

ORIGINAL RESEARCH

National review of first treatment change after starting highly active antiretroviral therapy in antiretroviral-naïve patients

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Objectives

The aim of the study was to explore the factors surrounding modification of the first antiretroviral (ARV) regimen where drug switch occurred 3 months or more after initiation. Reference was made to the British HIV Association (BHIVA) guidelines on HIV management.

Methods

A case note and questionnaire-based audit was carried out.

Results

Toxicity was the single most important reason for ARV change and was the only, or a contributory, cause in over half the patients. Virological failure, adherence issues, requirement for treatment simplification, and patient request were other significant reasons cited. In one-third of those with virological failure, six or more months had elapsed between first detection and the time of switching to a new ARV regimen.

Conclusions

This audit demonstrated broad adherence to the BHIVA guidelines, although the long time before switching ARVs in the setting of virological failure was of some concern, particularly given the continuing and significant occurrence of primary ARV resistance in the UK.

Keywords: audit, naïve, switch, toxicity

Received: 12 July 2006, accepted 26 October 2006

Introduction

Most drug-naïve patients treated with their first highly active antiretroviral therapy (HAART) regimen are now likely to achieve a viral load of <50 HIV-1 RNA copies/mL by 24 weeks. This is evident in clinical trials (>80%) [1,2] and observational cohorts (>70%) [3], and reflects not only the availability of better tolerated agents, but also improved understanding of the causes of treatment failure. Nevertheless, therapy discontinuation or modification is consistently identified as occurring in a significant minority of patients, especially in the first 3 months, with intolerance or toxicity rather than virological failure being given as the major reason for the change [4–6] (the projected probability at 1 year of therapy change is approximately 25% [7,8]).

Over 50% of patients on treatment in the UK in 2003 were no longer on their first regimen, with more patients than previously switching in the presence of low or undetectable viral loads. Of experienced patients with virological failure, two-thirds have resistance to one or more classes of antiretrovirals (ARVs) [9]. By 6 years, over 80% of patients on treatment have started at least one new drug and nearly half have started a new class of drug [10]. As durable success is most likely with the first regimen, with sequential regimens leading to progressively less durable and less effective virological suppression, the avoidance of toxicity is imperative [11–13]. Limited data exist as to the reasons for first HAART treatment failure after 3 months in the context of currently available drugs which have improved short- and long-term toxicity profiles and are more convenient.

The decision to switch may be either pre-emptive (because of the risk of long-term toxicity, poor adherence, a desire for pregnancy, a suboptimal regimen, comorbidity,

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etc.), when virological suppression is usually retained, or reactive to virological rebound (because of resistance or poor adherence) or an established toxicity.

Successive British HIV Association (BHIVA) guidelines have advised on the identification and management of first switch from initial HAART [14]. The aim of this audit was to explore the factors surrounding antiretroviral modification of established first ARV regimens in the context of the current availability of drugs and guidelines on management.

Methods

Questionnaire forms were posted in October 2004 to the lead audit consultant at 169 treatment centres providing adult HIV care in the UK and Ireland. The questionnaire sought information on the demographic characteristics of patients attending the centre as well as policies relating to management of viral load rebound, including use of resistance tests and therapeutic drug monitoring (TDM), and the provision and use of adherence support.

The second part of the questionnaire involved a case note review of up to 25 patients who had been on their initial ARV treatment for more than 3 months and who changed therapy between 1 April and 30 September 2004. The deadline for submission of forms was 7 January 2005. Patient identifying details were not requested, and ethical approval was not required for this anonymized audit. The data sought included timing and drug choice of initial ARVs and first change, dosing frequency, reasons for change, factors influencing the choice of the new combination, and any adherence issues. In addition, values and timing of viral load measurements before initial therapy and leading up to the time of treatment change were requested. Lastly, information on resistance testing, clinical trial participation, and details of toxicity, where causal to drug change, was sought.

Most data were pre-coded on the questionnaires in machine-readable format. Non-machine-readable data were transcribed from digital images by HC and reviewed by HC and EH.

Results

Completed questionnaires were received from 134 clinical centres (79%), with data supplied on 504 patients who changed therapy. Of the centres that responded, 19% were from the London NHS region and 77% from outside the London NHS region, and 4% did not state the region. The total current HIV case load varied, with the majority seeing between 51 and 500 HIV-infected patients (60%) followed

by 1–50 HIV-infected patients (26%): only 11% reported > 500 patients as currently receiving care in their centre. Seventy-one per cent felt they had seen an increase of > 10% in the number of HIV-infected patients receiving care in their unit in the year preceding this audit.

Regarding policies around resistance testing, adherence support, and use of TDM, 77 centres (57%) delayed switching therapy in those with virological rebound until the viral load was > 1000 copies/mL to allow resistance testing to be performed, 17 centres (13%) switched after a second viral load was > 400 copies/mL, and 11 centres (8%) switched after a second viral load was > 50 copies/mL. The remaining centres delayed for other reasons (2%), had no preferred practice or were not sure (11%), or gave no answer (8%). With respect to adherence support, 81% assessed this at every visit, 16% routinely but not at every visit, and 2% only if difficulties were suspected. Only 30% of the 134 centres felt that the treatment guidelines they used explicitly addressed the question of adherence support. Finally, in the context of virological failure, 44% used TDM only if drug interaction was suspected as a potential cause, 13% used TDM routinely for suspected poor adherence, and 18% used TDM rarely or never accessed testing; 25% used TDM for other reasons or did not answer.

After initial analysis, 67 patients were excluded as ineligible. These included those who had switched therapy within 12 weeks of starting therapy, those making a second or subsequent switch and those whose reported initial drug treatment was incompatible with date of availability in the UK, allowing for clinical trials and expanded access prelicensing. This left 437 patients in the final analysis. Of these patients, 57% were male, 41% were white and 44% were black African. As would be expected, the majority of patients (62%) who had been on their initial ARV regimen for more than 4 years were white. Interestingly, only a small proportion of patients were reported to be in a clinical trial (4%).

Approximately one-third of patients switched between 3 and 12 months after commencing their initial ARVs, with the majority switching before 2 years: 8% had been on therapy for more than 5 years (Fig. 1). Drug regimens prior to switch were varied and reflected the prescribing practice in the UK at the time patients commenced their first ARVs. Nevertheless, with the majority of patients switching between 3 and 24 months from commencement (60%), the commonest ARV combination was a nonnucleoside reverse transcriptase inhibitor (NNRTI) and zidovudine (ZDV)/lamivudine (3TC) (44%) (Fig. 2).

Toxicity was the only reason (35%) or a contributing reason (16%) for ARV change in the majority of patients and reflected the known side effects of the drugs.

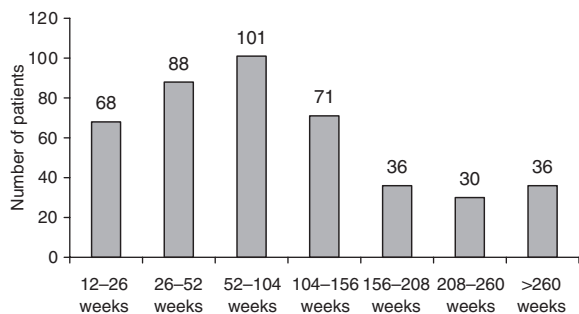


Fig. 1 Weeks on initial antiretroviral (ARV) treatment before first switch.

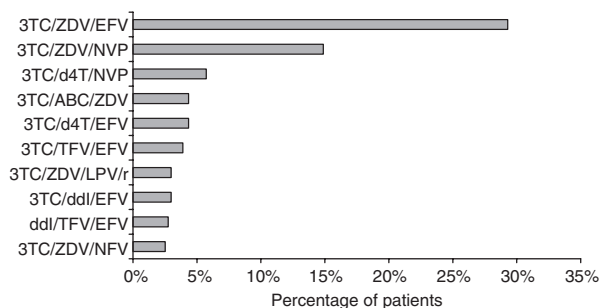


Fig. 2 Initial antiretroviral (ARV) regimens prior to switch. Note that 25% of patients were on a wide range of other combinations not shown in this figure. 3TC, lamivudine; ABC, abacavir; d4T, stavudine; ddI, didanosine; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NVP, nevirapine; TFV, (tenofovir); ZDV, zidovudine.

Virological failure (defined as either viral load rebound from undetectable, not reaching undetectability, and/or an increase in the viral load) was cited as a reason in 132 (30%) of patients, with adherence difficulties (14%), treatment simplification (10%), and patient choice (10%) being other reasons given for switching (Table 1). Forty-four per cent of those for whom adherence difficulties were cited as a reason changed to once daily therapy compared to 27% of those who switched for other reasons. Of the 38 who switched for simplification, seven switched to ZDV/3TC/efavirenz (EFV) and six to abacavir (ABC)/ZDV/3TC, whilst 17 switched to a once daily regimen. Of those who switched because of therapy not meeting current recommendations ($n = 15$), 12 were on stavudine (d4T), two on ABC/ZDV/3TC and one on two nucleoside reverse transcriptase inhibitors (NRTIs) before switching. Of 19 patients who were pregnant or planning pregnancy and who changed therapy, 15 were on EFV, three on ABC/ZDV/3TC and one on d4T before switching. Anti-tuberculous medication was cited as a reason to switch in six patients (two on completion) and antiepileptics in two. Lastly, two

Table 1 Reasons for changing initial therapy: more than one reason could be given

Reason for switching	Number of patients (%)
Toxicity	
Total	223 (51.0)
Metabolic	71 (16.2)
Virological failure	132 (30.2)
Adherence difficulties	63 (14.4)
Patient choice	43 (9.8)
Treatment simplification	42 (9.6)
Poor CD4 response	21 (4.8)
Comorbidity and/or potential for drug interaction	22 (5.0)
Planning pregnancy or pregnant	19 (4.3)
Therapy not conforming to current recommendations	15 (3.4)
Trial endpoint	3 (0.7)

patients switched to 3TC/TFV (tenofovir) regimens because of hepatitis B virus comorbidity.

Fat and metabolic changes were the most common toxicities cited as a reason for switching therapy, affecting 69 patients (16%) overall. This included 42 (10%) with lipoatrophy, 26 (6%) with hypercholesterolaemia, 17 (4%) with hypertriglyceridaemia, 12 (3%) with central obesity, and one patient with hyperglycaemia. With respect to individual drug associations, 54% of patients with metabolic and/or lipid toxicity were on a d4T-containing regimen and 28% on a protease inhibitor (PI)-containing regimen, compared with overall frequencies of 17 and 18%, respectively. Seventy-two per cent of patients with lipid and/or metabolic toxicity had been on their initial therapy for 2 years or more. Other reported toxicities precipitating therapy alteration included central nervous system (CNS)-related toxicity (40 patients), gastrointestinal tract-related toxicity (25), peripheral neuropathy (18), and anaemia (16). Nearly all persons with CNS toxicity were on EFV and all patients with anaemia were on ZDV. Of nine patients who switched because of hepatotoxicity, seven were on nevirapine and two on EFV.

Among 132 patients for whom virological failure was cited as a reason for switching, 95 (72%) switched after a resistance test result had been obtained and 12 (9%) switched while resistance testing was being performed but before results were available. Four patients (3%) had a sample stored for future resistance testing. Fourteen (11%) were neither tested for resistance nor had a sample stored, and in seven (5%) the information was unclear. In the 14 patients where a resistance test was not performed, five had a last viral load over 1000 copies/mL (including one who switched after only 3 months on treatment with toxicity as well as viral load failure, and one who switched after 5 months with viral load failure and poor CD4 response) and in the remaining eight, the last recorded viral load was below 1000 copies/mL.

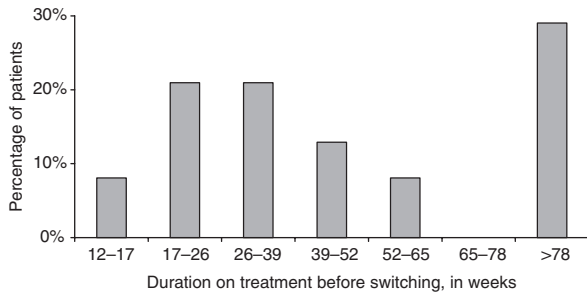


Fig. 3 Weeks between start of antiretroviral (ARV) treatment and treatment switch in those who did not achieve an undetectable viral load.

Sixty-four (48%) of the patients with virological failure switched to three or more new drugs [ritonavir (RTV) at booster dose and 3TC to FTC (emtricitabine) switches were not counted], 42 (32%) switched to two new drugs and 26 (20%) switched to one new drug. Eighty-eight per cent of those on an NNRTI regimen switched to a ritonavir-boosted PI, whilst 67% of patients on a PI or PI/ritonavir (PI/r) remained on or switched to a new PI (one patient) or PI/r (eleven patients) and 33% switched to an NNRTI. It can be seen from this that nine patients (12%) on a virologically failing NNRTI-based regimen remained on such a regimen. Of these nine patients, five switched because of failure to achieve an undetectable viral load (three before and two after 6 months), three had been on initial therapy for > 240 weeks and it is conceivable that these were not all first switches, and one change was guided by resistance testing; four patients had additional reasons for switching therapy (toxicity, adherence, etc.). Three patients switched from an NNRTI to triple NRTI regimens after reportedly failing virologically.

Looking at the subgroup of 70 patients who achieved a viral load < 50 copies/mL prior to switching, the time from the first consistently detectable viral load to the change of therapy was less than 4 months in 30 patients (43%), 4–6 months in 14 (20%) and more than 6 months in 24 (34%). Of these patients, 10 (14%) had been on therapy for less than 1 year, 19 (27%) for between 1 and 2 years and 41 (59%) for more than 2 years. In those not reported to have achieved a viral load < 50 copies/mL at any time, a similar picture was seen, with 50% not switching until at least 9 months after commencing therapy (Fig. 3).

Discussion

Given the very limited contemporaneous data that exist on switching established initial therapy in ARV-naïve patients, the result of this national audit is important in providing an insight into current practice and concordance with

published guidelines in the UK. It also highlights the changing epidemiological pattern of HIV infection in the UK, with changes in therapy being seen predominantly in persons of white ethnicity, for patients whose initial treatment commenced more than 4 years ago, and in black Africans for those starting more recently [15].

As has repeatedly been identified, toxicity is and remains the main reason for changing treatment, even after the first 3 months on therapy. Moreover, the fat and metabolic changes associated with lipodystrophy constitute the major cause of toxicity and this reflects both an improved recognition and identification of the importance of this complication, and the availability of newer and better tolerated drugs with limited evidence of long-term adverse effects [1,2,16]. The strategy of changing individual components of HAART in the face of toxicity has been shown to be successful in several studies. Recent data have demonstrated fat recovery in patients with thymidine-related lipodystrophy and reduction in PI- and d4T-related dyslipidaemia on switching away from these agents [17–20]. In this audit, switching for fat and metabolic toxicity (16% of patients) was more common in patients changing from an initial d4T-containing or PI-containing HAART regimen, which is evidence of the close association between these drugs and lipodystrophy. CNS toxicity was cited as being a reason to switch in 41 patients (10%), 40 of whom were on EFV. Given the infrequency of major CNS adverse effects with other ARV agents, this underlines the problem of persisting EFV-related toxicity in a significant proportion of patients [21–23]. As we enter a new era of HIV infection management where HIV-related complications are declining and patient longevity is approaching that of the normal population in many patients, the future challenges will be around minimizing drug toxicities. Physicians are increasingly tending to switch early to prevent these toxicities becoming established.

Virological failure was the next commonest reason given for changing therapy (30%). Worryingly, 19% of patients did not have a resistance test performed prior to changing therapy, although in 6% the viral load was < 1000 copies/mL and in a further 3% a serum sample was stored for future testing. Baseline resistance testing was not investigated because, being a switch audit, many patients had commenced treatment before this test was a recommended baseline investigation in all patients commencing HAART. However, virological failure as a reason for switching may reflect primary and not selected resistance.

Of those who had achieved a viral load < 50 copies/mL and subsequently rebounded, 34% did not switch therapy for 6 months or more after the first consistently detectable viral load. A similar pattern was observed in those who never obtained an undetectable viral load after initiating

HAART, with 71% being maintained on their failing regimen for over 6 months. It is possible that clinicians were confident that the presence of viraemia reflected poor adherence with a low likelihood of current or developing resistance and that correction of this would re-establish virological control. However, this is often the circumstance where resistant virus is selected. BHIVA guidelines are clear in recommending early resistance testing and guided switching to a new active combination likely to render the viral load undetectable. Failure to obtain a resistance test may lead to inappropriate modification of the ARV regimen and subsequent treatment failure. This may eventually result in further resistance, as may a delay in changing therapy in the milieu of a failing regimen, thereby reducing future options. Beneficial outcomes for the use of resistance testing in the setting of ARV failure in guiding choice for a new combination have been repeatedly demonstrated [24–27].

With respect to the many different combinations that people were on prior to switch, there are no denominator data and therefore no conclusions can be drawn regarding different ARV combinations and frequencies of switching. The predominance of NNRTI regimens in this switch audit is unlikely to represent a greater risk of treatment failure and is more likely to reflect the prescribing patterns for treating naïve patients when therapy was initiated [28]. In line with current recommendations, the majority of patients on a failing NNRTI regimen switched to a PI/r-based combination (88%). For those failing a PI or PI/r regimen, two-thirds switched to a new ritonavir-booster PI-based HAART and one-third switched to an NNRTI-based combination. Of those who switched therapy in whom adherence difficulties were cited as a reason, 44% switched to once daily therapy. Recognized as being preferable to patients [29], several clinical studies now support this strategy as a way of improving adherence [30,31]

Surprisingly few patients were participating in multi-centre clinical drug trials. The main factor is probably the fact that drug therapy studies are usually industry sponsored and restricted to larger centres where recruitment targets can be met. However, the availability of very convenient low tablet number combinations outside of studies may be contributing to dissuading some patients from enrolling. Given that HIV infection management and care remains a relatively new treatment area and is dependent upon evidence from clinical research, this finding is concerning.

Several limitations to this audit influence the conclusions that can be drawn. The sampling method was not strictly representative as centres were asked for data on up to 25 eligible cases only, and there were a high number of exclusions once data began to be analysed, which reflected

partly the complexity of the questionnaire and partly misunderstanding as to the exclusion criteria. Nevertheless, the overall adherence to the BHIVA guidelines was good, with a few exceptions, the most important of which is the delay in switching ARVs after virological failure had been demonstrated. This is particularly concerning in the context of the continuing and significant incidence of primary resistance in the UK [9]. These results have been provided to all participating centres to enable them to compare their own practice with the aggregate results of this study.

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