

HIV-2 in the United Kingdom – the North-East London cohort

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Background

HIV-2 infection remains incompletely understood and is often considered "less pathogenic" than HIV-1. HIV-2 is characterised by lower transmissibility; plasma viral loads and average levels of immune activation are consistently lower in HIV-2. Although proviral DNA loads are very similar between the two infections, replication rates for HIV-2 are about 100-fold lower than those for HIV-1. Although HIV-2 is associated with slower or reduced likelihood of progression to AIDS, the clinical consequences of progression are the same as for HIV-1. Cohort studies in West Africa suggest that a much smaller proportion of HIV-2 infected individuals will experience disease progression and require antiretroviral therapy compared to HIV-1. In a community cohort in Guinea Bissau, a substantial proportion of HIV-2 infected subjects had stable plasma viral load over 18 years of follow-up; those with an undetectable HIV-2 load (37%) at study entry had a normal survival¹. However, once disease progression has occurred, the clinical manifestations and severity are very similar although progression in HIV-2 occurs at higher CD4 counts. HIV-1 and HIV-2 dual infection is also well recognised.

Clinical management of HIV-2 remains challenging. HIV-2 has the same basic gene arrangement and intracellular replication pathways as HIV-1 but differences between genome sequences mean that many of the currently available antiretrovirals, which were all developed and tested against HIV-1, are ineffective or less effective. HIV-2 has intrinsic resistance to non-nucleoside reverse transcriptase and fusion inhibitors, diminished sensitivity to most of the protease inhibitors and demonstrates rapid emergence of broad-class nucleoside reverse transcriptase inhibitor resistance. Viral load quantification and genotypic antiretroviral resistance testing for HIV-2 are of limited availability; genotypic resistance data are scanty and less well characterised compared to HIV-1. To date, there have been no randomised controlled treatment trials for HIV-2 so observational cohort data remain crucial in enhancing understanding.

HIV-2 is most prevalent in West Africa, where it is endemic. Smaller cohorts are found in Asia, predominantly India, and European countries with links to West Africa, such as Portugal and France. Robust epidemiological data for HIV-2 are lacking but recent reports suggest that the prevalence is declining in some African countries³ but may be increasing in India⁴. By the end of December 2012, a cumulative total of 138 diagnoses of HIV-2 mono-infection had been reported in the UK. A further 45 diagnoses of HIV-1 and HIV-2 dual infections were also reported⁵. North-East London has an ethnically and virologically diverse HIV population with relatively high and increasing numbers of HIV-2 infected patients. There are specialist HIV-2 clinical services and the local Virology department can quantify HIV-2 load. We therefore characterised the North-East London HIV-2 population in order to establish a prospective cohort.

Methods

HIV-2 infected individuals were identified from the Virology database. Clinical details were collected from laboratory records and clinical notes. Undetectable HIV-2 loads were defined as <2.4 log copies/ml, although the local laboratory also reports 0 copies/ml.

Results

To date, 48 HIV-2 mono-infected individuals have been identified. These patients are receiving clinical care in North-East London; regular hospitals include Barts and the London, Homerton, Newham, Whipps Cross and Barking hospitals. The cohort is predominantly female (30 patients, 63%) with age range 18 to 77 years (Table 1). Most patients are African; Guinea-Bissau is the most common country of origin with Ghana, Cote d'Ivoire, Burkino Faso, Nigeria and Portugal also represented. Although the range of CD4 counts was wide, the median was low at 342 cells/μl (Table 1). Seventeen patients (35%) had never had a detectable HIV-2 load. However, within those with detectable loads there was a surprisingly large range with some unusually high results. Most patients are on antiretroviral therapy with some requiring second or third-line regimens following the development of resistance. First line antiretroviral regimens incorporated lopinavir / ritonavir or darunavir / ritonavir with tenofovir / FTC or abacavir / 3TC. Second and subsequent regimens included other agents such as raltegravir, maraviroc, etravirine and foscarnet.

Table 1. Summary of results

	Minimum	Maximum	Median
Age	18	77	46 years
CD4 count	5	1287	342 cells/μl
HIV-2 load (all results)	0	2300000	0 c/ml
HIV-2 load (>2.4 lg c/ml)	240	2300000	1800 c/ml

Conclusions

This is an interim analysis of the largest cohort of HIV-2 infected individuals reported in the UK. It is a commonly held view that patients infected with HIV-2 experience disease progression uniformly at a slower rate compared to HIV-1, yet more recent studies have demonstrated that this is an oversimplification of the natural history of HIV-2 infection. Outcomes in HIV-2 infection therefore, appear to be dichotomous, with some individuals remaining asymptomatic "elite controllers", whereas others experience CD4 count decline or clinical progression and require antiretroviral therapy. Although undetectable HIV-2 load predicts non-progression, some patients in the cohort had declining CD4 counts in spite of persistently undetectable viral loads and subsequently commenced therapy. The finding of a low median CD4 count is of concern as disease progression in HIV-2 tends to occur at higher CD4 counts and treatment initiation is recommended at higher CD4 counts than for HIV-1. In addition, there is a larger proportion of patients in this cohort who required antiretroviral therapy than would be predicted from earlier data. This may reflect under-diagnosis of HIV-2 in the UK whereby asymptomatic individuals with non-progressive disease remain unidentified. Alternatively, the UK cohort, which includes a diverse range of individuals from different countries, may be different to the more homogeneous cohorts previously studied in endemic areas. Patients in the cohort were treated in line with current BHIVA guidelines⁶ but some individuals have received less conventional therapy as a response to treatment failure. It is not clear why females are over-represented in this cohort but it may be due to higher rates of routine screening in ante-natal and fertility services. The age range, with a predominance of individuals over 40 years, corresponds with the apparent peak in HIV-2 prevalence in 1970-1980 with its epicentre in Guinea-Bissau. Although it is thought that the overall incidence and prevalence of HIV-2 is declining, our cohort continues to increase. This, and the observation of infection in younger individuals, concurs with the recent demonstration of on-going transmission of HIV-2 from new cases in Africa⁷. All cases in this cohort to date are mono-infected with HIV-2. Recently published data suggests that in dually infected patients who acquire HIV-2 infection first, HIV-1 infection is less pathogenic⁸. We therefore hope to identify individuals with dual HIV-1 and HIV-2 infection and surveillance to this end is continuing.

Future work

Recruitment to this cohort is on-going and it is hoped that this will facilitate further studies. Planned future work includes:

- A more detailed clinical study – ethical permission is in place for a prospective HIV-2 database (ACHIEV₂E UK).
- A bio bank for HIV-2 blood samples.
- Incorporation of UK data into the international consortium of HIV-2 cohorts (ACHIEV₂E: A Collaboration on HIV-2 Infection).
- Laboratory studies to determine viral subtype, HLA type and T-cell responses (in collaboration with Prof Rowland-Jones, Oxford).
- Recruitment of UK HIV-2 patients into forthcoming African/French naive treatment trial (in collaboration with Dr Chadwick, Middlesbrough).
- Patients from outside North-East London are welcome to join the cohort if they are interested in participating in studies.

Summary

- This is the largest UK cohort of HIV-2 infected patients
- At least one third of HIV-2 infected patients in the UK are receiving clinical care in North-East London
- HIV-2 infection may be under-diagnosed in asymptomatic patients in the UK, particularly in males
- Disease progression occurs even when HIV-2 loads are persistently undetectable
- There was a surprisingly high number of patients requiring antiretrovirals and unusually high HIV-2 loads
- New cases continue to be identified, including younger individuals, suggesting that HIV-2 transmission is on-going despite reported declines in prevalence in endemic areas

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References

1. Peppercorn SJ et al. *J Virol* 2003;74:1554-1557
2. van der Laan MF et al. *Retrovirology* 2010;7:46. doi:10.1186/1742-4690-7-46
3. Nyamwaya S et al. *Rev Med Virol* 2013. doi: 10.1002/rmv.1739
4. Chiano M et al. *Indian J Med Res* 2010;132: 1605-9
5. Public Health England www.hpa.gov.uk/web/HPAwebContent/HPAweb_content_12437/04_04_13. Accessed March 2013
6. Gillies Y et al. *J HIV Medicine* 2013;11:611-619
7. de Siqueira T et al. *AIDS* 2013;27:1253-4
8. Esteban J et al. *NEJM* 2012;367:224-232.