21st BHIVA Brighton

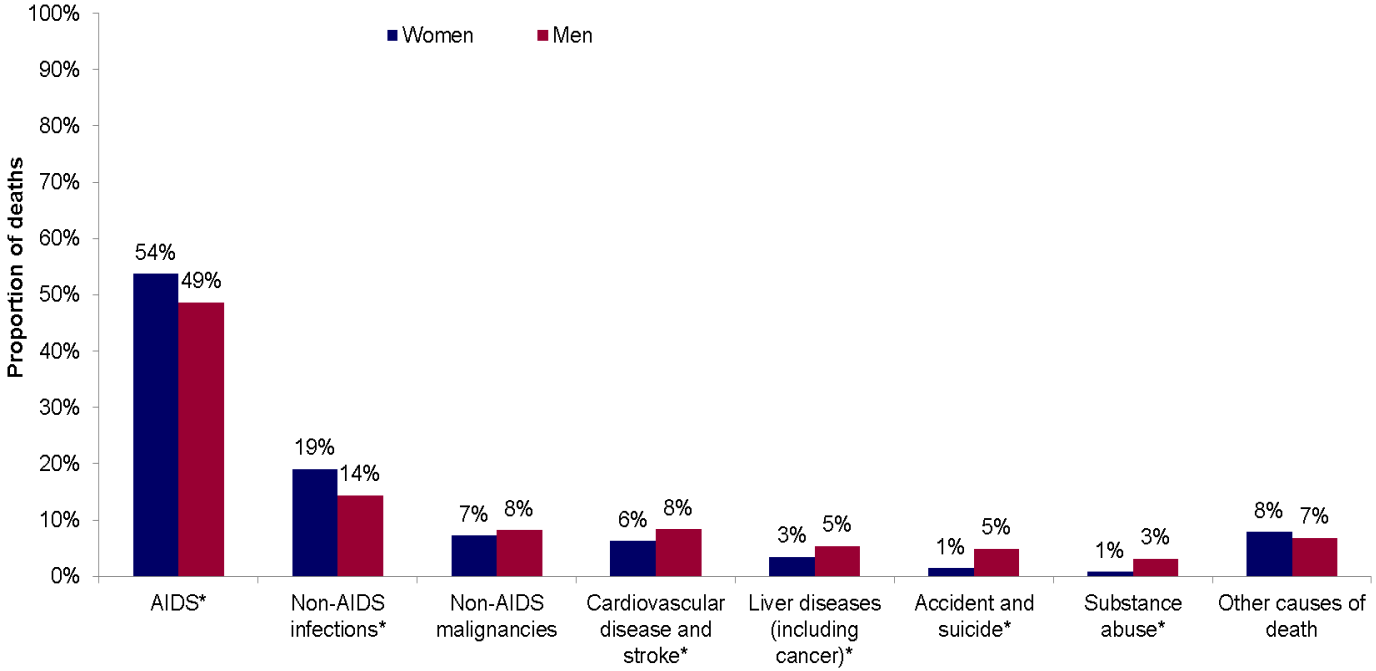
21-24th April 2015

Dr Christopher Wood

North Middlesex University Hospital

Public Health England

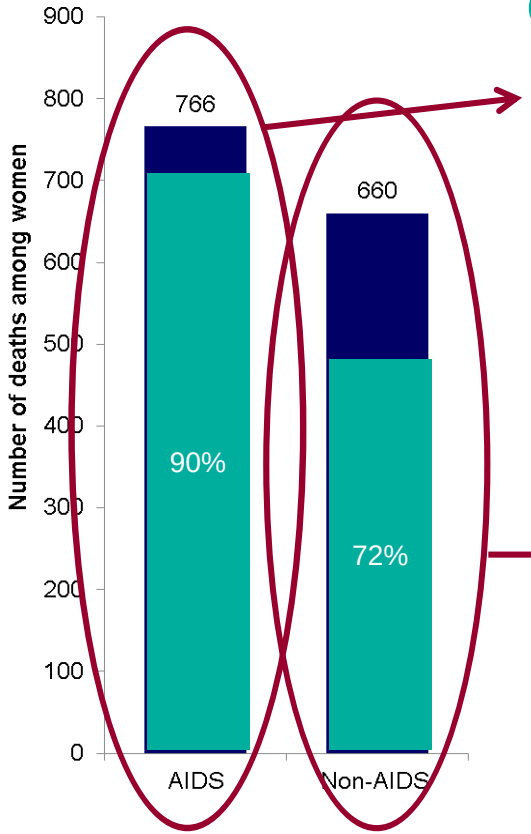
Mortality by cause of death and sex: E&W, 1997-2012



*Significant difference between men and women ($p<0.05$)

Public Health England

Mortality among women by cause of death: E&W, 1997-2012

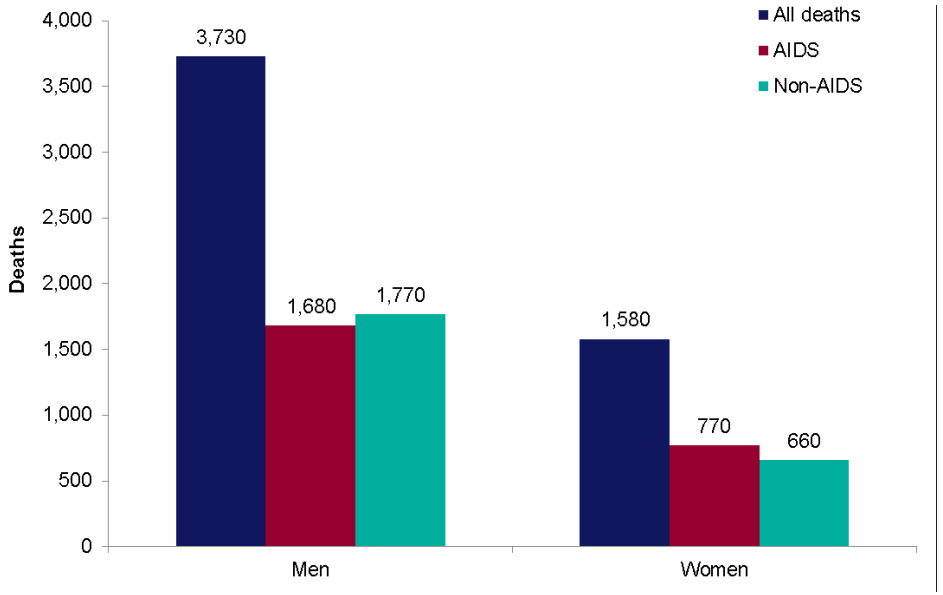


1. Pneumocystis (PCP)
2. Lymphoma
3. Tuberculosis

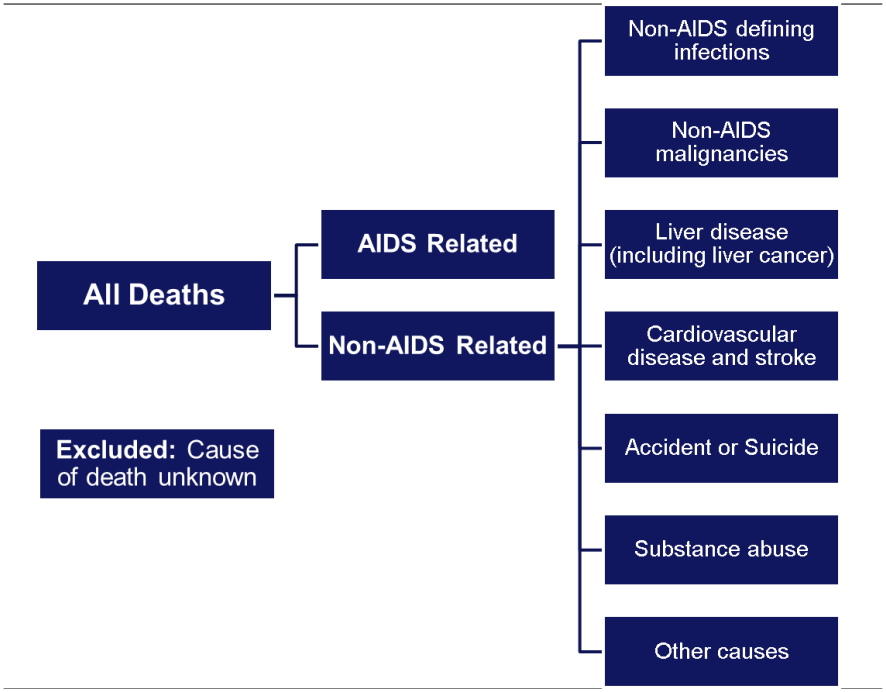
- Median age of death 39 IQR [33-46]
- 90% diagnosed late
- Median survival of 55 days [9-374]

- Median age of death 41 [34-49]
- 72% diagnosed late
- Median survival of 424 days [23-1,652]

Deaths among adults diagnosed with HIV in the era of ART: England and Wales, 1997-2012



Classification of deaths among HIV patients



Death Audit

- 2012 - London-wide death audit started
- 2013 – London - North Central Sector Network – Quarterly Morbidity and Mortality Meetings set up
- Mortimer Market/UCLH + Royal Free + North Middlesex Hospitals
- Approx 10,000 Adult patients
- Format of meetings – Present overall mortality data by unit
- Discuss selected individual cases in more detail
- Meetings are now minuted

Aims of the Mortality Meetings

- To optimise clinical care and improve patient outcomes
- Share experience and clinical practice
- Peer review
- Clinical governance
- Education
- Identify clinical issues – eg access to specialised procedures such as brain biopsies
- Develop shared protocols and local guidelines where appropriate
- Opportunity to share the lessons learned from post mortems more widely

Value of post mortems

- Patients presenting with AIDS often have wide differential diagnoses and multiple pathologies
- Aim is to improve patient outcomes and survival
- AIDS Medicine still a relatively young specialty
- Changing patterns of pathology
- Understanding has often driven by individual cases/case series
- Post mortems offer an opportunity to learn and maybe prevent further deaths and morbidity
- Can sometimes help families (and clinical staff) come to terms with a patient's death

Summary of deaths -2013 -2014

- 64 cases presented
- 53 males/ 11 females
- Average age 54 yrs (21 – 81)

- Antiretrovirals
  - Yes – 43 patients
  - No - 6 patients
  - Poorly adherent – 9 patients

CD4 & HIV Viral loads at Time of death (TOD)

CD4 counts nearest TOD

- > 500 = 19 patients
- 350-500 = 16
- 200-350 = 7
- < 200 = 19

HIV Viral Load TOD

- < 40 copies/ml = 40 patient
- 40 – 1000 = 5
- 1000 – 10,000 = 4
- 10,000 – 100,000 = 3
- > 100,000 = 4

Years post HIV Diagnosis

- < 1 year = 4 patients
- 1-5 years = 8
- 5-10 years = 22
- 10-20 years = 18
- > 20 years = 8

Causes of death

- Non-AIDS-related cancer: 12
- Sepsis & pneumonia: 11
- AIDS- related cancer: 9
- Liver disease: 7
- Not known/found at home: 6

- CVD: 4
- CNS 4
- AIDS OIs: 3
- GI: 2
- MTB: 2
- Respiratory: 2
- Suicide: 1
- Malaria: 1

Gender	Age	CD4	CD4 nadir	ARVs	V/Load	Year of HIV diagnosis	Ethnicity	Post mortem	Cause of death
Female	51	970	210	YES	< 20	1998	Black African	No	Pneumonia, Coma, CVA, BP
Male	55	640	80	YES	< 20	2000	White British	No	Cerebral mets, ?Primary Ca
Male	43	70	10	YES	< 20	2008	White - Europe	No	Liver failure, HCV/HBV + alcohol
Male	71	370	40	YES	< 20	1995	Middle-eastern	No	Oesophageal Ca + Widespread mets
Male	60	340	120	YES	< 20	2009	Black African	Yes – no change	Recurrent VTE + Sepsis
Male	67	140	50	YES	< 20	2002	Black Carib.	No	T – Cell Lymphoma
Male	68	410	?	NO	368,000	2008	White British	No	Alcoholic liver disease
Male	55	30	20	YES	< 20	2014	White - Europe	Yes – gave the diagnosis	'Intravascular' Non-Hodgkins Lymphoma
Male	67	490	40	YES	< 20	2006	White British	No	Lung fibrosis + bronchiectasis

Brief notes on the 9 cases

- 8/9 cases on suppressive therapy
- 2 Liver disease
- 2 Lymphomas (1 only diagnosed post-mortem)
- 2 Non-HIV related cancers
- 1 Catastrophic CVA
- 1 case of Idiopathic pulmonary fibrosis + aggressive bronchiectasis
- 1 Complex multi-system disorder (recurrent thromboembolic disease + sepsis)

The Pre-Mortem Virtual Post Mortem

- A useful thought experiment
- Confronted with a gravely ill deteriorating patient
- Try to imagine the Morbidity and Mortality Meeting and Post Mortem results –which tissue sample will give the result- can we access it?
- Wednesday's Case History of a case of disseminated Histoplasmosis – ITU team discussing the post mortem with the HIV team while patient in extremis but alive – patient now alive and recovered
- Compile experience of unusual cases form M&Ms and PMs
- For example, HHV8-related diseases, Lymphoma, CD8 encephalitis, Histoplasmosis and also common diseases presenting uncommonly

EQUALITY AND THE LAW

The *Equality Act 2010* states that all individuals living with HIV are protected from discrimination. People living with HIV are protected under disability discrimination as HIV is always defined as a disability under law. Protection against disability discrimination also includes discrimination in service provision. For example, a person cannot be denied a service on the basis of their disability. It also protects a person from being denied a service or being treated less favourably because they are linked or associated with a disabled person.

To deny families the right for an autopsy to be carried out on their loved one purely because he/she has lived with HIV risks claims of discrimination and is unlawful under current legislation. It cannot be argued that discrimination is necessary because of the risk of HIV transmission, as current evidence proves HIV does not pose a high risk to practitioners.

Published in 'The Biomedical Scientist', June 2013. Zoe Rutherford is a senior anatomical pathology technologist at St Thomas' Hospital, London.

"It is for that reason that as part of the 2014/15 planning guidance we enhanced our expectations around the systems and processes Trusts should have in place for mortality surveillance and monitoring, including;

- having an early warning system in place for deteriorating patients
- screening all deaths for evidence of sub-optimal care
- thorough reviews of any deaths with evidence of sub-optimal care
- a Trust wide mortality review group for a multi-disciplinary team to identify and consider themes of the reviews"

Circular from: **Mortality Assurance**
Stan Silverman, Deputy Medical Director, NHS TDA

Fatal CD8+ T-cell Encephalitis: An Observational Autopsy Study Of An Emerging Complication In HIV-1-infected African Patients On Effective Long-term Anti-retroviral Therapy

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Abstract

Background: Combination antiretroviral therapy (cART) has reduced disease complications in the brains of patients with HIV, such as HIV encephalitis, toxoplasmosis and JC virus encephalitis. It has introduced new brain syndromes, some fatal, such as the immune reconstitution inflammatory syndrome (IRIS) to HIV, JC virus, and Cryptococcus. We have identified a new group of patients on apparently successful cART, who unexpectedly deteriorated and died with characteristic brain pathology.

Methods: Review of autopsies performed in one London hospital, with pre-mortem clinical, imaging and laboratory data, and brain biopsy of one non-autopsied deceased patient. Inclusion criteria: on cART >6years, clinically stable, CD4 count >100, HIV viral load undetectable or <250, acute neurological deterioration with brain swelling, death within 1-4 weeks of onset, brain histopathology showed white matter CD8+ T-cell encephalitis.

Results: 6 patients, 4F:2M, median age 43 years, all African, were identified from 2001 to 2010. Pre-mortem they had diffuse cerebral oedema, raised intracranial pressure, and white matter hyperintensity on MRI scan, without focal lesions. Histologically, the whole neuraxis white matter showed perivascular and parenchymal CD8+ T-cell infiltration (CD3&+) and microgliosis. CD4+ T-cells, CD20+ B-cells and neuronophagia were scanty. HTLV1 antigen, NK cells, demyelination and identifiable infectious agents were absent. Pre-mortem CSF and post-mortem brain tissue PCR analysis, in two cases, showed no viruses on standard encephalitis screen. T-cell clonality analysis (I and γ genes) on paraffin-embedded brain tissue (cns) found no dominant clone. The extra-cranial tissue did not show infiltration by CD8+ T-cells. Blood CD8 counts at time of death were median 1042 (range 306-2001) with no consistent historical trend. All patients were on different cART regimes. 2 additional African patients, on similar long-term cART who had recently stopped treatment and had rising viral loads and falling CD4 counts, suffered a similar clinical syndrome and had identical pathology.

Conclusions: The pathogenesis of this acute brain pathology is not typical IRIS, HIV encephalitis, T-cell lymphoma, incidental viral encephalitis, diffuse infiltrative lymphocytosis syndrome, or known drug toxicity. It is an immune activation/dysregulation syndrome of uncertain trigger, probably with an associated abnormal blood-brain barrier. African ethnicity suggests a genetic factor.

Introduction

- Combination anti-retroviral therapy (cART) has transformed HIV disease and reduced mortality. But complications to cART affect a proportion of HIV-infected people, including drug toxicity and the immune reconstitution inflammatory syndrome (IRIS).
- Central nervous system (CNS) disease in HIV includes: HIV encephalitis, HIV-associated dementia (HAD), opportunistic infections (OIs) and lymphoma. There is also a NeuroIRIS that develops within 6 months of starting cART, which comprises a usually reversible neurological deterioration, related to OIs or HIV in the brain [ref 1]. A severe aseptic leukoencephalopathy as IRIS, without OIs, is probably the same clinical entity [ref 2]. A heterogeneous group of French cART-treated patients was reported with severe relapsing CNS deterioration during IRIS, with cerebral swelling, which responded to steroids and cART intensification, but included deaths: pathology showed a nearly-exclusive CD8+ T-cell encephalitis [ref 3]
- We describe a new fatal CD8 encephalitis syndrome in African HIV patients that develops years after starting cART, and investigate its pathogenesis.

Methods

- From autopsies on HIV-infected patients in southern England, since 2002 we noted six patients who had clinical characteristics listed in Table 1. All were African, from all parts of the continent. No Caucasians with this syndrome have been seen.
- All the available pre-mortem data was collected. All autopsy brains had full histopathology with immunohistochemical study for infection. One patient had pre-mortem CSF studies; another had full brain tissue virology studies by PCR. T-cell β and γ receptor gene rearrangement studies were performed (Biomed-2 primers) on 3 brains.
- Two further autopsies on African HIV-infected patients who had been treated with long-term cART, and died suddenly, demonstrated identical pathology. But they had stopped cART and were experiencing viral rebound.

Table 1: Patient description of the brain syndrome

On cART for >4 years; clinically stable
Blood CD4 count >200/µl
Blood HIV load <250 copies/ml or "undetectable"
Developed CNS deterioration, brain swelling and death within 1-4 weeks
No opportunistic infections
No evidence of drug toxicity
CNS tissues: CD8+ T lymphocyte-predominant inflammation mainly in white matter, with minimal demyelination

Results

- The demographic, HIV indices and cART data are shown in Table 2. The clinical and brain imaging features are summarised in Table 3. Representative pre-mortem brain imaging is shown in Fig 1 - diffuse white matter abnormality and swelling, cerebral compression, and absence of focal lesions.

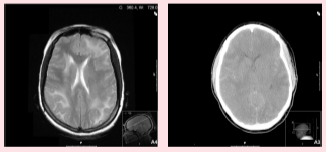
Table 2. Patient demographic and HIV characteristics

Patient	1	2	3	4	5	6
Sex/Age (yr)	F/28	M/45	F/47	M/43	F/29	M/44
Years known with HIV	>5	>7	>7	7	4	20
cART regime	Didanosine Lopinavir Ritonavir AZT	Foamprenavir Ritonavir Saquinavir	Atazanavir	Atazanavir Didanosine Ritonavir Tenofovir	Abacavir Lamivudine	Darunavir Etravirine Tenofovir
Last blood HIV viral load	<50	<50	238	<50	<50	<80
Last blood CD4 count	876	315	824	240	560	233
Last blood CD8 count	2001	306	1755	1290	940	896

Table 3. Patient clinical data

Patient	1	2	3	4	5	6
CNS disease: onset to death (days)	1	4	13	28	7	12
CNS disease	Sudden collapse at home	Confusion	7 days headache, then collapse	3 weeks headache	5 days vomiting and headache	Headache and confusion. Died following brain biopsy
CNS imaging	Nd	MR & CT: White matter lesions	CT: swelling and coning	CT: diffuse oedema, coning MR: diffuse white matter lesions	CT: diffuse swelling	CT: diffuse swelling

Figure 1: A. MRI scan. B. CT scan. White matter changes and cerebral swelling



- Pathology: all patients had diffuse cerebral swelling without focal lesions (Fig 2). Histopathologically, there was an encephalitis, predominant in the white matter throughout the neuraxis. This was a perivascular cuffing and parenchymal infiltration by non-atypical CD3+ T-cells, microgliosis, variable astrocytosis, minimal demyelination, and absence of neuronophagia in the grey matter. The T-cells were overwhelmingly CD8+ phenotype, CD38+ (ie activated), CD56 negative (not NK cells), and with only scanty CD4+ T-cells included. This is illustrated in Figs 3-6.
- Extra-cerebral organs did not show any CD8+ T-cell infiltrate (lung, spleen bone marrow).

Figure 2: Brain at autopsy, showing flattened gyri - cerebral swelling

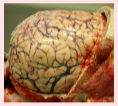


Figure 3: A & B. White matter encephalitis - perivascular and diffuse lymphocytic infiltration

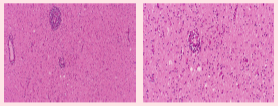


Figure 4: Phenotype = CD8+ T-cell lymphocyte infiltrationinfiltration

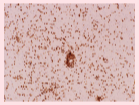


Figure 5: CD68+ microgliosis in white matter

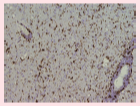


Figure 6: CD38+ CD8+ T-cells, indicating lymphocyte activation

- Studies of the aetiology of the CD8+ encephalitis are indicated in Table 4. In the cases so studied, there was no evidence for a banal community-acquired encephalitis, or an HIV-related viral encephalitis. One patient had HIV env by PCR on brain tissue. None of the three cases studied for T-cell receptor clonality showed a single dominant clone: the mixture of patterns included oligoclonal to biclonal peaks in polyclonal backgrounds (Fig 7).
- Pre-mortem blood CD8+ T-cell counts are shown in Fig 8 - there is no consistent trend.
- The demographic, HIV and clinical data for the second group of patients (n=2), who were off cART at the time of collapse, are shown in Table 5. The CNS pathology was similar to the main group; no infections were identified in the brains; in patient #2, T-cell receptor studies on brain tissue found a double clone on a polyclonal background.

Table 4. Autopsy and pre-mortem laboratory data

Patient	1	2	3	4	5	6
Pre-mortem CSF virology by PCR	nd	nd	nd	Negative for CMV, JC, HSV, VZV, EBV, enterovirus	nd	Negative for CMV, JC, HSV, VZV, EBV, enterovirus
Autopsy brain virology by PCR	nd	nd	nd	nd	Positive for EBV, HIV env. Negative for HSV, VZV, adenovirus, BJ9, JC, HHV6, HHV8, West Nile, enterovirus	nd
Autopsy brain infection screen by immunohistochemistry for : HIVp24, HSV, CMV, JC virus, toxoplasma,	neg	neg	neg	neg	neg	neg

Figure 7: T-cell receptor-beta PCR study. Polyclonal with a dominant clone

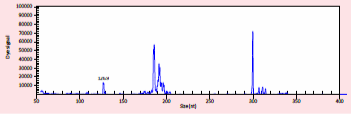


Figure 8: Serial blood CD8+ T-cell counts up to collapse and death

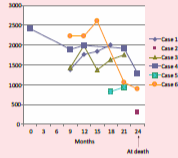


Table 5. Two other patients, off cART, but with similar clinical pathology

Patient	1	2
Sex/Age (yr)	F/46	F/37
Years known with HIV	>10	5
cART regime	Abacavir Ritonavir Saquinavir Tenofovir *Stopped 4 months before final illness*	Emtricitabine Ritonavir Saquinavir Tenofovir *Stopped >1 month before final illness*
Last blood HIV viral load	868,000	8,759
Last blood CD4 count	170	353
Last blood CD8 count	960	880

Discussion

- The six patients in the main study group were managing normal life on cART, with good HIV control indices. Unexpectedly they suffered rapid decline in brain function with headache, vomiting, and confusion. Where done, CNS imaging showed diffuse cerebral swelling from which they died. The pathology was an almost pure, activated CD8+ T-cell encephalitis, with predominant white matter involvement.
- Why has this developed? It is not T-cell lymphoma, drug reaction, diffuse infiltrative lymphocytosis syndrome (DILS) nor due to exceptionally high blood CD8 lymphocyte counts. Most likely is an immune activation syndrome, with or without a blood-brain barrier abnormality. But there is no clinical indication of an event that might precipitate such processes, and an underlying antigen that the T-cells are reacting to is not known
- A very late IRIS phenomenon (years rather than months after starting cART) is possible, but unlike other reports of earlier CNS IRIS reaction to HIV per se, HIVp24 immunostaining did not demonstrate any residual virus, nor were there multi-nucleate giant cells on histopathology [ref 4].
- Finally, they were all African adults - from different parts of the continent. This ethnic restriction may indicate a host-response factor in the pathogenesis.

Conclusions

- A small proportion of African HIV+ve patients in the UK, stable on long-term combination anti-retroviral therapy, unexpectedly suffer rapid cerebral deterioration and die. The pathology is a CD8+ T-cell encephalitis, with no identifiable infectious causation. Immune activation and late IRIS are possible mechanisms.
- Further follow-up is required to identify more patients, with more intensive immunological work-up. The African ethnicity needs confirmation through more case observation.
- **It is possible that this is fore-runner of other organ severe dysfunctions that will unexpectedly emerge over time with large numbers of patients on cART. This study reinforces the need for detailed autopsy investigations of death in HIV patients.**

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Fatal CD8$^+$ T Cell Encephalitis: An Observational Autopsy Study of an Emerging Complication in HIV-1-infected African Patients on Effective Long-term ART

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[1]King`s Coll London Sch of Med, UK; [2]Univ of Malaysia, Kuala Lumpur; and [3]Guy`s and St Thomas` Hosp, London, UK

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Results: From 2002 to 2010, we identified 6 patients: 4 female : 2 male, median age 43 years, all African. Pre-mortem they had diffuse cerebral edema, raised intracranial pressure, and white matter hyper-intensity on MRI scan, without focal lesions. Histologically, the whole neuraxis white matter showed perivascular and parenchymal CD8$^+$ T cell infiltration (CD38$^+$) and microgliosis. CD4$^+$ T cells, CD20$^+$ B cells, and neuronophagia were scant; HIVp24 antigen, natural killer (NK) cells, demyelination and identifiable infectious agents were absent. Pre-mortem cerebrospinal fluid (CSF) and post-mortem brain tissue PCR analysis, in 2 cases, showed no viruses on standard encephalitis screen. T cell clonality analysis (β and γ gene) on paraffin to embedded brain tissue (n = 4) found no dominant clone. The extra-cranial tissues did not show infiltration by CD8$^+$ T cells. Blood CD8 counts at time of death were median 1065 (range 306 to 2001) with no consistent historical trend. All patients were on different cART regimes; 2 additional African patients, on similar long-term cART who had recently stopped treatment and had rising viral loads and falling CD4 counts, suffered a similar clinical syndrome and had identical pathology.

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CASE REPORT

**Aurélie Vendrely · Boris Bienvenu · Jacques Gasnault
Jean Baptiste Thiebault · Dominique Salmon
Françoise Gray**

Fulminant inflammatory leukoencephalopathy associated with HAART-induced immune restoration in AIDS-related progressive multifocal leukoencephalopathy

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Abstract HAART-induced immune restoration is beneficial for patients with AIDS-related progressive multifocal leukoencephalopathy (PML). However, in rare instances, an immune-reconstitution inflammatory syndrome (IRIS) may cause paradoxical clinical deterioration. We report the neuropathological study of an AIDS perivascular infiltration by T lymphocytes, and (2) acute perivenous leukoencephalitis devoid of JC virus. Most lymphocytes were $CD8^+$ lymphocytes; $CD4^+$ lymphocytes were virtually absent. Two pathological reactions were associated with the paradoxical clinical deterioration related to dysregulation of the immune

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