, vomiting and abdominal pain. Unexplained haemorrhage seen as petechial rash, conjunctival bleeding, epistaxis, melena, and hematemesis.	Migranous headache, stroke, peripheral sensory neuropathy and focal peripheral nerve lesions. Psychiatric diagnoses-major depressive disorder and generalised anxiety disorder. Ophthalmological problems.	There is no cure or established drug treatment. Good supportive care essential. Most EBV infections can be prevented with proper use of PPE (personal protective equipment) when treating and caring for patients infected with EBV. Avoid handling animals suspected of being infected with EBV.	Ohuabunwo et al. (2019), van Paassen et al. (2012), Mehedi et al. (2011), de Greslan et al. (2016), Sagui et al. (2015), Billioux et al. (2016), Smith et al. (2017), Lotsch et al. (2017), Billioux (2017), Steptoe et al. (2016), Howlett et al. (2018)
Marburg virus Ravn virus	High fever, chills, asthenia, headache, muscle aches, anorexia, conjunctivitis, abdominal pain, nausea, vomiting and diarrhoea, pharyngitis, sore throat and chest pain and an Erythematous macular rash. Haemorrhage (petechia, ecchymoses, conjunctival haemorrhage, gingival bleeding, and frank bleeding from the gastrointestinal tract.	Restlessness, obtundation, confusion, dementia, coma and convulsions.	There is no cure or established drug treatment. Good supportive care essential. Suspected cases should be isolated, efforts to minimise possibility of human-to-human transmission through good nursing techniques and wearing personal protective equipment, such as gowns and gloves.	Rougeron et al. (2015), Ohuabunwo et al. (2019), van Paassen et al. (2012), Mehedi et al. (2011), de Greslan et al. (2016), Sagui et al. (2015), Billioux et al. (2016)

(*continued on next page*)

Table 2 (*continued*)

Virus	Systemic manifestations	Neurological manifestations	Treatment	References
Rabies virus	Nonspecific flu-like symptoms including low-grade fever, Malaise; Anorexia; Headaches; Chills; Pharyngitis, Nausea; Emesis; Diarrhoea. Focal symptoms at the portal of innoculation including pain, parasthesias, and pruritus	**Acute neurologic period** (a) *Encephalitic (Furious rabies)* (≈ 80% of cases) patient manifests with agitation, episodic delirium, hyperactivity, hypersalivation, restlessness, thrashing, biting, muscular fasciculation, seizures or aphasia, encephalitis manifesting as confusion, coma and hallucinations. Hydrophobia and aerophobia. This phase may end in cardio-respiratory arrest or may progress to paralysis. (b) *Paralytic rabies* (≈ 20% of cases) (dumb rabies) here paralysis (quadriparesis) occurs from the outset, and fever and headache are prominent. (c) *Coma stage* there is worsening of hydrophobia, prolonged apnea, and generalized flaccid paralysis which leads to respiratory and cardiovascular collapse.	Local treatment is important for all bites and scratches. Post-exposure prophylaxis (PEP) is recommended depending on the type of contact with the infected animal. Symptomatic rabies treatment is largely supportive, there is no known specific treatment.	WHO (2019d), Nigg and Walker (2009), Fishbein and Robinson (1993), WHO (2018a)
HIV-1 HIV-2	HIV-1 Fever, lymphadenopathy, pharyngitis, rash, myalgia, mouth and esophageal sores, headache, nausea and vomiting, oral/gential ulcers, weight loss, thrush, night sweats and diarrhoea. HIV-2 clinical manifestations are largely unstudied	**A: HIV-1** **(1) Primary disorders** (a) *Acute manifestations* Aseptic meningitis; meningo-encephalitis; & encephalitis. Rarely AIDP syndrome, (also known as GBS) (b) *Chronic manifestations* DSP; CIDP; HAND; HIVE; AR-PCNSL. **(2) Secondary disorders** (a) *CNS OIs* CNS TB; Toxoplasmosis encephalitis; CCM;PML; CMV encephalitis. (b) *Disorders related to HIV treatment* IRIS; Neurotoxicity from cART. **B:HIV-2** Neurological manifestations are largely unstudied	Generally symptomatic and specific treatment of the presenting opportunistic infections and suppressive cART. The appropriate selection of the ARV regimen is guided by the results of ARV drug resistance testing or the ARV resistance pattern of the source person's virus, if available. For some conditions: **AIDP**→ IVIg therapy; use of plasmapheresis ± corticosteroids **DSP**→ AEDs (e.g. lamotrigine & gabapentin) or Capsaicin 8% dermal patch treatments. **CIDP**→ IVIg therapy; corticosteroids; plasmapheresis; appropriate physiotherapy exercises. **HAND**→ cART **HIVE** → cART **AR-PCNSL**→ high-dose methotrexate-based chemotherapy regimens, whole-brain radiotherapy or immunotherapy treatments **CNS TB**→ standardized anti-TB treatment. **Toxoplasmosis**→ A combination of pyrimethamine with folinic acid plus sulfadiazine or clindamycin **CCM** → combination of amphotericin and flucytosine, with step-down therapy to fluconazole ± steroids for IRIS or cerebral edema. **PML**→ cART ± steroids. **CMV** → ganciclovir, valganciclovir, foscarnet and fomivirsen. **IRIS** → supportive care e.g. intravenous fluids, CSF drainage (in CCM) and oxygen, plus definitive treatment of the underlying O.I. Steroids used only for more severe cases, in the absence of contraindications	Howlett et al. (2016), Lotsch et al. (2017), Billioux (2017), Steptoe et al. (2016)
HSV-1 HSV-2	**HSV-1**- painful blisters or open sores called ulcers in or around the mouth and may also cause genital herpes manifesting with genital or anal blisters or ulcers. **HSV-2** genital herpes characterised by one or more genital or anal blisters or open sores called ulcers. In cases of symptoms of new genital herpes infections patient may have fever, body aches, and swollen lymph nodes	In the immunocompromised host, HSV-2 has the ability to cause encephalitis, nevertheless it is HSV-1 that is responsible for ˜90 % of HSV encephalitis found in adults and children and is the focus of this review. HSVE manifests as new onset seizures, alteration of consciousness and/or behavioural/speech disturbances.	In general antiviral medications, such as acyclovir, famciclovir, and valacyclovir, are the most effective and help to reduce the severity and frequency of symptoms, but cannot cure the infection. **HSVE**→ Initiate treatment with Intravenous acyclovir with the addition of broad-spectrum antibiotics until bacterial infection can be excluded. In cases of acyclovir resistance foscarnet or ganciclovir are useful alternatives.	Riancho et al. (2013), Schiff and Rosenblum (1998), Sili et al. (2014)

Abbreviation List: **ADEM** = acute demyelinating encephalomyelitis; **AEDs** = Antiepileptic drugs; **ARV** = antiretroviral; **AIDP** =Acute inflammatory demyelinating polyneuropathy; **AR-PCNSL** = AIDS-related primary central nervous system lymphoma; **cART** = combination antiretroviral therapy; **CCM** = Cryptoccocal meningitis; **CIDP** = Chronic inflammatory demyelinating neuropathy; **CMV** = Cytomegalovirus; **CNS** = Central nervous system; **DSP** = Distal Symmetric Polyneuropathy; **EBV** = Ebola virus; **GBS** = Guillain-Barré syndrome; **HAND** = HIV-associated neurocognitive disorders. **HIVE** = HIV Encephalopathy; **HSV** = Herpes simplex virus; **HSVE** = Herpes simplex viral encephalitis; **IUGR** = intrauterine growth retardation; **IVIg** = Intravenous immunoglobulin; **OIs** = Opportunistic infections; **PML** = Progressive multifocal leukoencephalopathy; **TB** = Tuberculosis.

male medical circumcision (Auvert et al., 2005; Gray et al., 2007).

With the recent extraordinary scaling up of HIV treatment in several settings, an increasing number of persons living with HIV are accessing ARV medications, estimated at 17 million people, as of December 2015 with the greatest gains made in the world's most affected region, eastern and southern Africa (UNAIDS Global AIDS update, 2016). Nevertheless, in spite of this campaign, the HIV epidemic continues to spread obstinately into new areas and to establish itself further in many other locations worldwide. The increased access to ARVs, coupled with early linkage to specialist care and appropriate prophylaxis for opportunistic infections, has led to persons with HIV living longer on effective treatment (UNAIDS Global AIDS update, 2016). Consequently, this situation directed the rising challenge of managing the increased incidence of non-communicable diseases in HIV patients, which include persistent neurological disorders further complicated by issues of ARV resistance, attendant neuronal toxicities and chronic immune activation (Nath and Sacktor, 2006; McArthur et al., 2010).

2.7. Herpesviridae: Herpes simplex viruses 1 and 2

Herpes simplex viruses (HSV) belong to the large family of double-stranded DNA viruses and comprise one of the most common pathogens affecting humans; they can remain dormant for prolonged periods of time in sensory and cranial nerve ganglia and reactivated episodically (Grinde, 2013). There are two types, HSV-1 and HSV-2, whose differences are noted not only genetically but also in the principal route of transmission, body site affected, rate of reactivation, pathogenicity, and seroprevalence (Chayavichitsilp et al., 2009) (see Table 1).

With respect to HSV-1, primary infections typically occur during infancy and childhood, following the waning of maternal antibodies in the first year of life, while HSV-2 in contrast, mainly affects adolescents and adults. The shedding of the virus from herpetic lesions (mainly lips-HSV-1 and genitals HSV-2) in symptomatic people with recurrent infections and excretion of the virus in the saliva and genitals of asymptomatic people are regarded as the most important source of the viral infection (Koelle and Wald, 2000).

HSV-2, unlike HSV-1, is primarily acquired through sexual activity (Smith and Robinson, 2002) and causes the great majority of genital herpes (Pena et al., 2010). Recurrent genital herpes serves as a risk factor for neonatal infections (Sauerbrei and Wutzler, 2007) which have high morbidity and mortality.

A systematic review of HSV-2 incidence within sub-Saharan Africa spanning the six countries of Uganda, Zimbabwe, South Africa, Kenya, Tanzania, and Ethiopia from 1990 to 2012 noted that HSV-2 incidence is overall high but variable across countries and populations. A higher incidence occurred especially among those with risky sexual behaviour. Other risk factors identified among women included prevalent HIV infection, younger ages at sexual initiation, and sexual activity. For the men however, condom use and circumcision had a protective effect, while prevalent HIV increased the risk of HSV-2 acquisition (Rajagopal et al., 2014). In the immunocompromised host, HSV-2 has the ability to cause encephalitis, nevertheless HSV-1 causes ˜90% of HSV encephalitis found in adults and children (Steiner and Benninger, 2013).

Herpes simplex encephalitis is the most important and common cause of fatal sporadic viral encephalitis in the industrialized world. The worldwide estimate of Herpes Simplex encephalitis (HSVE) is 2–4 cases/1,000,000 (Hjalmarsson et al., 2007). Cases have a bimodal distribution with peak incidence in the very young (up to 3 years of age), and another peak in adults aged > 50 years. There are no gender differences and the majority of cases occur above the age of 50 years (Hjalmarsson et al., 2007; Abel et al., 2010).

3. Clinical features and diagnosis

In general, the infections with the arboviruses (*Flaviviridae, Togaviridae, and Bunyaviridae*) differ in clinical presentation with some patients being completely asymptomatic, while others may have florid encephalitis with seizures, coma, and death (See Table 2).

3.1. Zika virus infection

Before the WHO's declaration of ZIKV infection as a public health emergency (Anon., 2016), human infections were reportedly mild, with 70% to 80% of infections being asymptomatic (Dick et al., 1952). If clinical symptoms manifested, they included 2–7 days of a flu-like illness with fever, maculopapular rash, nonpurulent conjunctivitis, fatigue, and arthralgia (Duffy et al., 2009) (see Table 2). Over the last several years, however, reports of neurotropism increased, reporting cases of microcephaly, retinal lesions, and GBS associated with ZIKV infection (Fernandez et al., 2017; Sarno et al., 2016).

The finding that infection with ZIKV can cause neurological disease and also affect the fetus of pregnant women has developed into a topic of great concern and concerted research efforts. There are also reports that other systemic effects independent of microcephaly occur after infection during pregnancy (Li et al., 2016). The knowledge that ZIKV causes Guillain-Barré syndrome strongly suggests that the peripheral nervous system can be affected, although the mechanism and direction of infection is not clear (Li et al., 2016). Ocular infections as well as auditory involvement may also occur with ZIKV infection (Fernandez et al., 2017). More recently a syndrome called the Congenital Zika Syndrome that presents with ocular changes along with microcephaly, athrogyposis, and auditory deficits (Saad et al., 2018) has been identified. Other systemic and neurological manifestations are shown in Table 2.

3.2. West Nile virus infection

Whereas most individuals infected with flaviviruses are asymptomatic, approximately one quarter of infected persons may present with symptomatic disease that is mild or neuroinvasive (Solomon, 2004). About 50% of symptomatic WNV infection manifest with a febrile illness with pharyngitis, myalgia or arthralgia, and rash (see Table 2) (Hayes et al., 2005). Neurological diseases constitute the other half with manifestation governed by the site of infection within the CNS as is shown in Table 2. Patients may develop diaphragmatic paralysis, which may require them to be on permanent mechanical ventilation (Wang et al., 2013).

3.3. Chikungunya virus infection

Patients with CHIKV infection may initially develop a flu-like illness with headache, fever, pharyngitis, and myalgia. In most instances this will be an acute illness with high fever and severe arthralgia lasting weeks to months, occasionally for years (Schilte et al., 2013). However, severe and fatal CHIKV disease with CNS involvement may manifest with encephalitis and other post-infectious syndromes as shown in Table 2 (Lemant et al., 2008; Gerardin et al., 2008; Lebrun et al., 2009; Gerardin et al., 2016).

3.4. Rift Valley virus infection

Most infections that arise from RVFV are often asymptomatic or cause a mild febrile illness with headache, myalgias, and mild hepatitis (see Table 2). However in a small percentage of symptomatic cases (< 2%), CNS involvement may manifest with meningoencephalitis and/or necrotizing retinitis leading to blindness (Ikegami and Makino, 2011). In some instances, patients may develop a hemorrhagic fever with the features shown in Table 2. The initial fatal case of RVF associated with hemorrhagic fever and encephalitis, occurred in South Africa in 1975 (van Velden et al., 1977).

3.5. Ebola and Marburg virus infections

Symptoms of Ebolavirus disease (EVD) or MARV disease occur after a short incubation period (˜4–10 days), which can sometimes last for 2–3 weeks depending on the virus species and subject vulnerability. Abrupt onset is characterized by 'flu-like' symptoms (low-grade fever, myalgia, chills) followed by gastrointestinal symptoms including nausea, stomach ache, vomiting and diarrhea. The acute phase is characterized by potential haemorrhagic complications, hypovolaemic shock, and multiple organ failure. A diffuse erythematous, non-pruritic maculopapular rash may develop 5–7 days post-infection. Subjects may also present with respiratory symptoms such as coughing, dyspnea and rhinorrhea, neurological symptoms (*vide infra*), and failure of the cardiovascular system resulting in shock and oedema (see Table 2). As the disease progresses, patients present with signs suggestive of a consumptive coagulopathy due to disseminated intravascular coagulation and they generally succumb within the two weeks following the onset of the disease (Rougeron et al., 2015; Ohuabunwo et al., 2019; van Paassen et al., 2012; Mehedi et al., 2011).

Neurological signs in the acute phase may include headache, seizures, meningo-encephalitis, encephalopathy and coma (van Paassen et al., 2012; de Greslan et al., 2016; Sagui et al., 2015; Billioux et al., 2016). Diagnosis is done on clinical and epidemiological grounds as well as laboratory testing for the detection of viral antigens and/or RNA or immunoglobulin specific antibodies, possibly in the cerebrospinal fluid (de Greslan et al., 2016; Saijo et al., 2006; Vernet et al., 2017; Billioux et al., 2017).

A large number of survivors of EVD may present with a "post-Ebola syndrome" which may include ophthalmologic, auditory, and neurological complications (Smith et al., 2017). Late onset neurological disease, notably encephalitis has been reported (Howlett et al., 2016). Other long-term sequelae include anxiety, headache, extreme fatigue, memory loss, post-traumatic reactions, and depression, reportedly prevalent in up to 50% of a select series (Lotsch et al., 2017; Billioux, 2017).

Steptoe et al. (2016) reported unique lesions of the retina specific to those infected with EVD; the lesions appear near to the optic disc or in the fundus of the retina. Those near the optic disc follow the distribution of ganglion cell axons, suggesting that the optic nerve may be the entry site into the retina. Although these lesions did not affect visual acuity, the EVD survivors were subject to white cataracts, which resulted in visual impairment. This work by Steptoe et al. also showed that the aqueous humor of individuals previously infected with EBV did not contain active virus, allowing safe surgery to remove the cataracts.

3.6. Rabies virus infection

The first signs of illness are nonspecific, fever, anxiety, and malaise following an incubation period, which varies from 2 weeks to 6 years (averaging 2–3 months) depending on the concentration of the virus, inoculation site and density of innervation (Singh et al., 2017). There may be tingling and severe pruritus at the site of the animal bite. There are two classic forms of rabies: encephalitic and paralytic with a third, much less common form leading to coma (see Table 2) (WHO, 2018d; Nigg and Walker, 2009; Fishbein and Robinson, 1993). In the encephalitic form, a patient manifests with episodic signs of CNS irritation including agitation, confusion, hydrophobia, aerophobia, hyperventilation, hypersalivation, and convulsions. Regarding the paralytic form, the patient develops flaccid paralysis in the bitten limb, which ascends symmetrically or asymmetrically with some developing choreiform movements of the bitten limb. During the coma stage the patient may become nonresponsive, and additionally experience worsening hydrophobia, prolonged apnea, and generalized flaccid paralysis with subsequent respiratory and cardiovascular collapse. The ultimate end point in the natural history of an untreated rabies infection is death.

The diagnosis of a case of rabies while the patient is alive is challenging because it depends on the widespread distribution of the virus through the nervous system thus requiring several tests to be performed before confirmation. Several techniques can be used to test for the presence of the RABV in saliva such as reverse transcription followed by polymerase chain reaction (RT-PCR); in the blood and CSF, antibody test using enzyme-linked immunosorbent assay (ELISA); and a skin biopsy to examine for rabies antigen in the cutaneous nerves at the base of the hair follicles. In the post mortem specimens, the detection of RABV antigen in infected tissues, such as by the direct fluorescent antibody test (dFAT) is the gold-standard diagnostic technique (WHO, 2018a).

3.7. HIV infection

Primary HIV infection is nonspecific as is shown in the systemic manifestations in Table 2. In spite of the increasing availability of potent antiretroviral therapy, neurological complications in persons with HIV remain highly prevalent. In the earlier years with the limited use of antiretroviral therapy, severe complications of opportunistic infections in the CNS such as toxoplasmosis, cryptococcus, cytomegalovirus, progressive multifocal leukoencephalopathy (PML) and CNS malignancy dominated the clinical presentation (Gonzales-Duarte and Simpson, 2006). In the current era of widespread use of suppressive combination antiretroviral therapy (cART), presentation with these opportunistic infections especially in industrialized countries, has somewhat reduced. In the low resource settings such as Africa, however, the panorama of neurological complications of HIV infection in the wake of the rapidly growing use of cART has generally not been the same as is illustrated in Table 2. Furthermore, the high prevalence of primary manifestations in the CNS such as persistent HIV-associated neurocognitive disorder (HAND), peripheral neuropathy and the disabling mild neurocognitive disorder (MND) remains (Gelman, 2015; Saylor et al., 2016).

The neurological manifestations of HIV may either be primary or secondary. The primary neurological disorders result from the direct effect of the HIV virus with indicators varying in adults and children, while the secondary disorders are as a result of complications of opportunistic infections resulting from HIV immunosuppression as well as other difficulties related to the HIV infection treatment (see Table 2). The diagnosis of HIV is made by the detection of HIV-specific antibodies in serum, plasma, urine or saliva by demonstrating the presence of the virus by nucleic acid detection using PCR, p24 antigen ELISA testing or by growing the virus in cell culture (Fearon, 2005).

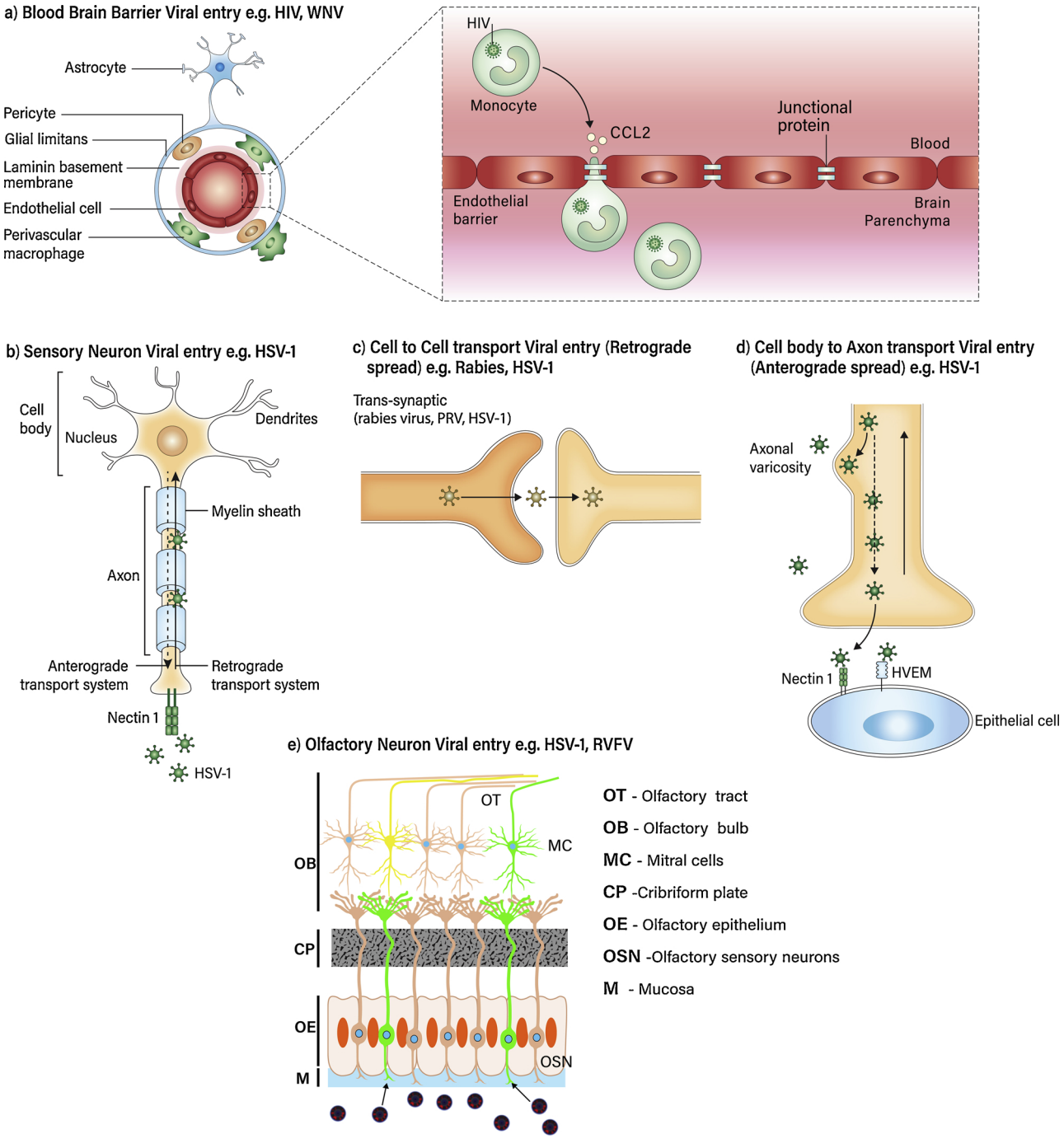

Fig. 1. Routes of Virus Spread into the Central Nervous System.
(a) The Blood–brain barrier (BBB) is a firmly controlled border comprising of a specialized system of a basal membrane, brain microvascular endothelial cells (BMECs) with extensive tight junctions (TJs), which are enclosed by pericytes and astrocytes. The BBB protects the brain from pathogens in the blood, supplies brain tissues with nutrients, and sieves toxic compounds from the brain back to the bloodstream. Viruses may enter via either direct infection of BMECs, passive diffusion through the BBB, transcellular transport through BMECs e.g. WNV, or by infected leukocytes facilitating CNS entry via paracellular or transcellular extravasation using a 'Trojan horse' mechanism e.g. HIV.
(b) Viral CNS entry also occurs through the peripheral neurons as exemplified by Herpes simplex virus 1 (HSV-1) entry into sensory neurons assisted by nectin 1 that is expressed on axons. The virus then rapidly spreads to the neuronal cell body via the fast axonal retrograde transport system (solid black arrow).
(c) Cell-to-cell viral entry is utilised by Rabies virus, pseudorabies virus (PRV) and HSV-1 which are released at a synapse and use a retrograde trans-synaptic pathway to infect neighbouring neurons.
(d) Cell body to axon viral entry can occur when the virus exits via axonal varicosities before reaching the axon termini resulting in infection of neighbouring cells. The HSV-1 virus uses this system in the course of reactivation via the anterograde system (dashed black arrow), as such it is able to reach axon termini and reinfect epithelial cells by binding to nectin 1 or herpesvirus entry mediator (HVEM) receptors.
(e) In the olfactory neuron viral entry, infection of olfactory sensory neurons (OSN) in the olfactory epithelium (OE) follows intranasal inoculation or OE infection from fenestrated vessels. CNS viral entry occurs after viral migration through the cribriform plate (CP), subsequent infection of mitral cells (MC) at the glomeruli of the olfactory bulb (OB), and dissemination along the neuronal tracts. e.g. HSV-1, RVFV.

3.8. Herpes virus infection

The clinical manifestations in HSVE lack specificity and most cases of HSVE may present with prodromal symptoms, suggestive of an upper respiratory tract or other systemic infection. The signs and symptoms of encephalitis may then evolve over the course of several days (Riancho et al., 2013). These include an acute onset of a febrile illness coupled with signs and symptoms of meningeal irritation, focal neurological dysfunction, new onset seizures, alteration of consciousness and/or behavioural/speech disturbances (see Table 2). Remarkably, immunocompromised patients are less likely to present with prodromal symptoms or with focal neurological deficits. In addition, there is a lack of pleocytosis in the CSF, they have more extensive brain involvement mainly distributed outside the temporal lobes and significant morbidity and mortality when compared to the non-immunocompromised (Schiff and Rosenblum, 1998).

The CSF profile of HSVE reveals extensive variation, which includes a moderate lymphocytic pleocytosis (10–200/mm (Buchanan and Bonthius, 2012)), raised erythrocyte levels (normal–minimally elevated counts are common), moderately elevated protein (50–100 mg/dl), and normal glucose (although hypoglycorrhachia may be present in a minority of patients) (Sili et al., 2014). The use of PCR on the CSF sample is the diagnostic tool of choice for HSV-1 since it has both a high sensitivity and specificity with the ability to discriminate between HSV-1 and HSV-2 (Sili et al., 2014).

4. Mechanisms of pathogenesis

The CNS is protected from most pathogens by the activation of effective immune responses and the presence of multi-layer barriers to its invasion. Despite this setting, viruses can replicate with unique strategies to relocate into the CNS, where they induce acute to subacute and/or persistent, potentially life-threatening infections. Mechanisms leading to CNS damage may be related to virus-activated mechanisms or any other type of indirect mechanism including systemic organ failure, whether immune-mediated or not. Despite similarities in mechanisms of viral infections, dissimilarities and specific host responses can shape the CNS response, therefore the timing and the extent of damage are summarized below in the specific sections.

4.1. Arbovirus infections

Scientists have used animal models to try to clarify the possible mechanisms involved in the pathogenesis of arbovirus (*Flaviviridae*, *Togaviridae, and Bunyaviridae*) infection in humans. In general, during the blood sucking meal of a specific vector (e.g. mosquito), approximately 10 (Dick et al., 1952) virus particles transmit to the host (Styer et al., 2007). This results in an initial period of replication in the skin keratinocytes and skin dendritic cells, including Langerhans cells (Lim et al., 2011). Replication in the skin is followed by trafficking of the infected skin dendritic cells to the draining lymph nodes which serve as a channel for the consequent entry into the host's circulation via the efferent lymphatic system and the thoracic duct. In addition, they create an avenue of causing another bout of infection. Once in the blood, the infection spreads to specific cellular targets of the visceral organs creating a level of viremia that correlates with the viral dissemination to the CNS (Goto et al., 2003).Whereas the exact mechanisms by which arboviruses enter the CNS after viremia remain unclear, several mechanisms dependent on the prevailing host and viral factors have been postulated. One possibility is CNS invasion via the olfactory neuron system (Monath et al., 1983) (see Fig. 1(e)). In this type of infection the virus presents in the mucosa of the upper respiratory tract directly involving the olfactory sensory neurons found in the olfactory epithelium. Anterograde axonal transport occurs within the axonal bundles that pass through the cribriform plate into the olfactory bulb. Once inside the olfactory bulb, the virus disseminates rapidly to brain tissues. This may be the pathway used by viruses that spread via the aerosol pathway to spread and do not require development of viremia for neuroinvasion (Reed et al., 2007) (e.g. RVFV, see Fig. 1(e)). Other avenues include infection of peripheral nerves resulting in retrograde axonal transport of the virus to the spinal cord and brain (see Fig. 1(c)); and subsequent entry across the blood–brain barrier (BBB) (see Fig. 1(a)) - which may occur via direct infection of the brain microvascular endothelial cells e.g WNV (Wang et al., 2009). Alternatively infection may diffuse passively through the disrupted BBB (Solomon and Vaughn, 2002).

4.2. Zika virus infection

The exact mechanism that results in disrupted neural development leading to microcephaly (or other neurological involvement) is not known. It is also not clear exactly when during gestation the infection occurs to cause reduced brain volume or the proportion of infected mothers that result in babies with abnormal brain size. ZIKV likely gains entry into host cells through endocytosis via receptor tyrosine kinases, which can facilitate virus replication. One of these receptors, AXL, is strongly represented in several cell types that implicate both preferential access to the placenta and that also populate the cerebral cortex. Richard et al (Richard et al., 2017) report that ZIKV has privileged entry to the placenta because it infects endothelial cells of the umbilical vein through the AXL entry site with high efficiency compared to other flaviviruses. Additional evidence suggests that the ZIKV replicates in other tissues of the placenta (Quicke et al., 2016). Infection of the placenta can lead to impairment of the developing fetus and disrupted development of the brain and skull. Furthermore, neural progenitor cells appear to be direct targets of the ZIKV. For example, radial glial cells, neural stem cells that generate neurons populating the neocortex, show genetic and immunohistochemical evidence of the AXL entry site (Nowakowski et al., 2016). Other cells in the ventricular zone and subventricular zone of the developing cerebral cortex show specificity of Zika attack. The ZIKV thus appears to have preferential access to neural progenitor cells, which may explain its privileged effect on the fetus and potential microcephaly (Wen et al., 2017).

4.3. Ebola and Marburg virus infections

The pathogenesis of EVD or MARV-related neurological complications have yet to be elucidated. EVD results from a robust pro- and anti-inflammatory response often referred to as a "cytokine storm" (Younan et al., 2017). If the acute neurological symptoms are caused by a surge in cytokines production is not known. Several reports have suggested that both cytokines and chemokines, and auto-immune responses may play a role in the pathogenesis of filovirus complication (Bixler and Goff, 2015; Wong et al., 2014). Evidence from the West Africa outbreak including findings from experimental studies also indicate that both EBOV and MARV may enter the nervous system. The impact of such virus entry on the specific brain immune responses has not been elucidated (Mehedi et al., 2011; de Greslan et al., 2016). Challenges to the identification of exact pathogenetic mechanisms are compounded by the existence of profound systemic changes including dehydration, imbalance in electrolytes, and propensity to hemorrhage.

4.4. Rabies virus infection

After the entry of virus into the skin or mucous membranes of the host, an incubation period occurs dependent on the concentration of the virus inoculated, the site of infection and density of innervation (Greene and Rupprecht, 2006). Shorter incubation periods occur for bites on the hands, neck, face and head associated with bleeding due to the decreased length of travel to the CNS and involvement of a greater number of neurons. At the inoculation site the RABV attaches through G-protein receptors to the target cells (myocytes, local sensory and motor neurons) and amplifies in muscle cells and in macrophages (Tsiang et al., 1986). The duration spent at the site of the bite may persist for more than 18 days giving the immune system of the host an opportunity to clear the RABV as well as the chance for post-exposure treatment (Hemachudha et al., 2002). Through the muscle spindles of the sensory nerves or neuromuscular junction of motor nerves the virus migrates towards the CNS through sensory and motor axons via an axonal retrograde transport system to infect nerves cells (Mazarakis et al., 2001) (see Fig. 1(b), (c)). The use of the retrograde transport pathway allows for viral translocation to neuronal cell bodies and thus rapid CNS entry. There is also a possibility of the RABV having haematogenous spread due to the presence of large inoculums at the site of bite. Mouse models of rabies show that the RABV alters a variety of mitochondrial parameters and increases mitochondrial Complex I activity and reactive oxygen species production (Kammouni et al., 2015), as such, it may be considered a mitochondrial disease.

4.5. HIV infection

Within the CNS the virus infects the microglia and perivascular macrophages, while the role of astrocytes is less established. The immune pathogenic mechanisms of HIV infection are complex, not fully understood and characterized by the interaction of both viral and host factors (Agosto et al., 2014). In normal instances, the CD4 lymphocytes are not present in the brain, however the HIV virus binds to them as primary receptors of entry, together with CCR5 and CXCR4 as co-receptors, to facilitate cell attachment and entry into the brain. The infection causes progressive destruction of the cell-mediated immune system, primarily by eliminating activated CD4+ T-helper lymphocytes which are its principal target (Maartens et al., 2014). Through multifaceted interactions with the CD4+ lymphocytes and the chemokine co-receptors, CCR5 or CXCR4, expressed by the perivascular and parenchymal macrophages/microglia, the host cell CD4+ T-cell pool is depleted resulting in host immunodeficiency (Lane, 2010).

Approximately 1–2 weeks following systemic infection, the HIV virus traverses the BBB while enclosed within blood-borne monocytes that are non-susceptible to HIV infection,] through a 'Trojan horse' mechanism (Meltzer et al., 1990) (see Fig. 1(a)). Later these monocytes differentiate into macrophages, and become highly susceptible to HIV infection (Williams et al., 2012).The HIV infected macrophages in the brain cause an alteration in the chemotaxis gradient across the BBB through the secretion of proteins, pro-inflammatory cytokines and chemokines. These attract additional monocytes from the periphery into the CNS, resulting in a cascade of neuroinflammation and further neuronal injury consequential to the secondary effects of glial reaction and the release of neurotoxic viral proteins and cytokines (Kaul et al., 2005; Hesselgesser et al., 1998). This turn of events leads to further spread of the virus to macrophages, microglia and possibly astrocytes, with the development of neuronal compromise and establishment of viral reservoirs (Clay et al., 2007).

Whereas neurons are not directly infected by HIV (Gonzalez-Scarano and Martin-Garcia, 2005), in some brains of HIV infected individuals neuronal loss has been noted in the telencephalic structures such as the basal ganglia and in the hippocampus. The pathways to these neurodegenerative effects of HIV neuropathogenesis are postulated to be either the direct effects of the virus and secreted viral proteins (e.g HIV-Tat, gp120) on neurons or an indirect effect produced from inflammatory mediators released from infected and uninfected brain cells resulting in neuronal death (Kaul et al., 2005; Gonzalez-Scarano and Martin-Garcia, 2005; Eugenin and Berman, 2013; Avdoshina et al., 2016; King et al., 2010). A vacuolar myelopathy may also result from HIV proteins causing neuronal and glial injury in the spinal cord (Minami et al., 1997).

Whereas ARVs curb HIV replication in several organs of the body, their penetration in the brain is not ideal, causing persistent CNS infection and identifying it as a latent viral reservoir (Churchill and Nath, 2013). This situation is compounded by the high selectivity of the BBB to a number of ARVs, reducing their concentration in the brain and limiting their efficacy (Eisfeld et al., 2013). Other studies show that HIV infected astrocytes and macrophages are protected from cell death (Eugenin and Berman, 2013; Swingler et al., 2019) through virus dependent mechanisms thus further participating in the creation of viral reservoirs in the CNS.

4.6. Herpes virus infections

The initial port of entry of HSV into host tissues is via the mucous membranes or damaged skin. Following primary infection, HSV undergoes various interactions with cell-surface glycosaminoglycans such as heparan sulfate (Shieh and Spear, 1994), and cell adhesion molecules such as nectin-1 (Shukla et al., 2012) that aid infection of sensory neurons via fast retrograde axonal transport (Smith, 2012) towards the dorsal root ganglion (see Fig. 1(b) and (c)).

The mechanisms by which HSV obtains entry to the CNS in humans are not quite clear, it is postulated that it could be via retrograde transport through the olfactory or trigeminal nerves where the latter innervates the meninges (Shukla et al., 2012; Jennische et al., 2015) or via hematogenous dissemination (see Fig. 1(e)).

It is also not clear whether HSVE is a reactivation of latent virus or caused by primary infection, however, both may occur. The suggested pathogenic mechanisms include reactivation of dormant HSV in the trigeminal ganglia with ensuing proliferation of infection to the temporal and frontal lobes, primary CNS infection, or reactivation of dormant virus within the brain parenchyma itself (Steiner, 2011; Fraser and Clemmons, 1989) (see Fig. 1(d))

The body responds with a strong reaction from the innate immune system following infection with HSV which contributes to clearing active infection. An inflammatory cascade ensues recruiting innate immune cells and priming adaptive immunity, leading to necrosis and apoptosis of infected cells. While this host immune response is very important in the ultimate clearance of the virus, occasionally the inflammatory response, particularly recruitment of activated leukocytes, may contribute to tissue destruction and consequent neurological sequelae (Lundberg et al., 2008).

If the immune response to HSV is deficient, however, the host is made susceptible to HSVE (Zhang and Casanova, 2015). After primary infection, the virus establishes a dormant state within the host and remains inactive unless reactivated (Rock and Fraser, 1983). In order to establish and maintain latency, a number of complex processes must be balanced and include: silencing of viral lytic-phase genes; cancellation of host cellular defence mechanisms (e.g., apoptosis); evasion of host immunity, both innate and acquired immune responses (Knipe and

Cliffe, 2008); and residence of HSV-specific CD8 + T cells in the trigeminal ganglia (Egan et al., 2013).

5. Future perspectives

Further insights into the epidemiological, biological and molecular fingerprints of CNS viral infections are required in order to provide a clear understanding of mechanisms, prevention tools, and therapies for infection-related CNS damage. Epidemiological studies should focus on the ecology of pathogens, changes in ecosystems that may coincide with virus translocation into human populations, human behaviour and individual risk factors. Basic science research should be focusing on understanding virus-host interactions at molecular and cellular levels to identify molecular targets of interventions. Special attention should be placed on the distinction between naïve infection, subclinical infection, reactivation and overt disease whether active or of late onset. Supportive care, immunotherapies, gene therapies and vaccines hold promises. In some instances, however, priority may be given to the development of antiviral drugs. Research lines should be developed to further understand the differences between various strains of these neurotropic viruses, identify the exact pathogenetic mechanisms, disentangle drug-induced effects from those naturally inherent to the disease process and also test the capacity of new viruses to infect humans such as Bombali EBV, which can enrich our understanding of emerging viral diversity circulating in wildlife.

Conflict of interest

None.

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