High rate of lymphoma among a UK cohort of adolescents with vertically-acquired HIV-1 infection transitioning to adult care in the era of antiretroviral therapy

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LETTER

HIV-1-infected (HIV+) children and adolescents are at significant risk of non-Hodgkin lymphoma (NHL), most typically diffuse large B-cell (DLBC), high-grade plasmablastic, or Burkitt variants [1, 2]. The risk of developing lymphoma in HIV-infected individuals appears directly related to nadir CD4 count [3-5] and to ongoing HIV viraemia. Consistent virological suppression with antiretroviral therapy (ART) is, by contrast, highly protective [5, 6]. During the pre- and early-ART era, profound immunosuppression and detectable viraemia were common occurrences in HIV+ children, and antiretroviral options were limited by significant toxicities, unpalatable formulations and poor virological durability [7,

8]. Early ART regimens were frequently unlicensed, therefore underpinned by low-quality clinical evidence, in paediatric populations. As a result, inadvertent under-dosing was observed in up to 62% of children in the United Kingdom (UK) and Ireland between 1997 and 2005 [9]. Virological failure and subsequent accumulation of resistance-associated mutations are therefore common in this population at the point of transition to adult services [10]. Thus, despite the advantages of modern ART regimens and multi-disciplinary care in resource-rich countries, many adolescents with vertically-acquired HIV will bear the burden of chronic, sub-optimal virological control in childhood alongside the significant challenges of maintaining consistent treatment concordance (and virological suppression) during adolescence [11].

We conducted a retrospective review of all new lymphoma diagnoses in a cohort of adolescents transitioning from paediatric to an adult HIV service between January 2007 and January 2015. Our service, based at Mortimer Market Centre in Central London, provides free HIV-care for around 4500 patients aged over 15 years from all areas of the UK including a dedicated adolescent clinic to support transition between paediatric and adult HIV services.

Over the eight-year period, 147 individuals transitioned their HIV care to our service from paediatric services. Among these, we identified five new cases of lymphoma. The total observation time was 1176 person-years. Three patients were male. The median age at HIV-1 diagnosis was 6 years (range 0-17 years) and 19 yrs (range 18-23) at lymphoma diagnosis, respectively. Median (range) CD4 counts at lymphoma diagnosis and pre-ART nadir were 340 (180 -550) and

157 (90-220) cells/μL, respectively. All five patients were known to have a history of intermittent or complete non-adherence in the five years prior to transitioning care, although three were known to have an undetectable HIV-1 VL at lymphoma diagnosis. Full, historical HIV-1 VL data were available for four patients (Figure 1). The mean time from initial engagement with HIV services to lymphoma diagnosis was 114 months (range 30-199). Mean estimated cumulative exposure to detectable HIV-1 viraemia (obtained *via* historical VL data, clinic attendance notes and electronic prescriptions for ART) was 170.5 months (range 118-234). Dual and triple-class ART resistance was present in one and two patients, respectively; all patients had durable therapeutic options available to them at lymphoma diagnosis.

Four patients had DLBC, the fifth had marginal zone lymphoma which transformed during chemotherapy to a high-grade DLBC. All five patients had disseminated disease (Ann Arbor stage III or IV) at initial presentation: B symptoms were present in four. Immunohistochemistry showed four were positive for Epstein-Barr virus (EBV)-encoded small RNAs (EBERs). Quantitative assessment of blood/tumour EBV load is not part of routine clinical assessment at diagnosis of HIV-associated lymphoma in UK [12]. Likewise, markers of immune activation, such as tumour necrosis factor-α, β-microglobulin, and interleukin-10, are not assayed routinely in HIV-infected patients in our treatment centre.

The lymphoma incidence-rate (IR) for these five patients over the eight-year period is 0.425/100 person-years [95% Confidence Interval (CI) =0.424-0.426].

This figure is similar to rates previously reported in HIV-infected children and infants during the pre-ART era [IR =0.386/100 person-years, 95% CI =0.386-0.387: IR ratio (IRR) =1.10; 95% CI =0.98-1.24, p =0.1] [1]. Moreover, the IR of NHL seen in this cohort signficantly exceeds the average rate observed between 2008-2010 among 15-24 year-olds in the UK general population (IR =6.4/100,000 person-years, 95% CI =4.93-8.17: IRR =25.9; 95% CI =8.31-61.7, p <0.0001) [12].

It is established that the risk of developing HIV-associated lymphoma at any given time-point directly relates to the magnitude of immunosuppression. More specifically, data from several cohort studies suggest that current (rather than nadir) CD4 count and HIV-1 viral load are the most significant parameters in determining lymphoma-risk in multivariate analysis [6, 14, 15]. It is also suggested that cumulative exposure to detectable HIV-1 viraemia increases lymphoma-risk in a dose-dependent fashion [16]. These observations are borne out in the wider epidemiology, such that the observed incidence of HIV-associated NHL has fallen by up to 90% during the ART era [15, 17]. Nevertheless, the incidence of NHL observed in our cohort is in stark excess of that observed in both the age-matched UK general population and in a cohort of HIV-infected adults with undetectable viraemia on ART – a reasonable model, we suggest, for the wider UK population in specialist HIV care [18]. Likewise, despite the universal availability of effective ART, the observed rate of lymphoma in our cohort was comparable to that seen in UK children with AIDS in the pre-ART era. All of the lymphoma cases observed in our cohort occurred in adolescents with a prolonged history of poor ART concordance and detectable HIV-1 viraemia

during childhood and early adolescence. While the small sample size limits firm conclusions, we hypothesise that this represents a perfect scenario for the development of lymphoma. Uncontrolled HIV-1 infection engenders a significant pro-inflammatory state, with high levels of immune activation occurring synchronously with immunosuppression [19, 20]. B-lymphocyte hyperstimulation, as indicated by polyclonal hypergammaglobulinaemia, is a key feature [21]. This phenomenon is amplified in the HIV-infected child as the nascent immune system fails to co-ordinate an efficient response to HIV-1 with higher viraemic set points and a faster progression to AIDS compared to those infected during later life [22-24]. Therefore, HIV-infected children bear a particularly heavy burden of immunosuppression, resulting in impaired surveillance and cytotoxic control of malignant cells and oncogenic viruses.

EBV is the most common oncogenic virus involved in the pathogenesis of HIV-associated lymphoma, with plasma EBV VL correlating directly with risk [25]. Higher plasma EBV DNA loads have been observed in children with uncontrolled HIV-1 infection compared with age-matched counterparts taking effective ART [26, 27]. Moreover, co-infection with EBV types 1 and 2 appears more common in children with uncontrolled HIV-1, which may further increase the risk of lymphomagenesis [28]. We therefore postulate that the potent theoretical interactions between uncontrolled HIV-1 infection, oncogenic viruses and an immature immune system serve to greatly increase lymphoma-risk in HIV-infected adolescents with vertically-acquired infection over that seen in those infected *via* other routes. However, we acknowledge that the lack of

supplementary data concerning quantitative EBV exposure and immune activation in our patients may limit firm conclusions in this regard.

With increased survival of children with vertically-acquired HIV infection, the numbers of adolescents transitioning from pediatric to adult HIV services in the UK has significantly increased in recent years, and although numerically a small group, these patients require considerable specialist care. This is important not only to support ART concordance at a time of immense psychosocial challenge, but also to monitor for nascent complications associated with past or present immunosuppression. Our findings suggest that clinicians caring for adolescents with vertically-acquired HIV infection should maintain a high level of vigilance for symptoms suggestive of lymphoma and should have a low threshold for diagnostic evaluation, even in the presence of undetectable viraemia on ART.

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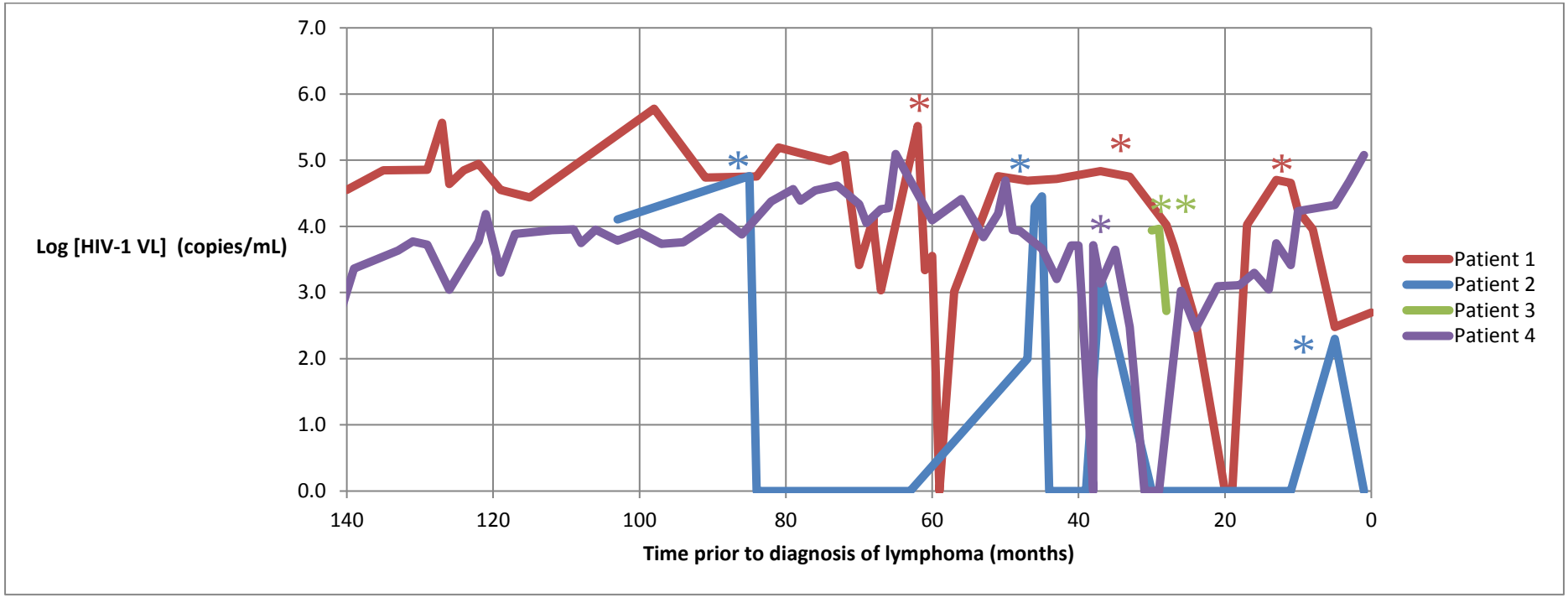

Figure 1: **HIV-1 viraemia in the time period prior to diagnosis of lymphoma**

Key: Historical viral load data was available for four cases. The remaining patient was known to have an undetectable HIV-1 viral load at the time of lymphoma diagnosis. *: Antiretroviral therapy (ART) (re)commenced. **: This individual was diagnosed with HIV-1 infection, and was commenced on ART immediately. He defaulted from care after 1 month, stopping ART and represented 24 months later with lymphoma-related symptoms and an HIV-1 VL of 3.4 log copies/ml.