HIV as a chronic disease

Tabitha W Mahungu, Alison J Rodger and Margaret A Johnson

ABSTRACT – The 25th anniversary of the first reports of a catastrophic illness later classified as AIDS and the 10th anniversary of highly active antiretroviral therapy (HAART) both occurred in 2006. Where available, HAART has revolutionised the treatment of HIV. This success has brought challenges – the unknown long-term history of treated HIV infection, the development of toxicity and drug resistance, and the ageing HIV-infected patient. Despite these advances, the number of HIV cases continues to rise in vulnerable populations in under-resourced areas of the world. These anniversaries allow us to appreciate the milestones achieved thus far and those yet to be achieved. Only a collaborative global effort will stop the epidemic from overwhelming efforts to contain it.

KEY WORDS: chronic disease, HIV, highly active antiretroviral therapy

Introduction

It is over 25 years since the first case of what was then a devastating illness was identified as AIDS.[1] By 2007, the Joint United Nations Programme on HIV/AIDS reported that an estimated 33.3 million individuals were living with HIV worldwide.[2] In 2007, the Health Protection Agency (HPA) revealed that despite high numbers of new diagnoses in the UK, the rate of AIDS events and deaths had declined significantly.[3]

During the HIV pandemic, the Centers for Disease Control (CDC) redefined AIDS three times, moving from a system that relied solely on the presence of 'AIDS-defining' illnesses (ADI) to one that supplements this with CD4 values and the patient's symptomatology. The spectrum of progression of HIV infection has also been appreciated – some patients rapidly progress to clinical disease while the poorly understood long-term non-progressors do not. In between these two poles lies the majority of the infected population.[4,5] There is no doubt that where available, the use of highly active antiretroviral therapy (HAART) has significantly transformed the face of HIV-1 infection from a terminal illness to a chronic manageable disease. A Danish study recently estimated that a 25-year-old HIV-positive man without hepatitis C co-infection has a remaining lifetime of more than 35 years.[6]

Challenges, however, remain. The natural history of treated HIV infection and the long-term efficacy of antiretroviral agents remain unknown. The entire spectrum of short and long-term HAART-related side effects also needs to be understood. In addition, the rising prevalence and the improved life expectancy of HIV infection creates a need for the restructuring of care pathways along chronic disease models. Finally, and most importantly, greater impetus needs to be given to ensuring that HIV-infected patients have access to treatment and care on a global scale.

The impact of HAART on the natural history of HIV infection

HAART normally consists of three drugs – a backbone of two nucleoside reverse transcriptase inhibitors (NRTI) co-administered with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). The course of HIV infection in the absence of HAART is well described. HIV-infected individuals experience immunological suppression as their immune system succumbs to ongoing viral replication – the exception being the atypical long-term non-progressors. The time to clinical (ie the development of an ADI) or numerical (ie a CD4 count below 200 cells/mm^3) AIDS in an individual is a function of the relationship between the virus and individual host immune responses.[7] HAART suppresses viral replication subsequently allowing reconstitution of an individual's CD4 population. However, due to the persistence of viral reservoirs, HAART does not eradicate HIV.[8] There are little data on the efficacy of HAART in maintaining viral suppression in the long term. A four-year study in treatment-naive patients showed that if adherence was maintained once viral suppression was achieved, the rate of virological failure decreased with increasing years on therapy.[9] Another seven-year study on the efficacy of lopinavir-containing HAART in treatment-naive subjects showed sustained virological responses of 59% and 95% in patients by intent to treat and on-treatment analyses respectively.[10] These results are encouraging but can similar durability be expected from the more often prescribed fragile NNRTI-based regimens? And what happens after seven years? We can remain optimistic as the increasing armamentarium of antiretroviral agents means patients have a vast choice of options should they fail or not tolerate their current regimens.

Tabitha W Mahungu
BMedSci(Hons) DTMH MRCP, Clinical Research Fellow in HIV Medicine

Alison J Rodger
MRCP FFPH MSc DipHIV MD, Senior Lecturer and Honorary Consultant in Infectious Diseases

Margaret A Johnson
MD FRCP, Professor of HIV Medicine

Department of HIV Medicine, Royal Free NHS Trust, London

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Side effects of antiretroviral therapy

Nucleoside reverse transcriptase inhibitors

The success of HAART is coupled with concerns about drug toxicity.[11] The first antiretroviral agent zidovudine (AZT) was approved by the Food and Drug Administration in 1987. AZT was followed in quick succession by ddC (zalcitabine), ddI (didanosine) and d4T (stavudine) heralding the era of dual therapy. Despite reduced mortality rates, adequate virological suppression was not achieved as a result of the emergence of resistant virus. Unfortunately, many patients exposed to first-generation NRTIs have subsequently developed metabolic side effects not apparent at the time of licensing that have often persisted despite withdrawal of the offending drug. The NRTIs described above can cause peripheral lipoatrophy, non-alcoholic steatohepatitis and the potentially fatal lactic acidosis. In addition AZT is associated with anaemia and myopathy, ddI can cause pancreatitis and d4T is associated with peripheral neuropathy.

In resource-rich countries, first-generation NRTIs have been replaced by better tolerated, less toxic NRTIs such as tenofovir and abacavir. However, these drugs also have their own toxicities. Tenofovir can be associated with renal tubular dysfunction and there are concerns about reduced bone mineral density. Abacavir is known to cause a hypersensitivity reaction (HSR) affecting up to 8% of Caucasian patients within six weeks of initiating of treatment.[11] This can be potentially fatal if the drug is continued or restarted. The features of the HSR are vague but include varying combinations of rash, constitutional symptoms, gastrointestinal and respiratory symptoms worsening with each subsequent dose. The strongest predictor of abacavir HSR is the presence of human leucocyte antigen (HLA) subtype B*5701. Prospective screening of patients for this HLA subtype significantly reduces the rate of abacavir HSR.[12] However, this must not substitute clinical vigilance as there have been rare occasions in clinical practice where HLA-B*5701 negative patients (but with positive skin patch tests) have been observed to present with symptoms suggestive of HSR.[13]

Non-nucleoside reverse transcriptase inhibitor

Efavirenz can cause neuropsychiatric side effects as well as dyslipidaemia and lipoatrophy as reported in the AIDS Clinical Trials Group (ACTG) 5142 trial.[14] Nevirapine is associated with an immune-mediated HSR usually presenting as a macular erythematous rash or transaminitis. In very severe cases, patients can develop Stevens–Johnson syndrome with or without fulminant hepatitis.

Protease inhibitors

Protease inhibitors (PIs) are normally co-administered with a small dose of ritonavir (a PI in its own right at higher doses) to improve the pharmacokinetic properties of the co-administered PI.[15] The resulting increased drug exposure improves virological and immunological outcomes. Unfortunately, the ritonavir boosting also results in gastrointestinal intolerance, dyslipidaemia, the accumulation of visceral fat and increased insulin resistance. The newer PIs such as tipranavir have a black box warning regarding hepatotoxicity.

New antiretrovirals

Newer agents such as fusion, CCR5 and integrase inhibitors appear to have good side effect profiles on preliminary data. Only time will tell what the long-term risks of exposure to these drugs are.

Cardiovascular risk

Initial reports from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study showed that use of HAART was associated with a 26% relative increase in the rate of myocardial infarction (MI) per year of exposure.[16] A sub-analysis of the same cohort identified that PIs had a 16% increased risk of MI for each year of exposure.[17] However, the increased risk associated with PIs was not as high as the risk of smoking in the same cohort highlighting the need to focus on smoking cessation in these populations.

Drug resistance

The HIV virus is unforgiving and suboptimal compliance facilitates the emergence of drug resistance and subsequent treatment failure. Boosted PIs tend to be more forgiving than first generation NNRTIs,[18] the latter requiring just one mutation in the hosts HIV genotype to render the entire drug class obsolete. Of increasing concern is transmitted drug resistance (TDR) in resource-rich countries where suboptimal pre-HAART regimens coupled with poor adherence resulted in the accumulation of drug resistant virus in treatment experienced patients who go on to transmit these viruses.[19] The rates of TDR in resource-poor nations are still very low but may increase as treatment scale up continues. As transmitted mutations may become undetectable over time, local guidelines stipulate that patients are genotyped as close to diagnosis as possible in order to maximise the chances of detecting TDR.[20]

HIV infection and ageing

There has been a notable increase in the number of HIV-positive patients over the age of 50. This in part is as a result of infected individuals living longer but also new infections being diagnosed in older patients. In the USA, by the end of 2000, over 60,000 HIV-infected individuals were estimated to be over the age of 50.[21] Cohort analyses of HIV progression have shown that age is a risk factor for poorer treatment outcomes. This may be explained by delayed, poorer immune responses associated with age-related thymus involution.[22] However, once on HAART older patients show a marked reduction of mortality rates.[23] We must therefore ensure that our older patients are not receiving delayed

therapy or being diagnosed too late. Problems related to polypharmacy and drug toxicity can be expected in older patients. The Liverpool HIV Pharmacology Group (LHPG) website (www.hiv-druginteractions.org) provides comprehensive information and advice on drug-drug interactions.

Treating HIV as a chronic disease

Implementing a chronic disease care model

The British HIV Association (BHIVA) in conjunction with the Royal College of Physicians, British Association for Sexual Health and HIV Infection and the British Infection Society recently published *Standards for HIV clinical care*. This report recognises the fact that HIV-infected patients are best managed within chronic disease models and makes recommendations on the level of service provision expected from centres providing HIV care and the level of professional expertise required from healthcare providers.

Optimising treatment response

The question of when to start treatment in established HIV infection is yet to be answered by a randomised control trial (RCT). The decision rests on a balance between the risk of disease progression and the development of toxicity. The CASCADE cohort was used to characterise the risk of progression to AIDS in the absence of treatment over a six-month period based on CD4 count and HIV viral load (VL).[24] It showed that the risk was highest in individuals with CD4 counts less than 200 cells/mm^3 and HIV VL of greater than 100,000 copies/ml compared to the risk in individuals with CD4 counts of over 350 cells/mm^3 and HIV VL of less than 10,000 copies/ml (22.4% *v* 0.2% respectively). It also showed that in older patients the risk of progression to AIDS was higher for any given CD4 count and HIV VL. A recent multi-cohort analysis showed that HAART-naive patients with CD4 counts over 350 cells/mm^3 had higher mortality rates than the general uninfected population.[25] Within this group, lower CD4 counts and higher viral loads were associated with higher mortality rates. These findings add weight to the ongoing discussion on the consideration of HAART in individuals with CD4 counts greater than 350 cells/mm^3 in various risk groups. The BHIVA, European AIDS Clinical Society (EACS) and the American Department of Health and Human Services (DHHS) guidelines recommend that treatment is initiated before the CD4 count drops below 350 cells/mm^3.[20,26,27] If patients with a CD4 count of greater than 350 cells/mm^3 have an AIDS diagnosis, hepatitis B or C co-infection, a low CD4 percentage (<14%), or a high risk of cardiovascular disease, BHIVA advises consideration of antiretroviral therapy.[20]

An effective repertoire of antiretroviral agents exists. Antiretroviral agents have been reformulated to improve tolerance and fixed dose combinations have reduced pill burden significantly. In December 2007, the European Medicines Agency (EMEA) approved the license of the first triple-drug combination (tenofovir/emtricitabine/efavirenz) in one pill.

Diagnosing the undiagnosed

HIV infection in the UK, as in the rest of the world, is often diagnosed late. Individuals presenting with a compromised immune system are more likely to have advanced disease, present with opportunistic infections and have poorer outcomes.[28] According to the HPA, 31% of new HIV diagnoses are in individuals with CD4 counts below 200 cells/mm^3.[3] In the UK, apart from antenatal testing or in genitourinary clinics, HIV testing is offered as an opt-in test. There is a global trend towards opt-out testing as outlined by the CDC. An alternative would be the universal recommendation of a test in individuals presenting with 'indicator diseases'. These include oral thrush, oral hairy leukoplakia, herpes zoster, intractable skin disease, cervical dysplasia, chronic viral hepatitis, recurrent bacterial pneumonia, *Mycobacterium tuberculosis* and lymphoma.

Prevention

One of the most successful interventions has been the prevention of mother to child transmission (MTCT).[29] Studies have shown that the use of antiretroviral therapy results in a significant reduction in MTCT. In the UK, the rate of MTCT is less than 1%, compared to a risk of 25% when no intervention is used. Three RCTs in sub-Saharan Africa were halted prematurely after interim analyses revealed that male circumcision reduces the acquisition of HIV infection in the uninfected male via penile-vaginal sex by up to 60%.[30,31] Other important prevention measures include optimal screening and treatment of sexually transmitted infections and safer sex education. There is evidence that antiretroviral treatment given shortly after the exposure to HIV can significantly reduce HIV transmission.[32] On the basis of this, post-exposure prophylaxis (PEP) is recommended to individuals who have had significant exposure (occupational or sexual) to blood or any high-risk body fluid from a known HIV-positive individual or an individual considered to be at high risk of HIV infection.[33] There is increased interest in the efficacy of antiretroviral treatment administered *before* exposure to HIV – pre-exposure prophylaxis (PrEP). There have been promising results from primate studies where the use of tenofovir as PrEP has reduced the transmission of simian HIV.[34] There are ongoing studies evaluating the efficacy of tenofovir as PrEP in humans. In established HIV infection, BHIVA recommends screening for hepatitis C at HIV diagnosis and subsequently according to risk.[35] BHIVA also recommends screening for hepatitis B and initiating vaccination in all non-immune individuals.[36] Unfortunately, the quest for a successful vaccine and the development of effective vaginal microbicides has been disappointing. Education is the most important tool in the prevention of new infections. Unfortunately, the 1980s national AIDS campaign was not sustained. National public health campaigns must be retained as there will always be a new generation of adolescents to educate.

Conclusion

In order to plan for the future, past achievements must be evaluated. Where a HIV-positive diagnosis 25 years ago was seen as a death sentence, today where HAART is available patients can expect to lead productive lives with improved, and possibly normal, life expectancies. In the absence of a cure or an effective vaccine, prevention initiatives must remain a priority. Despite global efforts to scale up prevention, care and treatment in resource-poor nations, the face of HIV infection in many areas remains that of an uncontrolled epidemic. Our efforts need to be collective in reducing the disparity between care models in 'developed' and emerging countries.

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