Neurological disorders in HIV in Africa: a review

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Abstract

Background: Neurological disorders in HIV infection are a common cause of morbidity and mortality. The aim of this paper is to provide a narrative overview of up to date information concerning neurological disorders affecting HIV infected persons in Africa.

Methods: Seminal research concerning neurological disorders among HIV-infected adults in sub-Saharan Africa from prior to 2000 was combined with an in-depth search of PubMed to identify literature published from 2000 to 2017. The following Mesh terms were used. "Nervous System Diseases" "HIV Infections" and "Africa South of the Sahara" and "Seizures" or "Spinal Cord Diseases" or "Peripheral Nervous System Diseases" or "AIDS Dementia Complex" or "Opportunistic Infections" or "Immune Reconstitution Inflammatory Syndrome" or "Stroke". Only those articles written in English were used. A total of 352 articles were identified, selected and reviewed and 180 were included in the study. These included case series, observational studies, interventional studies, guidelines and reviews with metanalyses. The author also included 15 publications on the subject covering the earlier phase of the HIV epidemic in Africa from 1987 to 1999 making a total of 195 references in the study. This was combined with extensive personal experience diagnosing and treating these neurological disorders.

Results: Neurological disorders were common, typically occurring in WHO stages III/IV. These were in three main categories: those arising from opportunistic processes mostly infections, direct HIV infection and autoimmunity. The most common were those arising from direct HIV infection occurring in >50%. These included HIV-associated neurocognitive dysfunction (HAND), neuropathy and myelopathy. Opportunistic infections occurred in >20% and frequently had a 6-9-month mortality rate of 60-70%. The main causes were cryptococcus, tuberculosis, toxoplasmosis and acute bacterial meningitis. Concurrent systemic tuberculosis occurred in almost 50%.

Conclusion: Neurological disorders are common in HIV in Africa and the main CNS opportunistic infections result in high mortality rates. Strategies aimed at reducing their high burden, morbidity and mortality include early HIV diagnosis and anti-retroviral therapy (ART), screening and chemoprophylaxis of main opportunistic infections, improved clinical diagnosis and management and programme strengthening.

Keywords: Neurological disorders, HIV, Africa, opportunistic infections, direct HIV infection and inflammatory disorders.

DOI: https://dx.doi.org/10.4314/ahs.v19i2.19

Cite as: *Howlett WP. Neurological disorders in HIV in Africa: a review. Afri Health Sci.2019;19(2): 1953-1977. https://dx.doi.org/10.4314/ahs.v19i2.19*

Introduction

Neurological disorders (NDs) in persons infected with HIV are caused by three main mechanisms, direct HIV infection, opportunistic processes as a result of loss of cell mediated immunity, and inflammation or autoimmunity[1].

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While they occur during all stages of HIV infection, they occur most frequently in advanced HIV disease where their overall pattern and frequency at clinical presentation is mostly a reflection of the person's level of immunity and previous environmental exposure1. NDs in persons with HIV in Africa are common, with opportunistic processes, mostly infections occurring in over one fifth of infected persons[1-8] and neurological disorders/abnormal findings present in over two thirds in those with advanced disease[24,28]. Mortality caused by central nervous system (CNS) opportunistic infections (OIs) is particularly high in Africa with their reported 6-9-month case fatality rates

(CFR) of over sixty percent. This is in stark contrast to the much lower CFRs of around twenty percent for similar infections reported in high income countries (HICs). Among the main reasons for this threefold increase in mortality in Africa are late clinical presentation, advanced levels of immunosuppression and a high burden of frequently undiagnosed concurrent systemic infections, in particular tuberculosis (TB) and difficulties in diagnosis and treatment.

The overall aim of this paper was to review the main NDs occurring in adult persons infected with HIV in Africa in order to provide a practical framework for health care workers involved in managing and treating patients with the disease. In order to achieve this, the paper focusses on the following main objectives: measuring overall burden and documenting their aetiology, clinical presentations, diagnosis, management, outcome and prevention. The paper explores evidence starting with postmortems and mortality studies as the gold standard, followed by clinical studies. The main opportunistic processes are discussed; these include cryptococcal meningitis (CM), tuberculous meningitis (TBM), acute bacterial meningitis (ABM), toxoplasma encephalitis (TE), syphilis and primary CNS lymphoma (PCNSL). The role of immune reconstitution inflammatory syndrome (IRIS) in CNS OIs is reviewed. The effects of direct HIV infection on the nervous system are presented including HIV associated neurocognitive dysfunction (HAND), neuropathies and myelopathies. Stroke seizures, paraplegia, radiculopathy and inflammatory neurological disorders are also discussed. Finally, a way forward outlines proposed intervention strategies aimed at reducing the mortality and morbidity of NDs in persons with HIV in Africa.

Materials and methods

This involves an analysis of the published literature including paper and electronic based journals and textbooks on the main neurological disorders(NDs) occurring in HIV-infected adults >18 years of age in Africa. A search was made of published scientific literature using PubMed at the following webpage address: https://www.ncbi.nlm.nih.gov/pubmed. The following Mesh terms were used to search for relevant articles published from Jan 2000 up to July 2017: "Nervous System Diseases" "HIV Infections" and "Africa South of the Sahara" and "Seizures" or "Spinal Cord Diseases" or "Peripheral Nervous System Diseases" or "AIDS Dementia Complex" or "Opportunistic Infections" or "Immune Reconstitution Inflammatory Syndrome" or "Stroke". Only those articles written in English were used. A total of 352 articles were identified, selected and reviewed and 180 were included in the study. These included case series, observational studies, interventional studies, guidelines and reviews with metanalyses. The author also included 15 seminal publications on the subject covering the earlier phase of the HIV epidemic in Africa from 1987 to 1999 including articles, reviews and book chapters. A total of 195 references are presented in this paper. The author uses the clinical narrative based method for review and incorporates his knowledge, experience and discussions with colleagues and recognised experts. The term "Africa" is used throughout this paper to mean "Sub-Saharan Africa". This review refers to HIV-1 unless otherwise stated. The information presented in this paper follows the pattern of analysis of disease burden, aetiology, clinical presentation, management, outcome and strategies for prevention. A glossary of abbreviations is presented.

Results

Mortality

Infections are the leading cause of death in HIV infection with TB and pulmonary infections being the most common. In a review of the autopsies in Africa carried out in the pre-ART era tuberculosis (TB) was present in 37-57%, involved two or more organs in 80-100% and considered to be the cause of death in 32-45%[1–8]. In two more recent autopsy studies during the post-ART era using needle sampling TB was found to be present in 47-76% and to be the main cause of death[4,9]. A high burden of concordant bacterial infections 33-68% was found in both those recent studies. Pneumonia was the second leading cause of death 20-25% with the reported frequencies of the individual causes: bacterial 9-39%, pneumocystis carinii 9-14% and interstitial pneumonia 1-5%[3,4,6,7].

CNS infections were the third leading cause of death and accounted for 23% of all deaths in the first major autopsy series in Africa involving 294 cadavers[8]. Reported frequencies of CNS/HIV infections in Africa ranged from 9-35%[5,6] with their overall frequency being approximately 20%[6]. The main causes were cryptococcal meningitis (CM) 0-17%, tuberculous meningitis (TBM) 6-11%, acute

bacterial meningitis (ABM) 2-9% and toxoplasmosis encephalitis (TE) 0-15%[2,4–8]. The frequencies of primary CNS Lymphoma (PCNSL) 0-1.4% and progressive multifocal leukodystrophy (PML) 0-1% were generally low suggesting that these are relatively uncommon in Africa although a higher frequency of PML 3% was reported in one small study[5,6,8]. The burden of previously undiagnosed disease discovered at autopsy was also large 45-49%. These included TB 26-46%, pneumonia 18-35% and bacteraemia 33-68%[1–9]. These were either not considered, unsuspected or wrongly diagnosed suggesting a leading role for multiple concurrent infections contributing to mortality in HIV in Africa. Together tuberculosis, bacteraemia/sepsis/pneumonia and CNS infections were responsible for over 80% of all HIV related deaths in Africa[5,6].

In keeping with the autopsy series clinical studies in Africa have also demonstrated that CNS infections are a major cause of death accounting for >20% of HIV related deaths[6,8,10,11]. The case fatality rates (CFR) in individually treated CNS OIs are particularly high in Africa. In the pre-ART era, the pooled estimated "6-9 months" CFRs Africa were 68% (9-70%) for CM, 67% (13-72%) for TBM, 62% (54-70%) for ABM and 22% (10-30%) for TE with the majority of these deaths occurring during the first three months of illness. In the post ART era the pooled estimated "6-9 months" CFR post ART still remain high, CM 60% and TBM 58% with lower CFR rates reported in CM, 30-41% and TBM 49% when patients are optimally managed in clinical trial settings[4,11–22]. Risk factors for death include advanced HIV infection, WHO stages III/IV, low CD4 counts <50 cells/mm³, altered mental status, seizures, lack of CSF pleocytosis and early initiation of ART during the course of the treated OI. The presence of concurrent infection in particular TB, frequently undiagnosed and unsuspected in up to 50% is a major contributor to the very high mortality reported in HIV in Africa[4,6,8,11,13,23,24]. In a review of patients started on ART in Africa a high overall mortality rate 8-26% was noted during the first 12 months of treatment, the majority dying within the first 3-6 months with TB and pneumonia as the leading causes[25,26].

Neurological Disorders (NDs)

A high frequency 72-75% of NDs and abnormal neurological findings has been reported in clinical studies in HIV-1/AIDS in Africa[24,27,28]. The pattern of presentation of NDs is typically that of major NDs occurring in 10.5-22.2% of patients and a range of less obvious but more frequent NDs/abnormal neurological findings occurring in 34.4-75% of patients[24,27–43]. Major NDs include meningitis, altered level of consciousness, focal neurological disorders, stroke, seizures, myelopathy, radiculopathy and neuropathy and are caused by opportunistic processes, mostly infections, inflammation or infrequently by autoimmune inflammatory processes. In contrast, the less obvious but more frequent abnormal neurological disorders/findings are caused by the direct effects of the HIV virus itself and include HIV associated neurocognitive dysfunction (HAND), distal sensory neuropathy (DSN) and pyramidal weakness/signs secondary to vacuolar myelopathy (VM). In HIV-2 infected persons from West Africa a lower overall frequency of NDs has been reported, these include neurological impairment 10.3% and CM 4.6%,[44], however a high frequency of neuropathy 50%, was reported in one study[45].

These two main patterns of clinical presentations are clearly illustrated in a major study reported from South Africa involving a total of 506 consecutive inpatients presenting with advanced HIV (mean CD4 = 107cells/mm³, range <1-867)[24]. A total of seventy five percent were diagnosed with neurological illness. These included isolated NDs occurring alone as the presenting complaint in 11% (mean CD4 = 143 cells/mm³) and NDs occurring in association with systemic illness occurring in 64% (mean CD4 = 38 cells/ mm³). A total of 32% had neurological illness as either the whole or part of the presenting complaint. CNS opportunistic infections (OIs) occurred overall in 20% of patients and included meningitis in 17%:(CM 7%, TBM 6%,and ABM 3%, viral 1%), tuberculoma 1%, TE <1% and neurosyphilis (NS) <1%. The pattern of NDs also differed between the two main groups. In the group presenting with NDs alone OIs 81% and strokes 12% were the most common causes whereas NDs occurring as a result of direct HIV infection: HAND 4% DSN 5% and VM 0% were distinctly uncommon. This was in contrast to NDs presenting in association with systemic illness where NDs resulting from direct HIV infectionwere the most common: HAND 59%, neuropathy (DSN) 41% and vacuolar myelopathy (VM) 4% in contrast to those resulting from OIs 15% and strokes 1% which were much less frequent. The main non-neurological concurrent systemic illnesses were TB 46%, gastroenteritis 15% and pneumonia 12%[24].

Opportunistic infections (OIs)

Cryptococcal Meningitis (CM)

Africa accounts for >70% of the global burden of CM with almost 140, 000 CM related deaths estimated to occur there annually[46]. It is the most common CNS OI in persons in HIV in Africa[12,14,47–54] and is responsible for 10-20% of all HIV related deaths there[12–14,46,53,55–59]. In a review of 1303 cases of all cause HIV related meningitis in 7 countries in Africa CM accounted for 52% (19-68%), followed by TBM 19.6% (1-36%), ABM 14.2% (6-30%) and others 14.2% (7-49%)[14]. In a more recent study from SA, involving a large series of 11,891 cases of confirmed meningitis the main causes were CM 62.3%, TBM 24.6%, ABM 10.1% and others 2.1%[60]. The reported frequency of CM in HIV varies within Africa from 3.25% in West Africa to 7% in Ethiopia, 40.4% in Uganda and 1.7-9% in the Central African Republic with an overall estimated frequency there of 10.5%[12].

Clinically CM meningitis is characterized by a slow onset of symptoms of meningitis occurring over days or weeks (median 14 days)[14,50,54,61–66]. In areview of CM in Africa the main presenting clinical features were headache 62.5%, fever 75% and meningeal signs 49%[12]. In another large series involving 501 patients, mostly from Africa[13] clinical features included headache 99%, fever 57%, nausea/vomiting 54%, visual symptoms 51%, and seizures 19%. Neurological signs in CM though frequently absent included neck stiffness 75%, altered mental status 25%, cranial nerve palsies (CNPs) 13%, and papilloedema 12%. Diagnosis is based on a combination of clinical findings and cerebrospinal fluid (CSF) examination. Lumbar puncture (LP) in CM typically reveals a CSF with an increased opening pressure >20 cms, which is clear in appearance 75% (58-89%) with normal or elevated lymphocytes and protein. India ink staining is positive in 60-80% of cases on single CSF examination and >90% on repeated examinations. Cryptococcal antigen (CrAg)/lateral flow assay (LFA) tests are positive in >95% of cases[47,67–72].

The preferred treatment regimen for CM is in 3 phases: Induction phase with Amphotericin B 0.7mg/kg/day IV + 5 Flucytosine 100mg/kg/day administered orally for 14 days followed by consolidation phase with Fluconazole 400mg/day for 8 weeks or until CSF is sterile followed by a secondary suppressive phase of maintenance therapy with Fluconazole 200mg/day until CD4 counts are >200/mm^3. However, in the absence of Amphotericin B and Flucytosine the standard treatment for CM in many countries in Africa is with Fluconazole monotherapy 1200mg iv or oral once daily for 2 weeks followed by 8 weeks of consolidation phase and suppressive phase until CD4 counts are >200/mm^3 [56]. If the CSF pressure at diagnosis is elevated (>20 cm H20) then serial daily/alternate day lumbar punctures are indicated to decrease intracranial pressure) which has been shown to reduce mortality[13,73]. Routine steroids are not indicated in CM. Reported case fatality rates (CFR) are high in Africa 35-68% as compared to 14-26% in high income countries (HICs)[12–14,22]. In a recent global review a one year post treated CM mortality rate of 70% (59-81%) was reported in low income countries, mostly in Africa[46]. However when managed optimally with fungicidal drugs (amphotericin based regimen) and delayed ART for 4-6 weeks after CM diagnosis in order to prevent immune reconstitution inflammatory syndrome (IRIS) significantly lower long-term CFRs of 30-41% are reported in Africa[13,16,74,75].

The main risk factors for death in CM in persons with HIV in Africa are advanced immunosuppression as measured by low CD4 counts (<50/mm^3), lack of access to rapidly acting fungicidal treatments such as Amphotericin B plus Flucytosine, starting ART treatment early within two weeks after CM diagnosis and treatment, IRIS and concurrent TB infection/nosocomial infections. The reported frequency of IRIS/CM occurring in Africa varies from 10-40%[4,76].

Tuberculous Meningitis (TBM)

TB is the most frequent OI in HIV in Africa occurring in over 50% of patients and accounting for 35-45% of all deaths there[2,6,9,77]. The main NDs arising from TB/HIV are meningitis (TBM), tuberculoma, myelo-radiculopathy and Potts disease of which TBM is the most common and associated with greatest morbidity and mortality. TBM is the second leading cause of meningitis in HIV patients in Africa after CM accounting for 10% of the TB/HIV cases and >20% (1-36%) of all cause meningitis[14,15,38,60,78,79]. A higher frequency of 57% was reported in one more recent study in South Africa (SA) in the post ART era[21].

In TBM the mean age of onset in adults ranges from

26-37 years, the duration of symptoms ranged from 9-42 days. The clinical features are largely similar in TBM/HIV and non-HIV[78].

TBM/HIV presents with a subacute or chronic meningitis occurring over days or weeks.

Patients present typically with headache 40-100%, fever 68-100%, nausea/vomiting 26-50%, seizures 3-50%, meningeal signs 19-100%, confusion, altered level of consciousness 30-70%, and CNPs/focal neurological deficit 13-80%[78]. Findings outside of the CNS are more common in TBM/HIV than in TBM/non-HIV including multiorgan TB dissemination and anaemia in most patients. Clinical algorithms predicting TBM have low sensitivity 78% and specificity 43% in populations with high seroprevalence of HIV[78,80]. This is partially explained by the other infections, in particular cryptococcus presenting with similar symptoms and signs and the clinical differential diagnosis includes all causes of meningitis in HIV.

The diagnosis of TBM particularly in HIV is often presumptive based on a combination of clinical, laboratory and radiological findings. In TBM/non-HIV the CSF is typically clear or slightly yellow but on microscopy shows elevated leukocytes, mostly lymphocytes, raised protein and decreased glucose (<50% blood glucose). However, in TBM/HIV the CSF may be normal microscopically in 10-20% of cases particularly in advanced immunosuppression, and neutrophils rather than lymphocytes may predominate, particularly in TBM-IRIS. Direct acid-fast bacilli (AFB) smear has a low overall sensitivity of 10-20% in TBM unless large volumes of CSF (>7mls) are used and increased time (>30 mins) is spent on microscopy[14]. The rate of TB positive CSF culture rate in TBM/HIV 42%, is higher as compared to TBM/non-HIV 30%, because of abundant organisms but the result may take one to four weeks. There has however been a significant improvement in the laboratory diagnosis of TBM with the use of newer point of care (POC) rapid diagnostic tests. These tests include Gene Xpert MTB/RIF (Xpert), with a sensitivity of 27-86% and specificity of 95-100%, and lipoarabinomannan (LAM) lateral flow assay (LFA) and LAM antigen detection enzyme-linked immunosorbent assay (ELISA), sensitivities 29-70%, and specificity 93%, in advanced HIV[14,81]. When using centrifuged CSF in TBM/HIV Xpert has consistently high sensitivities 72-82%[82,83] and although a significant improvement on culture it cannot be used to rule out TBM. POC tests with their increased sensitivities and high specificities in proven TBM have an important role in the diagnosis of TBM and Xpert is recommended by WHO for use in Africa[81]. Radiological findings indicate that TBM/HIV patients are more likely to have disseminated extra pulmonary TB with an abnormal chest X-ray reported in 53-67%[78]. On neuroimaging, abnormal findings suggestive of TBM brain are present in 55-100% of cases. These include basal meningeal enhancement, infarction and tuberculomas and are found with the same frequency as in TBM/non-HIV but hydrocephalus is notably less common in TBM/HIV 0-6% v 20-64%[78].

Current management of TBM/HIV is similar to TBM/non-HIV and involves treatment with the standard TB drugs, rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months followed by rifampicin and isoniazid for a period of 10 months. Studies in TBM/non-HIV evaluating the use of higher doses of rifampicin (>10 mgs/kg) administered intravenously or orally and the additional use of fluoroquinolones have conflicting results and have yet to be evaluated in TBM/HIV. The role of anti-inflammatory treatment with steroids is of uncertain benefit in TBM/HIV although their use in TBM/non-HIV is recommended for a total period of 8 weeks, the main danger being increased risk of other infections. Multi drug resistant (MDR) TB is more common in TBM/HIV 13-17%% versus TBM/non-HIV 4%, particularly in those patients with a history of previously treated TB 8-58%[78,84]. Mortality in MDR/TBM is 100% unless managed early and treated appropriately with second line drugs. Surgery may be indicated in a small number of TBM/HIV cases for mass lesions and hydrocephalus but has a particularly high mortality. Starting ART during TB treatment reduces mortality but it is recommended to delay starting ART until 4-6 weeks after starting TB treatment in order to decrease the risk of IRIS[17].

TBM has a high CFR in Africa, 59.9% (40.3-87.9%)[15]. In a global review of treated TBM/HIV meningitis[21,78] the in-hospital CFR ranged from 13-72% and the 6-9 month CFR was 41-67% with the highest rates >60% reported from Africa. In a retrospective study in SA the 9 month post ART CFR in optimally treated TBM was 49% with 12% lost to follow up[17]. The main risk factors for early death in TBM in Africa included late clinical stage; British Medical Research Council grades II & III, advanced im-

munosuppression, and CD4 <50 cells/mm³ at presentation. Notably HIV related concurrent illness accounts for up to 50% of all-cause mortality in TBM/HIV patients not on ART who don't survive. Reported IRIS rates in TBM/HIV in Africa are 8-43%[17,78,85].

Acute Bacterial Meningitis (ABM)

The risk of acute bacterial meningitis (ABM) is significantly increased in HIV infection in Africa and accounts for approximately 14% (6-30%) of all cause HIV/meningitis[14,60]. The relative risk of pneumococcal meningitis (PM) is significantly higher in HIV than in the general population[14,18]. In Malawi, out of a total of 715 cases of ABM, 87% of whom were HIV infected, 84% were caused by *S. pneumoniae* and 4% by *N. meningitides*[18]. The main clinical features in that series were similar in ABM/HIV and in ABM/non-HIV patients and included headache/meningism 99%, fever 86%, seizures 45% and confusion/altered level of consciousness 44% median Glasgow Coma Scale (12/15). The 10 and 40-week CFRs of 45%/53.4% reported in that series were independent of HIV status[18].

Toxoplasmosis Encephalitis (TE)

Toxoplasma encephalitis (TE) is the most common CNS OI in HIV in HICs. The incidence and prevalence vary significantly across continents and within individual countries with worldwide toxoplasma IgG seroprevalence rates varying from 20 to 75%. A similar pattern exists within Africa ranging from 29% in Gauteng province SA to 34% in Kwa-Zulu Natal SA and 46-94.4% reported in Ethiopia with particularly high rates in HIV infected cohorts[32,87,88]. Toxoplasmosis and HIV co-infected persons are at increased risk of developing TE with the majority of TE cases 85-95%, due to reactivation, mostly affecting the CNS with very occasional involvement of retina and lungs. The reported frequency of TE in HIV varies significantly within Africa from 0-1% in parts of SA/Botswana/Uganda/Malawi to 2.7% in Kenya and increases to 10% in West Africa and Ethiopia[2,6,11,32,89,90]. In the post ART era in Africa the reported frequency varies from 0-10% with the highest rates in West Africa[11]. A recent report from Gabon in West Africa reported TE as accounting for two thirds of CNS/HIV infections 91. The main risk factors for TE are low CD4 counts of <200 cells/mm³ and the presence of a positive toxoplasma IgG/IgM serology.

The main clinical features of TE are headache and fever 40-93% coupled with focal neurological signs; hemiparesis/cranial nerve palsies 50-73%, seizures 30-58% and confusion/lethargy 31-40% developing sub-acutely usually over weeks or more uncommonly days[19,20,32,92]. Treatment is with high dose trimethoprim-sulphamethoxazole for 4 weeks followed by continuation phase for 8 weeks and then maintenance therapy until CD4 counts >200 cells/mm³ [93]. Steroids are not recommended. Post starting treatment there is typically clinical improvement by day 3 in 50% and by day 14 in 90% with complete resolution in 90% within 6-26 weeks[32]. The diagnosis of TE is based on clinical features, the presence of a focal neurological deficit, IgG antibodies, the finding of a ring enhancing lesion(s) on CT and response to treatment. Typical CT findings are those of single or multiple hypodense >5mm ring enhancing lesions with edema in the basal ganglia and or in the grey/white matter zone present in > 80% of cases. Radiological improvement usually occurs by the third week of treatment. The main differential diagnosis for any focal brain lesions in HIV in Africa includes toxoplasmosis, tuberculoma and cerebral lymphoma[38]. As a general guide to their diagnosis a CD4 count in the range of 100-200 cells/mm³ suggests TE, while a CD4 count of <50 cells/mm³ suggests primary CNS lymphoma (PCNSL) and a CD4 >200 cells/mm³ suggests tuberculoma.

CFR in treated Toxo/HIV in Africa is 10-30%[19,20], with a higher rate of 44.1% reported in one study in Ethiopia[22]. CFRs one year after infection range from 20-60% with the higher rates reported in resource poor settings[68].

Immune reconstitution inflammatory syndrome (IRIS)

The immune reconstitution inflammatory syndrome (IRIS) is an exaggerated activation of immune system with increased inflammatory response against persisting antigen (paradoxical) or pathogens (unmasking). It is characterized by deterioration clinically and radiologically after a period of initial improvement following initiation of ART treatment. Its onset is very variable from a few days to 3 months and rarely 6-12 months after starting ART[26]. Its overall frequency in the first 6 months of ART in HIV in Africa is estimated to be around 10%[26,76,94] with higher rates reported in TB 15.7% (9.7-24.5%)[95]. In a recent autopsy series in SA, IRIS was reported as contributing to 73% of early ART mortality[3]. The main risk fac-

tors for IRIS are degree of immunosuppression including low CD4 (<50 cells/mm^3), high viral load, high antigenic burden or disseminated OI and shorter duration of OI/ART treatment. CNS IRIS contributes to most of the burden of IRIS and mortality attributed to CNS/IRIS is high 13-30% depending on type. The main causes of CNS/IRIS are CM and TBM and less frequently PML. IRIS is uncommon in TE and is unmasking rather than paradoxical in type[17,76,96,97]. The differential diagnosis of IRIS includes other concurrent CNS infections, MDR in TB, lack of compliance, drug reactions and toxicities.

Cryptococcal CM/IRIS occurs with a frequency of 21% (13-45%) in those patients who start ART soon after treatment for CM[76]. It occurs typically 4-9 weeks post ART initiation with a median of 29 days (range 23-45 days) reported in one study[13]. CM/IRIS is most commonly paradoxical but can also be unmasking in a small number, (1%) of patients starting ART. It occurs in a significantly larger number of those with subclinical cryptococcal antigenemia[47,68]. Clinical features are those of a recurrence of meningeal symptoms, headache, and visual disturbances, vomiting along with impaired consciousness, seizures and occasionally focal neurology. Non-neurological presentations are less common and include lymphadenitis, pneumonitis and ophthalmic involvement. Mortality attributed to IRIS in CM is estimated to be around 20% (13-36%)[55,76,95], although no increased mortality was reported in one large study involving 266 patients from SA with CM[13]. Risk factors for IRIS include abnormal mental status, high baseline fungal burden load and low CD4 count at onset and early ART treatment. The timing of ART is important and based on randomized controlled studies in Uganda and SA using delayed ART mortality rates decreased from 45% to 30%[16]. Treatment of IRIS is in the usual way for CM/HIV with antifungals, repeated LPs and steroids if severe. Specific strategies to decrease CM/IRIS include delaying ART until 4-6 weeks after initiating CM treatment.

TB-IRIS occurs with an overall frequency >15% in TB/HIV patients of which approximately 75% is paradoxical and 25% unmasking[95]. Neurological TB-IRIS accounts for overall 12% of all TB-IRIS. Its onset is variable but in a recent prospective study in SA involving steroid treated previously ART-naive culture confirmed TBM/HIV patients, a high rate of TBM-IRIS 47% was reported at a median of 14 days (range 4-20) after starting ART[17]. Treatment of TBM-IRIS in that study involved standard TB drugs, delayed ART and the use of steroids for 109 days (range 69-141 days)[17]. Mortality attributable to TBM-IRIS at 9 months was 13%[17]. The clinical features in TBM/IRISare those of a worsening of the underlying TBM including headache, meningism, confusion, vomiting and seizures or of tuberculoma spinal TB or systemic TB. Risk factors for developing TBM-IRIS include: disseminated TB, a shorter time interval from starting anti TB to ART treatment (2 weeks), severe immunosuppression, a rapid immune recovery, and high CSF cell counts, in particular neutrophils, activated innate immunity[98] and a positive TB/CSF culture. Specific strategies to decrease TBM-IRIS include delaying starting ART prophylaxis until 4-6 weeks after initiating TB treatment.

Neurosyphilis (NS)

The overall global burden of syphilis is 12 million new cases of primary infection every year approximately two thirds of which are in Africa and South East Asia[99]. The reported seroprevalence of syphilis in Africa is high, varying between 2-17% in antenatal clinics and 7-10% in HIV patients[100]. Despite the high burden of primary syphilis in Africa there are few published reports of neurosyphilis in HIV and those suggest a low overall burden. One large study from SA involving 506 patients presenting with AIDS reported just a single case[24]. In a large study in SA involving[4,549] adults presenting with meningitis a diagnosis of NS accounted for 3% (22/820) of confirmed CSF microbial diagnoses however the HIV status was not stated in that study[62]. In Mozambique in a series of 21 patients presenting with latent syphilis and HIV co-infection 4 cases of asymptomatic NS were reported however none had a positive CSF rapid plasma regain test on LP[101]. In Nigeria in a series of 31 patients with syphilis and HIV co-infection no case of NS was reported[102]. Syphilis has been reported in association with myelopathy in HIV in Africa[103,104]. The overall risk of NS developing in untreated syphilis/HIV is known to be increased, 23% versus 10% in-untreated syphilis/non-HIV suggesting a 2-3 fold increased risk of NS in HIV[99,105].

Clinically the natural history of NS may also be altered in HIV disease with an increased rate of early neurological involvement including meningitis, meningovascular and ophthalmic syphilis whereas tabes dorsalis and gener-

alised paralysis of the insane (GPI) remain as the classical late manifestations. The diagnosis of NS relies on a high index of clinical suspicion combined with characteristic CSF findings and serological evidence of syphilis in blood and CSF. Typical CSF findings include >20 lymphocytes/mm³, elevated protein and normal or reduced glucose. Serological screening tests include Venereal Disease Research Test (VDRL) and rapid plasma regain tests (RPR) and confirmation tests include *Treponema pallidum* haemagglutination assay (TPHA) and flocculation Treponema antibody absorption (FTA-ABS). The gold standard for diagnosing NS is a reactive CSF on VDRL testing, however CSF VDRL is notably unreactive in 30-70% of cases of NS[32]. The *Treponema* antibody tests TPHA/FTA are more sensitive but less specific because of cross-reaction with possible leaked blood in CSF (antibody). While a negative screening test makes NS less likely[99] notably they can also be negative in the presence of NS/HIV. Neuroimaging may show meningeal enhancement, infarction or gammas.

Treatment for NS is recommended in HIV infected patients if the serum/CSF screening tests are positive and in the case of negative CSF VDRL but with abnormal CSF findings consistent with NS. First line treatment is with soluble penicillin or ceftriaxone for 14-21 days duration, however treatment may not be effective in as many as 23-60% of HIV/NS infected patients. In these a longer course of treatment for 3-4 weeks may necessary or doxycycline 200 mgs twice daily where a hospital stay or outpatient antibiotics are not possible[99]. Relapse of infection is also more likely in HIV[32,99], and a follow up CSF examination should be done every 6 months for up to 2 years. Retreatment may be necessary if clinically disease persists or recurs or when there are persistent lymphocytes in CSF.

Lymphoma

The overall frequency of malignancies in HIV deaths undergoing autopsy in Africa ranges between 11-16% with the most common being Kaposi sarcoma 8-16% and systemic lymphoma 1-3%[6]. A recent autopsy study in SA on 39 adults, (64% on ART) reported a higher overall frequency of malignancy 23%, (Kaposi sarcoma 15%, and systemic lymphomas 8%)[4]. The reported frequency of primary CNS lymphoma (PCNSL) in clinical and postmortem series in Africa is either very low (0-1.3%) or absent[6,8,11,24,106]. This is in contrast to HICs where higher rates are reported[107]. PCNSL typically presents in advanced HIV disease as nonspecific headache lasting weeks coupled with neurological features of a focal brain lesion. The diagnosis is based on the clinical presentation, coupled with the finding of a homogenous, solid, focal or multifocal hypodense enhancing periventricular lesion on CT with no or relatively little surrounding edema, CD4 <50 cells/mm³, evidence of positive Epstein Barr virus in CSF and no response to TB/Toxo treatment. Management of focal brain lesions in HIV in Africa is mostly empirical treating first for toxoplasmosis or tuberculosis or both depending on whichever is most endemic in that region. The prognosis for CNS lymphoma in HIV is particularly poor in Africa[4,106].

Stroke

The frequency of strokes is increased in HIV infection in Africa[108,109]. A community based stroke study in Tanzania in 2013 showed an increased frequency of HIV infection in new onset strokes, 25% versus 6.6% in controls, odds ratio (OR) 5.6[110]. A similar trend, (OR) 2.1 was reported in SA[111]. Notably some earlier studies in Africa showed no such association[112–114]. Possible reasons included the exclusion of patients with an AIDS defining illness, a group that is more likely to develop stroke. In SA in a hospital-based study involving 506 adult HIV patients, stroke was present in 2%, 80% of which occurred in association with CD4 counts <200/mm³. The majority of strokes two thirds, occurred without any known underlying cause while less than one third occurred in association with meningitis[24]. These findings agree with reported increased TIA/stroke prevalence in HIV disease, its more frequent occurrence in WHO HIV stages III/IV and also occurring at a younger age[115].

The main mechanisms of stroke in HIV infection are cerebral ischaemia/infarction 80-96% and intracerebral haemorrhage 4-20%. In a large stroke study in SA, a HIV infected subgroup of 6.1% (67/1087) was identified, of whom cerebral infarction occurred in 96% and intracerebral haemorrhage occurred in 4%[116]. In ischaemic stroke/HIV in Africa the main identified causes were infectious meningitides/vasculitis 28%, coagulopathy 19%, cardio embolism 14%, HIV associated vasculopathy 20% and multiple causes 11%[113,115]. Large vessel site in cryptogenic stroke was identified in one study in SA suggesting

the presence of a co-existent prothrombotic state as a risk factor[114]. Concurrent systemic infection, the first 6 months of ART treatment and IRIS may be independent risk factors for stroke in Africa[116,117]. The natural history of stroke/HIV appears unchanged from that of stroke/non-HIV stroke but stroke inadvanced HIV disease has a poor prognosis. While primary prevention of stroke is the main aim, secondary intervention measures include ART, strict control of BP and the use of antiplatelet drugs and statins[108,118].

Seizures

New onset seizures occur in up to 11% of HIV infected persons[14,40,119–126]. They occur at all stages of HIV infection but mainly at WHO stages III/IV[119]. The main causes are opportunistic processes, mostly infections including: meningitis mainly cryptococcus, viral encephalitis, toxoplasmosis and less commonly, antiretroviral medications and hyponatraemia[119,123]. In HIV in Africa up to 75% of seizures occur in the context of known treated or untreated HIV infection whilst in 25% the seizures are the presenting complaint of previously undiagnosed HIV infection[120]. The seizure type identified most commonly in Africa is generalized tonic clonic with multiple or recurrent seizures occurring in >50% of cases and status epilepticus occurring in 15%[119]. Investigations in Africa should include laboratory screening of blood and CSF for evidence of treatable pathogens in particular for cryptococcus, toxoplasmosis, TB and NS and also neuroimaging if available. Clinical or radiological evidence of a focal cause may be present in up to two thirds of seizure patients[119]. Management includes treating the underlying cause and the use of antiepileptic drugs that do not interact with ART. Mortality is significantly increased in seizures in HIV and a mortality rate of 37% was recently reported in a cohort of 81 seizure patients from Zambia with a median follow up period of 306 days[119]. The main risk factor for death as an outcome in that study was late WHO HIV stage at initial clinical presentation.

Direct HIV infection

The main NDs occurring as a result of direct HIV infection are HIV-associated neurocognitive dysfunction (HAND), neuropathy and myelopathy. These disorders are reported in clinical studies across Africa[24,28], their presence and frequency largely considered to be a function of the clinical stage of the patient at presentation and degree of underlying immunosuppression.

HIV associated neurocognitive disorder (HAND)

HIV is a major cause of neurocognitive impairment. The term neurocognitive impairment was redefined in 2007 by the American Academy of Neurology as HIV associated neurocognitive disorders (HAND) which includes the following: asymptomatic neurocognitive impairment, mild neurocognitive disorder and HIV-associated dementia (HAD). Collectively they can also be grouped as minor cognitive and motor disorders and HIV-associated dementia (HAD)[127]. HAND in SSA is mostly measured by the International HIV Dementia Scale (IHDS) which measures motor speed (timed finger tapping), psychomotor speed and learning (timed alternating sequence test), registration (naming 4 items) and memory (recall of 4 items at 2 minutes) and scored out of 16, a score of 10 or less being significant in Africa. The IHDS has a reported low sensitivity 45-69% and specificity 74-80% in HIV in Africa[127–129] possibly because of comorbidity and advanced disease. However, a recent cohort study involving 266 adults on ART in Zambia with a prevalence of HAND of 34.6% has established its validity using a comprehensive battery of neuropsychological tests[130]. Also important normative baseline data is provided in a recent multi country study including some from Africa[131]. There is a wide variation in the reported frequency of HAND in Africa as reported from individual countries[132,133]: SA 18-80%[134], Malawi 14%[135], Zambia 22%[136], Uganda 64.4%[137], and Cameroon 85%[138].

In one study in West Africa involving a HIV-2 infected cohort no significant increase in HAND was found compared to HIV-2 negative controls[45]. A high frequency of HAD 54%, was reported in a cohort of patients presenting with advanced HIV disease[28] in an early study in Tanzania. A high frequency of frontal lobe release signs: snout reflex 87% and palmomental reflex 69% has also been reported in advanced HIV disease in Africa[28,139]. In Uganda a high rate of HAND 89%, was reported in association with HIV subtype Clade D, in contrast to 24% in Clade A[140,141]. However a subsequent study there showed no association of HAND (41%) with HIV subtype[142,143]. HIV subtype Clade C predominates in SA where a frequency of HAND 38% was reported[24]. In a recent review of HAND, the reported mean prevalence in Africa in the pre-ART era was 42.3% (15.6-80%) and in Uganda 46.5% (30.6-62.4%)[127]. ART improves HAND with reported rates six months post ART significantly lower in Uganda 28.5% and in Africa 30.4% with a 63% improvement reported in similar subjects in Uganda[127]. However

in one study in Uganda while ART use overall was associated with improvements in cognitive functioning among HIV+ persons, these were no greater than those seen among HIV+ persons who did not initiate ART possibly suggesting patient test learning bias[144].

Noticeably any improvement in the rate of HAND peaks and plateaus after nine months ART with persistence of the milder asymptomatic or dysfunction forms[129,145,146]. Qualitatively there are also differences with pre-ART HAND characterized by psychomotor slowing: inattention, slow thinking, forgetfulness, unsteady gait, tremor and social withdrawal, whilst post ART HAND is characterized by more cortical involvement, with impaired learning ability, memory executive function and extrapyramidal motor features. There is little evidence of clinically significant chronic neurological dysfunction in chronic HIV-2 infection in West Africa[140,146]. HAND is a process caused by the direct effects of HIV virus infection which are independent of opportunistic processes. While some studies in SSA report a number of risk factors for HAND in particular advanced age, advanced WHO clinical stage, low CD4 counts, and anaemia[147,148], other studies report no such association or a less strong association with HIV stage[127,129]. An independent association with cardiovascular disease and inflammation has also been reported[146]. While the burden of HAND decreases significantly post ART, it is important to remember that despite ART one third to one half of HAND affected persons in Africa will remain affected with persistence of the milder forms. Strategies aimed at decreasing the burden of HAND include starting combined ART as early as possible in HIV infection, the development and use of ART regimes with better CNS penetration and effectiveness for the control of replication and elimination of HIV from its main CNS reservoirs in microglia and macrophages. Other strategies in HICs including the use of adjunctive therapies including anti-inflammatory measures such as low dose methotrexate, statins and antiepileptic medication have either proved ineffective or not significant. At present the strategy of choice available in Africa is starting ART as early as possible in HIV infection and decreasing or treating known risk cardiovascular risk factors[145,146].

Distal Sensory Neuropathy (DSN)

Neuropathies occur at all stages of HIV infection. The main neuropathies are distal sensory neuropathy (DSN), inflammatory neuropathies, radiculopathies and mononeuropathies. DSN is the most common occurring mostly during the symptomatic stage of HIV disease (WHO stages 3 & 4) and was reported early on in the HIV epidemic in Africa[28,36]. The main symptoms of DSN are a burning, stabbing pain and paresthesia or numbness in the soles of the feet ascending symmetrically and less commonly involving the hands. Notably the pain or discomfort is most apparent on touching the soles or palms. Sensory symptoms are reported to be present in about 75% (50-90%) of DSN patients in Africa[148]. Signs of DSN include reduced or absent ankle reflexes and/or impaired light touch and/or impaired vibration and joint position sense.

The prevalence of DSN depends on the criteria used to define it and include any two of three signs with or without symptoms (symptomatic and asymptomatic) or any one sign with symptoms (symptomatic)[149,150]. More recently a clinical tool using 4 items: pain, numbness, ankle reflexes and vibration has been validated for use in Africa[151]. The pathophysiology of DSN is a distal axonal neuropathy secondary to activated dorsal root inflammation most probably due to viral proteins, gp[120]. The estimated pooled frequency of DSN in the pre ART era in Africa was 27% (11-37%)[149,152,153]. A much lower frequency of 3.9% was reported in a single large study from SA[154]. The worldwide prevalence during the same period ranged between 20-57%[149]. A frequency of 50% was reported in HIV2 in one study in West Africa using just one sign+/-symptoms[45]. In the post ART era in Africa there was a significant increase in frequency of DSN with pooled frequencies of DSN of 52% (36-60%)[149,150,152,153,155–159]. This increase was attributed to the widespread use of dideoxynucleoside reverse transcriptase inhibitors as a first line ART, in particular stavudine with the neuropathy typically beginning 5-6 months post starting ART[153,158,160]. In a recent study from SA involving a cohort of patients 2 years after starting ART (60% on stavudine) a slight increase in the frequency of symptomatic DSN from baseline 16% to 18% was reported with a 50% decrease in significant pain[161]. The rate of symptomatic DSN decreased from 22 to 17% in another study in SA involving 2nd line ART patients with an almost 2 year follow up period, notably the rate of asymptomatic DSN in that study increased from 21% to 29%[162]. Some studies from West Africa report a decrease in the frequency of DSN at three months post starting ART which may have been too early to observe

this side effect of stavudine[163,164]. The main risk factors for DSN are advanced HIV disease, lower CD4 count, high viral load, advancing age, and a history of prior TB or alcohol intake[149,153,162]. Up to a quarter of ART treated HIV persons in Africa may be affected with symptomatic DSN for life[162–164].

The management of DSN involves pain control with available neuropathic specific medications including amitriptyline, gabapentin, pregabalin and lamotrigine and the use of opioids only if necessary, however most patients tolerate their symptoms without medications. Strategies aimed at decreasing the burden of DSN in Africa include an early test and treat HIV policy, avoiding dideoxynucleoside reverse transcriptase inhibitors, an increased awareness of other possible concurrent causes of neuropathy i.e. alcohol, diabetes mellitus and pyridoxine deficiency secondary to isoniazid.

Mononeuropathies

Mononeuropathies are common in HIV infection in Africa[149]. The most common are facial nerve palsy or Bell's palsy and neuropathy complicating reactivation of herpes zoster in dorsal root ganglia[165–168]. Facial nerve palsy occurs most frequently at or around the time of seroconversion after primary infection and during the asymptomatic phase of HIV infection. During the early epidemic in Africa >50% of patients presenting with facial nerve palsy tested seropositive for HIV[169]. Facial nerve palsy/HIV is characteristically unilateral but may infrequently be bilateral or occur as part of a generalized acute inflammatory demyelinating neuropathy. Investigation, management and response to treatment are similar to facial nerve palsy/non-HIV. Herpes zoster reactivation is one of the earliest and most recognizable clinical presentations of HIV with its characteristic locally aggressive multi dermatomal involvement, involvement of atypical sites including face, cranium and sacrum and subsequent marked scarring. It affects 5-10% of HIV infected patients in Africa with the mean survival time estimated in the pre-ART era to be around 42 months[166,168]. It most commonly involves the thoracic and trigeminal nerves. Complications include dissemination, myelitis and pain, post herpetic neuralgia. Acute management is with acyclovir and pain control as for non-HIV. Other neuropathies that occur in HIV include other cranial nerve palsies, optic neuritis and mononeuropathies[149,170]. These are mostly either autoimmune based or secondary to opportunistic processes e.g. TB/lymphoma resulting in entrapment/infiltration in advanced disease.

Myelopathy

Paraplegia is common in Africa and the main causes of non-traumatic myelopathy in adults are TB, transverse myelitis and metastatic disease. Myelopathy also occurs in HIV infection, the main causes being opportunistic infections and tumours and vacuolar myelopathy (VM), the latter occurring as a result of direct HIV infection of the spinal cord. In a series of 97 patients from SA presenting with non-traumatic myelopathy a total of 50% were found to be HIV positive in which infections accounted for 72% of the causes[171]. These infections included TB 50%, VM 16%, varicella zoster (VZ) 4% and cytomegalovirus infection (CMV) 1%. Other causes included demyelinating disorders, acute demyelinating encephalomyelitis (ADEM) 8%, neuromyelitis optica 4%, neoplasms 12% and B12 deficiency 2%[171]. In another large series of HIV myelopathies from SA, TB accounted for 68% (84/123) of the cases of CSF culture or biopsy proven causes including all the cases of spondylitis (Potts Disease) and 40% of the myeloradiculopathies[172]. Syphilis and human T-cell lymphotropic virus type 1 have also been reported in association with myelopathy and HIV in Africa with alterations of their natural history characterized by a shortening of time to clinical onset[103,104].

Vacuolar myelopathy

VM occurs as a consequence of direct HIV infection of spinal cord and immunosuppression and in its severe form it is characterized by a slowly progressive painless spastic paraparesis with sensory ataxia and bladder involvement occurring mainly in association with symptomatic HIV disease. While VM has been reported in myelopathy/HIV series in Africa with varying frequency from 1.4 to 16%[103,171,173] there are few reports of VM in symptomatic HIV disease. Notably VM was reported to be present in 2% of patients in a large series of 507 symptomatic HIV infected patients in SA[24]. This contrasts with higher rates of 5-10% reported in HIV in HICs. However in an early study in Africa it was reported to be present in >20% of a series of advanced AIDS patients presenting mainly as a subclinical finding characterized by isolated hyperreflexia at the knees and extensor plantar reflexes[28]. Notably myelopathy was not reported in a study involving a cohort

of HIV-2 patients in West Africa[139]. The main pathology in VM is vacuolation of the white matter in the thoracic/cervical spinal cord present in 20-55% patients. The main risk factor for VM is advanced immunosuppression. Management is aimed at excluding a treatable underlying cause of myelopathy and symptomatic treatment. The use of ARTs appears not to be effective in terms of decreasing the existing burden of VM and strategies aimed at preventing it include earlier ART intervention before it develops.

Radiculopathy

Radiculopathy in HIV is uncommon and is mostly confined to the lumbosacral nerve roots with patients typically presenting over days or less frequently weeks with a rapid onset progressive flaccid paraplegia with areflexia and urinary incontinence without upper limb involvement. The main causes in HIV in SSA are tuberculosis and CMV[149,166]. Radiculopathy caused by TB arises either direct as a granulomatous arachnoiditis involving the cauda equina or from Potts disease of the lumbar spine. Investigations for TB include CSF examination and spinal and chest X-rays. CSF examination in spinal TB shows elevated cells, mostly polymorphs early in the course of the disease and later lymphocytes, coupled with an elevated protein and low glucose but may be normal with a typically negative TB culture and normal chest x-ray. A recent report from Tanzania describes a case of tuberculous spondylitis/HIV diagnosed through Xpert assay in urine[174]. Cytomegalovirus infection typically occurs in persons with advanced HIV disease (<50 CD4 cells/mm^3) and results in a rapidly progressive and painful flaccid paraplegia with bladder involvement. CSF typically shows increased white blood cells mainly polymorphs, elevated protein and low glucose but may be normal. PCR is highly sensitive and specific with 97% negative predictive value[149]. There may also be clinical evidence of CMV infection elsewhere e.g. retinitis. Treatment is empirical with ganciclovir iv for 14 days coupled with early ART. Uncommon causes of radiculopathy include an early manifestation of HIV virus infection, CD8 infiltrative lymphocytosis syndrome, Epstein-Barr virus related metastatic lymphoma,herpes simplex virus type 2 and syphilis[149].

Inflammatory disorders

Autoimmune mediated inflammatory disorders are increased in HIV but are relatively uncommon[175]. These include acute inflammatory demyelinating polyneuropathy ADEM, myasthenia gravis, polyneuropathies and polymyositis. ADEM/HIV affects both children and adults and its onset in HIV is characteristically associated HIV seroconversion with a relatively intact immunity. However in a recent series of 7 adult patients from SA the mean CD4 count was 368 (range149-533) suggesting its onset can occur with more advanced immune dysregulation[176]. Atypical clinical features in that series included frequent optic neuritis, mass lesions mimicking opportunistic processes and a more aggressive sometimes relapsing course though remaining responsive to immunomodulation. Myasthenia gravis is associated with HIV and while the overall incidence rate of MG in SA[177] is similar to that reported in HICs there are no published reports of MG/HIV from Africa. MG/HIV typically occurs as part of post ART immune restoration or IRIS and responds to standard MG treatment[178].

The main immune mediated polyneuropathies in HIV are acute inflammatory demyelinating polyneuropathy (AIDP or Guillain-Barre syndrome) and chronic inflammatory polyneuropathy (CIDP). These are uncommon NDs and an estimated frequency of AIDP has been reported as 0.8/100,000 in Tanzania[179]. A strong association of AIDP and HIV was reported early in the epidemic in Africa in consecutive series of AIDP patients with HIV seropositive rates ranging from 31-84%[179–181]. The reported frequency of CIDP in HICs ranges from 1 to 7.7/100,000. There is less information on its frequency in Africa but it is described there in association with HIV[36,181,182]. CIDP differs clinically from AIDP in that its onset is slower, over 8 weeks, progression and remission can occur, and it is usually steroid sensitive. The clinical findings in both are largely similar to those in non-HIV. AIDP typically present with symmetrical limb weakness, areflexia and mild or absent sensory symptoms or signs whereas CIDP presents with symmetrical weakness both proximal and distal, areflexia coupled with sensory symptoms and signs. AIDP/HIV tends to occur in association with relatively intact immunity or at seroconversion whereas CIDP tends to occur in association with moderately advanced HIV disease with lower CD4 counts but it can also occur with higher CD4 counts. A progressive clinical course in CIDP/HIV rather than relapsing as occurs in CIDP/non-HIV was reported recently in SA[183]

An association of CIDP with IRIS post ART is also described. Laboratory investigations including elevated CSF protein are similar but a CSF pleocytosis (<50 cells/mm³) is more likelyin HIV infection. The differential diagnosis for CIDP includes CMV/TB/lymphoma related radiculopathies and deficiency states including B6 (pyridoxine) and B12 deficiency. Management is the same as for AIDP/CIDP/non-HIV including immunomodulation in AIDP and steroids in CIDP. The response to immunomodulation treatment and outcome are reported to be largely similar in both HIV and non-HIV groups[149,180] a higher mortality rate was reported in AIDP/HIV in one study in Tanzania[178].

Muscle disease is increased in HIV infection and is of two main types, myopathy and polymyositis. Myopathy is the most common type and is characterized by painless, generalized muscle weakness and wasting and typically occurred in the majority of patients with advanced HIV infection in the early epidemic in Africa when AIDS was named slim disease184. Polymyositis/dermatomyositis in HIV have both been described in Africa[185,186]. In a series of polymyositis reported from SA involving 14 ART naïve adult patients, all of whom were female, the mean CD4 was 261/mm³ (range10-820); they had significantly lower creatinine kinase levels than polymyositis/non-HIV controls and responded well to steroids[185].

Discussion

Early HIV diagnosis and ART

Historically in Africa the WHO recommended level of CD4 counts/mm³ for starting ART has gradually increased from 200 cells in 2006 to 350 in 2009 and 500 cells in 2013. A significant decline in the incidence of the main CNS/OIs was recently reported in a paper from SA involving a 4-year study period 2009-12. During that study the incidence of CM decreased by 23%, TBM by 40% and ABM by 41%[60]. This was attributed to expansion of the national antiretroviral treatment program and to TB program strengthening and pneumococcal vaccination. In Sept 2015 WHO announced a new "Test and Treat" policy globally for persons/patients with HIV regardless of CD4 level. This new policy was based on studies involving the use of early or immediate ART in HIV positive adults and isoniazid chemoprophylaxis which resulted in significantly improved outcomes[187,188]. A major benefit of adopting this new test and treat policy will be the reduction in the burden of NDs in HIV in Africa.

Cryptococcal Meningitis (CM)

The estimated global prevalence of asymptomatic cryptococcal antigenaemia in persons with CD4 <100 cells/mm³ is 6.0% (r2-15%) with even higher rates, 16% reported from Africa46. CM can be prevented by identifying subclinical infection by screening for CrAg in serum at the same time as when screening for HIV on entry into ART programs, a time when the majority of HIV diagnoses are made[189]. It can be detected weeks to months before the onset of meningitis. CrAg is highly sensitive and specific with 100% negative predictive value and costs less than 4$/test[69,70]. Targeted screening and preemptive therapy for CrAg positives in persons with CD4 <100 cells/mm³ and chemoprophylaxis with fluconazole is now recommended for Africa[46]. Newer, cheaper, recently approved, rapid, easy to use, point of care diagnostics including lateral flow immunoassay may prove particularly useful for establishing the diagnosis of CM in Africa[190,191]. The optimum management for CM is with amphotericin-based treatment however a major limitation is expense with standard amphotericin costing $8-10 a day and liposomal Amp B $16/a day in contrast to $0.15 per single 200 mg fluconazole tablet. Research into the efficacy of shorter Amp B based treatment courses combined with high dose fluconazole is already underway in Africa[192]. A recent study in Tanzania and Zambia incorporating CM screening in combination with a short period of community based support reduced mortality by 28%[193].

Intervention strategies for CM in Africa include 1) HIV "Test and Treat" policy, 2) screening for cryptococcus during HIV screening programs and chemoprophylaxis if CrAg or LFA positive and CD4 counts are <100/mm³, 3) improved point of care diagnosis with a lower threshold for both diagnostic and therapeutic LPs, 4) the use of fungicidal Amp B based treatment regimens, 5) deferred starting ART for 4-6 weeks after starting CM treatment and 6) community based support.

Tuberculous Meningitis (TBM)

TB is the leading cause of death in HIV in Africa. The adoption of the recently introduced "Test and Treat" ART policy will serve to decrease the huge burden and mortality of TB in HIV in Africa and in turn TBM[60]. This

is supported by the use of intermittent 6 month isoniazid prophylaxis therapy (IPT) which has shown in Africa to reduce incidence of TB by 33% and by 64% if tuberculin skin positive and mortality by almost 70% in one study but for sustained benefit the strategy needs to be repeated intermittently probably every 2 years[14]. In 2010 WHO introduced a "Three I's" strategy of 1) TB intensive case finding 2) isoniazid prophylaxis and 3) infection control together with intensified ART. However its implementation has been variable across Africa[194]. An increased effort must now be made to support the implementation of the "Three I's" strategy together with the new "Test and Treat" ART policy across Africa. The possible benefit of using combined preventative therapy of isoniazid for TB together with co-trimoxazole for pneumocystis carinii in a fixed dose single tablet formulation to facilitate compliance has also been proposed[195]. The clinical recognition and confirmatory diagnosis of TBM is notoriously difficult particularly in Africa and is traditionally based on clinical, laboratory and radiological findings with poor sensitivities[80]. Any new strategy targeted at improving outcome must involve having a lower clinical threshold for carrying out diagnostic LP in suspected cases coupled with the use of the newer rapid POC diagnostics on CSF because of their higher sensitivities 60-80% and specificities 95%. These POC tests include Xpert LAM (LFA) and LAM (ELISA). The next generation assay Xpert Ultra appears to be significantly more sensitive than Xpert in diagnosing TBM.[77,81,83]. Xpert has the additional benefit of MDR-TB screening and recommended for Africa by WHO the major limitation being expense. In TBM the optimum time for starting ART prophylaxis is 4-6 weeks after initiating TB treatment, in contrast to 2 weeks in systemic TB/HIV[17]. BCG is highly protective against TBM in children however its protective role in TBM/HIV is uncertain[14]. Research into intensified anti-tuberculous therapy using agents with better CNS penetration is ongoing.

Intervention strategies for TBM/HIV in Africa include 1) HIV Test and Treat" policy, 2) intermittent isoniazid chemoprophylaxis to decrease the overall TB/TBM burden, 3) improved TBM clinical case finding and diagnosis using Xpert and best management, 4) deferred starting ART initiation for 4-6 weeks after starting TBM treatment and 5) community-based support.

Other Opportunistic Infections

The other main CNS/OIs are TE, ABM and syphilis. In TE the diagnosis and treatment are often empirical in persons presenting with NDs suggestive of focal brain lesions coupled with a positive toxoplasmosis serology. The treatment of TE has been already outlined and steroids are only indicated where there is substantial mass effect and should be discontinued early.

Intervention strategies for TE in Africa include 1) HIV Test and Treat" policy 2) serological screening for toxoplasmosis IgG antibodies especially in low prevalence areas with primary chemoprophylaxis with trimethoprim-sulphamethoxazole in IgG positive HIV infected persons until CD4 is >200/mm^3 for at least 3 months 32, 3) early clinical diagnosis and 4) ART initiation 2 weeks after the start of TE treatment.

In ABM vaccination offers an important strategy in prevention. The polysaccharide pneumococcal vaccine showed no benefit when used in Africa and is not recommended there. However, in a recent study involving Malawian adults, 88% of whom were living with HIV and had recovered from a pneumococcal disease, the use of a pneumococcal conjugate vaccine (PCV-7) decreased recurrent episodes of pneumococcal invasive disease by 74%. The use of a combination of polysaccharide pneumococcal vaccine and PCV7 suggests a potentially strong benefit as a method of primary prevention of bacteraemia, pneumonia and meningitis in HIV infection in Africa[14,18,60]. Similarly the introduction in 2009 in West Africa of a new meningococcal conjugate serogroup A vaccine has decreased epidemics and outbreaks there by 80-85% suggesting a preventative role in HIV[14].

Intervention strategies aimed at decreasing the burden and mortality of ABM/HIV include 1) vaccination 2) early antibiotics based on clinical suspicion 3) better POC diagnostic tests and 4) informed antibiotic choice[18,60]. In cases of suspected neurosyphilis a low threshold for serological and CSF screening is recommended[99,105].Other opportunistic processes reported in HIV in Africa including PML, primary CNS lymphoma and MDR TB are presently non-curable[107].

Direct HIV infection

The main intervention strategy aimed at decreasing the

burden of HAND, DSN and VM in Africa is the recently introduced WHO HIV "Test and Treat" policy in order to prevent or decrease their occurrence in the first place. It is likely that this group of disorders will be one of the major beneficiaries of the new policy to "Test and Treat" with early or immediate ART[187,188]. The availability and selection of ART drugs with better CNS penetration remains a critical issue for the future but not just in Africa. There is also a need for longitudinal cohort studies for a better understanding of the long term social, cultural, economic and medical impact of HAND in Africa with an ageing HIV infected population.

Conclusion

This paper has reviewed the burden, clinical features, causes and outcome of the main NDs in HIV in Africa. Opportunistic infections, in particular cryptococcus and TB have been identified as major causes of mortality and direct HIV infection as the main cause of morbidity. The high rates of mortality and morbidity are in turn related to late clinical presentation, advanced immunosuppression and difficulties in recognition, diagnoses and management. It is imperative that the intervention strategies presented in this paper be adopted.

Acknowledgements

The author wishes to thank Marieke Dekker, Ines Said, Sven Hideracker, Neema Minja, Mathew Ruback, Susan Tyzack, Patrick Howlett, Fiona Cresswell, Joe Jarvis and David Lawrence for reading the manuscript.

Funding

The author has no support or funding to report.

Competing interests

The author has declared that no competing interests exist.

Abbreviations

HIV, human immunodeficiency virus; NDs, neurological disorders; CNS, central nervous system; OIs, opportunistic infections; CFR, case fatality rates; HICs, high income countries; TB, tuberculosis; CM, cryptococcal meningitis; TBM, tuberculous meningitis; ABM, acute bacterial meningitis; TE, toxoplasma encephalitis; IRIS, immune reconstitution inflammatory syndrome; NS, neurosyphilis; PCNSL, primary CNS lymphoma; HAND, HIV associated neurocognitive dysfunction; OIs, opportunistic infections; DSN, distal sensory neuropathy; VM, vacuolar myelopathy; PML, progressive multifocal leukodystrophy; ART, antiretroviral therapy; CSF, cerebrospinal fluid; LP, lumbar puncture; CrAg cryptococcal antigen; LFA, lateral flow assay; POC, point of care; LAM, lipoarabinomannan; ELISA, enzyme-linked immunosorbent assay; CT, computerized tomography; MR, mortality rate; MDR, multidrug resistant; PM, pneumococcal meningitis; GCS, Glasgow Coma Scale; VDRL, Venereal Disease Research Test; RPR, rapid plasma reagin tests; TPHA, Treponema pallidum haemagglutination assay; FTA-ABS, flocculation Treponema antibody absorption; OR, odds ratio; SSA, Sub-Saharan Africa; SA, South Africa; WHO, World Health Organization; DSN, distal sensory neuropathy; AIDP, acute inflammatory demyelinating polyneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; CMV, cytomegalovirus; ADEM, acute demyelinating encephalomyelitis; IPT, isoniazid prophylactic therapy; PCV-7, pneumococcal conjugate vaccine; Xpert, Gene Xpert TB/RIF;

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