Novel strategies to treat antiretroviral-naive HIV-infected patients

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Although guidelines exist that provide recommended strategies for treating HIV-infected patients who are naive to antiretroviral therapy, treatment needs to be tailored to individual circumstances. Here we discuss the current recommendations and the evidence used in their development, along with new and emerging treatment strategies.

Keywords: HAART, antiretroviral therapy, antivirals, therapy, treatment

Introduction

The advent of highly active antiretroviral therapy (HAART) revolutionized the lives of those infected with HIV, with substantial reductions in the morbidity and mortality associated with this condition. We now have a wide range of antiretrovirals with which to treat individuals as initial therapy, along with agents that have been specifically developed to treat individuals harbouring resistant virus (see Table 1). Initial therapy for treatment-naive individuals based on two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI), or two nucleosides and a protease inhibitor (PI), has its pitfalls but generally results in high rates of successful virological suppression in the majority of patients (80%–90% of patients in the most recent studies).

It is important to recognize, however, that individuals still fail antiretroviral therapy with the development of resistance and cross-resistance to other agents. Additionally, there is increasing concern over the long-term implications of failing to penetrate ‘sanctuary sites’ such as CSF, seminal and cervical fluids, which may be an area of increasing concern due to the possibility of transmission of low levels of the virus to others. In addition, the present antiretroviral agents are associated with both short-term and long-term toxicities. For example, the long-term implications of the nucleoside class on body-shape image and increasing concerns over the possibility of increased incidence of cardiovascular disease have given cause for physicians to re-examine whether the standard regimen of two nucleosides and a non-nucleoside or PI may be improved upon through the utilization of novel strategies in antiretroviral therapy, with a particular focus on new classes of agents.

In recent years we have seen the development of several new antiretrovirals, including the launch of a second-generation NNRTI, etravirine, new PIs that were developed to target PI-resistant virus, such as darunavir and tipranavir, along with new classes of drugs such as the chemokine C-C motif receptor 5 (CCR5) antagonist, maraviroc, and the integrase inhibitor, raltegravir.

Current guidelines

There are several sets of guidelines available for the treatment of HIV-infected individuals. These include guidelines from the United States Department of Health and Human Services (DHHS), the European AIDS Clinical Society (EACS) and the British HIV Association (BHIVA).1–3 In addition, the WHO issued guidelines for the treatment of individuals in resource-poor settings.4 Guidelines differ in the diversity of choice of antiretroviral agents. For example, WHO guidelines and BHIVA guidelines suggest commencement of therapy with a backbone of two NRTIs and an NNRTI base, with the substitution of a PI base for specific cases. In comparison, the EACS and DHHS guidelines provide a much broader range of therapeutic options, with a choice of an NNRTI or a PI in combination with two NRTI agents. Guidelines are developed to address what is thought to be best for the target population concerned, and not for the individual. Therefore, although these guidelines show distinct differences, it is also important in all areas of the world that we should specifically tailor the choice of antiretroviral agents to the individual. There are several factors that may be taken into account when developing a tailored antiretroviral regimen, including age, sex, body weight, route of administration, possible drug interactions and also late-presenting disease.

The increasing importance of the CD4 cell count

Antiretroviral guidelines in Europe, the UK and the USA have recently changed to recommend therapy in asymptomatic...
individuals with a CD4 count <350 cells/mm³. All of the guidelines also suggest considering treatment in patients with CD4 counts >350 cells/mm³ in specific individuals, including those with a viral load >100000 copies/mL, those who have a rapid CD4 count decline of >500 cells/mm³ per year, those of older age, those with risk factors for non-HIV disease such as malignancy or ischemic heart disease, those with HIV nephropathy and those co-infected with hepatitis C and/or hepatitis B virus. Indeed, the US guidelines may change again in light of more recent American data suggesting that commencing treatment in patients with CD4 counts >500 cells/mm³ is beneficial. Multiple cohort studies have also suggested that the CD4 count is an important predictor of morbidity and mortality, with increasing incidence of death from all causes and from non-AIDS causes being seen in individuals with a CD4 count below the normal range in the DAD and CASCADE studies.5, 6

Furthermore, studies have shown that although antiretroviral therapy is effective in reversing the immunosuppression associated with HIV, the survival of patients with CD4 counts >500 cells/mm³ is similar to but does not return to that of the general, non-HIV-infected population.7 The possibility of starting therapy even earlier has been suggested from recent cohort studies. The NA-ACCORD study suggested that even in those individuals with a CD4 count >350 cells/mm³, there was a reduced risk of AIDS and death, and a second study that compared individuals with CD4 counts >500 cells/mm³ who deferred HAART with individuals in whom HAART was initiated immediately suggested that mortality was significantly lower in those who started HAART earlier.8

It is important that we do not base initiation of HAART on CD4 count alone however. It seems to make little sense that a CD4 count slightly above 350 cells/mm³ means deferment of treatment, whilst a CD4 count slightly below this level means that the individual must be treated. We may be able to individualize exactly when to start treatment based on other factors, thus including those with high viral loads or a rapid decline in CD4 count. HIV progression has also been associated with other factors such as CD38+HLA-DR+CD8+T cells, CCR5 receptor status, the human leucocyte antigen (HLA) status of the individual, the particular HIV clade, and neopterin, β-2-microglobulin and interleukin-6 (IL-6) levels. Other coexisting diseases such as cardiovascular disease and osteoporosis may have complex implications for treatment, based on large cohort numbers in which multiple factors are taken into consideration for initiation of therapy.

It may be possible to increase the CD4 count by utilizing therapeutic modalities other than antiretroviral therapy. Two studies have recently been published that examine the utility of the cytokine IL-2, the use of which has previously been associated with changes in CD4 count. The ESPRIT study randomized individuals with a CD4 count >300 cells/mm³ to HAART with IL-2 given at three cycles of 7.5 MIU (million international units) twice daily for 5 days, 8 weeks apart, with additional cycles to maintain a CD4 count twice that recorded at baseline or >1000 CD4 cells/mm³, or HAART alone. The IL-2-treated group had an average difference in CD4 counts of 160 cells/mm³, with time spent below 300 cells/mm³ occurring in 6% in the adjuvant IL-2 arm and 9% in the control group, and above 600 CD4 cells/mm³ in 57% of those receiving IL-2 compared with 36% of the control group. The rates of viral load suppression were high at >80% of participants, 7 years after cessation of the study. Although there was a positive effect on CD4 cell count, there was no difference in opportunistic infection or death. There was also a significantly higher incidence of grade 4 toxicity in the IL-2 arm. The authors suggested that the results of this study may be explained by dysfunctional CD4 counts arising as a result of viral load suppression with HAART, or the possibility that there may be harmful effects of IL-2 by way of pathways that are not mediated via the CD4 cell count.9

The second evaluation, the SILCAAT study, was designed in a similar fashion but recruited individuals with a CD4 count between 50 and 299 cells/mm³. Again, there was a positive effect on CD4 count, with the average CD4 count in the IL-2-treated group being 57 cells greater in those given HAART alone. Twenty-three percent of the IL-2 arm had follow-up counts <200 cells/mm³, compared with 29% in the control arm, and 38% individuals in the IL-2 arm had follow-up CD4 counts >350 cells/mm³, compared with 28% in the control arm. Again, there was no difference in rates of viral load suppression, which approached 90% after 8 years of follow-up. There was no significant difference in opportunistic disease, death or a combination of these two factors, although there was a trend to reduction of opportunistic disease in the IL-2 arm.10

These two studies would suggest that there is not a role for IL-2 in reducing morbidity and mortality associated with the immune suppression of HIV. Other drugs, such as the CCR5 inhibitor, enfuvirtide and maraviroc, may be more effective in this regard.

### Antiretrovirals available in 2009

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NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors.
antagonist maraviroc, have been associated with increases in CD4 count that appear to be greater than in individuals not treated with this drug, and several studies are ongoing, looking at whether this may be associated with reduced HIV-associated morbidity and mortality.

**Use of new drugs in antiretroviral-naive individuals**

Over the last 2 years several drugs have been licensed that may have a role in treatment of naive individuals, possibly replacing the existing NNRTI or PI base within the combination antiretroviral regimen. These include the NNRTI etravirine, the PI darunavir, the CCR5 inhibitor maraviroc and the integrase inhibitor raltegravir.

No data have yet been presented on the use of etravirine in naive individuals, although studies have suggested that substituting the NNRTI efavirenz with etravirine allows continued antiviral suppression, with a reduction in the toxicity associated with efavirenz.11 The next second-generation NNRTI to be developed, TM278 (rilpivirine), has been assessed in a Phase II study using dosages of 25, 75 and 150 mg versus efavirenz. The rates of virological suppression were similar in all arms. Similar results have been reported with raltegravir, with 86% versus 82% of individuals achieving an undetectable viral load at 48 weeks.12

The data on maraviroc are complicated as individuals needed to undergo co-receptor tropism testing prior to study entry in order to identify individuals who are CCR5 and CXC chemokine receptor 4 (CXCR4) tropic. The tropism test that was used originally led to the misinterpretation of several samples, and the initial results of the MERIT study at 48 weeks suggested that maraviroc failed to reach non-inferiority when compared with efavirenz.14 On re-analysis of these data in the MERIT-ES study, it was suggested that by retrospectively utilizing an improved tropism test, the results of this study were affected by the efficacy of the initial test, with maraviroc actually reaching non-inferiority in MERIT-ES. Therefore, the new agent may not—in any study—have been associated with an increased efficacy of efavirenz. It is apparent that this drug is associated with both short-term toxicity affecting the CNS and other, long-term toxicities in certain individuals. Furthermore, it is recommended by the manufacturer, and by the authors of all of the treatment guidelines outlined here, that the use of efavirenz should be avoided in women who may conceive, due to reported teratogenic effects in animal studies and several cases of CNS developmental defects reported to the Antiretroviral Pregnancy Register.

All of the studies suggested that there was a reduction in CNS side effects with the utilization of new agents. With rilpivirine, there was a reduction in CNS side effects from 48% to 31%, mostly driven by reductions in dizziness and insomnia.16 In the STARTMRK study of raltegravir versus efavirenz, by week 48 CNS events were significantly less with raltegravir (10.3% and 17.7%, respectively, \( P = 0.015 \)) and these differences persisted through week 48.17

The MERIT-ES study showed very similar results, with adverse events being reduced from 14.2% in the efavirenz arm to 4.2% in the maraviroc arm. It became clear in this study, however, that there may still be differences in efficacy between the two agents, despite the initial analysis of similar viral load undetectability, with 9.3% of individuals discontinuing maraviroc being investigated to find a lack of efficacy, compared with 4% in the efavirenz arm.15

**Nucleoside-reducing regimens**

There have been studies looking at reduction in exposure to nucleoside analogues, agents that have caused increasing concern to both physicians and individuals due to reports of toxicity. The FOTO study looked at whether it is possible—in view of the long half-lives of tenofovir, emtricitabine and efavirenz—to dose for 5 days per week, with individuals taking 2 consecutive days off within a 7 day period. Participants were suppressed on a regimen of tenofovir, emtricitabine and efavirenz with a viral load below the levels of detection, and were randomized to continue daily antiretroviral therapy, or to change to the 5 days/2 days off approach. At week 24, virological suppression was 100% in the FOTO arm, compared with 86% in the continuous therapy arm.18

A second study was initiated to investigate whether individuals could reduce the number of nucleoside analogues that they were taking. In the COOL trial, individuals on stable HAART regimens for at least 3 months, with a viral load that was undetectable for >6 months and with no history of virological failure, were randomized to receive either tenofovir and efavirenz, or tenofovir with lamivudine and efavirenz. At week 48, by intent-to-treat analysis, 97% in the triple therapy arm still had an undetectable viral load, compared with 82% in the tenofovir and efavirenz arm. Looking at on-treatment analysis, 100% were undetectable in the triple-therapy arm compared with 90% in the dual-therapy arm. There were three viral load rebounds in the dual-therapy arm, compared with the triple-therapy arm.19 This study would suggest that a reduction in the number of nucleosides, at least in a regimen in which the backbone is combined with a non-nucleoside, leads to a reduction in efficacy of the regimens. The FOTO study is interesting, but care must be taken due to issues such as individuals being non-adherent to the 5 days on approach, and it really only highlights the fact that the long half-life of a drug is associated with virological ‘forgiveness’.

**Nucleoside-sparing approaches**

With the advent of multiple agents outside the nucleoside class along with the increasing recognition of toxicity associated with nucleosides, there is growing interest in the possibility of nucleoside-sparing approaches. This may include a combination of PIs with an NNRTI, PIs with either maraviroc or raltegravir, or PIs alone. Several studies have investigated the use of an NNRTI with a PI. Indeed, Study 006, which was the landmark study for efavirenz, randomized individuals to efavirenz, randomized individuals to efavirenz with combinations of lamivudine and zidovudine (lamivudine/zidovudine), efavirenz with indinavir or indinavir with lamivudine/zidovudine. The efavirenz with indinavir arm gave similar responses to indinavir with lamivudine/zidovudine, but was virologically inferior to the efavirenz with lamivudine/zidovudine arm.20

More recently, the ACTG 5142 study randomized individuals who were antiretroviral naive with a viral load >2000 copies to receive ritonavir-boosted lopinavir (lopinavir/rt) with efavirenz, lopinavir/rt and two nucleosides or efavirenz with two nucleosides. This study demonstrated several points of interest. The
primary analysis—time to virological failure—was similar in the lopinavir/r and efavirenz arm to the other two arms. Individuals receiving lopinavir/r had a greater CD4 rise than those in the efavirenz arm, although this did not reach clinical significance with the lopinavir/r with efavirenz arm (273 versus 230 cells/mm³, respectively). Interestingly, a substudy that examined fat loss suggested that there was a lower rate of limb fat loss of >20% in the lopinavir/r with efavirenz arm, compared with the other two arms, with 9% of individuals reaching this level of limb fat loss in the nucleoside-sparing arm versus 17% in the two nucleosides with lopinavir/r arm, and 32% in the two nucleosides with efavirenz arm.21 The positive results of the nucleoside-sparing approach must be tempered in view of other findings within the study. In individuals with a viral load >100000 copies, there was less virological success in the lopinavir/r with efavirenz arm when compared with the efavirenz arm. In addition, in individuals who virologically failed the regimen, there was a higher rate of major resistance mutations in the lopinavir/r with efavirenz arm compared with the lopinavir/r arm. Seventy percent of individuals on lopinavir/r with efavirenz who failed virologically developed a major resistance mutation, compared with 48% of those on efavirenz with two nucleosides, and 21% of those who received lopinavir/r with two nucleosides.22 In addition, the lopinavir/r with efavirenz arm had a worse metabolic profile, with median increases of cholesterol, triglycerides, high-density lipoprotein (HDL) and cholesterol being greater in the nucleoside-sparing approach.23

PI with a new-class agent

Ongoing studies are assessing PIs in combination with both maraviroc and raltegravir. There are only limited existing data on this type of approach. The EPIC study, which has only been reported at 12 weeks, randomized individuals who were antiretroviral naive with R5/X4 tropic virus to receive either lamivudine/zidovudine with lopinavir/r or the CCR5 antagonist, aplaviroc, with lopinavir/r. Aplaviroc was dosed at 200, 400 or 800 mg twice daily. The levels of virological success were slightly lower in the aplaviroc arm compared with the lopinavir/r arm, although this did not reach clinical significance.24 Aplaviroc has now been withdrawn, however, due to issues of hepatic toxicity.

PI monotherapy

There has been renewed interest in PI monotherapy. The PIs, utilizing a novel method of potency known as unostentatious inhibitory potential, have been shown to be the most powerful drugs as monotherapy, through stopping single-cycle replication. The most widely used monotherapy has been lopinavir/r, which has been studied in naive individuals as part of induction, in the 516G

T mutation had a significantly higher risk of early virological failure, and there was no detectable atazanavir in the plasma in two of these individuals. No PI mutations were seen in any of the three individuals.28

Choice of therapy based on an individual’s characteristics

The science of pharmacogenetics is expanding rapidly and the identification of those individuals who may be at risk of toxicity with particular drugs has been investigated by examining single nucleotide polymorphisms (SNPs) in specific genes. The most widely used genetic test is the HLA-B*5701 allele test for hypersensitivity to the NRTI abacavir. In the PREDICT study, the test produced excellent results in terms of reducing the rates of abacavir hypersensitivity. Individuals who were abacavir naive were randomized to undergo either HLA-B*5701 testing or no screening prior to receiving abacavir. Of those screened, the individuals who were positive for the genetic marker were excluded from treatment with abacavir. Of those individuals who underwent HLA-B*5701 testing but had a negative result, 3.4% developed a clinically suspected abacavir reaction, although skin patch testing was negative in all of these patients. In those individuals who were not screened, there was a doubling of the rate of abacavir hypersensitivity to 7.8%.29

Efavirenz is metabolized by CYP2B6. Individuals with the wild-type CYP2B6 have significantly lower efavirenz levels when compared with those with a mutation in CYP2B6. This mutation, CYP2B6 516G>T, is especially common in those of African-American descent. In ACTG A5097s, individuals with the 516G>T mutation had a significantly higher risk of early CNS side effects with efavirenz compared with those with the wild type.30 Similarly, one can screen for those individuals at risk of jaundice on atazanavir by looking for homozygous UGT1A1*28,31 and ritonavir-induced hyperlipidaemia by screening for apolipoprotein C3 (APOC3) and apolipoprotein E (APOE).32 More recent data suggest that the SNP at −24C>T in multidrug resistance protein 2 (MRP2, also called ATP-binding cassette subfamily C member 2 or ABCC2) may be associated with tenofovir-associated renal dysfunction. Individuals with an age ≥50 years, body weight <60 kg and the genotype MRP2 −24C>T are at increased risk of a uniquely uniform development of tubular dysfunction.33 Tenofovir is not a substrate for MRP2, so the exact mechanism remains unclear.
How can we utilize these data for a novel strategy for antiretroviral agents?

Initiation of therapy must take into account both the individual and the virus. It is important that we utilize pharmacogenetics and also observe the individual’s wishes concerning treatment. It is also important that this is individualized for the virus based on tropism testing and resistance testing to exclude primary resistance. The increasing data on toxicities associated with nucleosides would favour a nucleoside-sparing approach, and this could utilise a ritonavir-boosted PI when there is a low genetic barrier to resistance, perhaps using the highest potency of this class of agent in combination with raltegravir.

In the STARTMRK study it is interesting to note that in raltegravir-naive individuals there is an extremely rapid viral load reduction and although this appears not to have any long-term consequences, in the short-term (48 weeks) when one looks at rates of viral load suppression, it is unclear whether this rapid viral decline may actually have advantages in the long-term. Once individuals attain an undetectable viral load then they could switch to PI monotherapy. If these individuals fail this treatment, then clearly they should undergo intense adherence support, and could then receive a combination of two nucleosides, which in the present climate would probably be tenofovir or emtricitabine, in combination with a non-nucleoside. Although most physicians would presently choose efavirenz for this, the use of etravirine or rilpivirine—with their reduction in CNS toxicity—may be entertained. Individuals who have undetectable viral loads on PI mono-therapy should undergo cervical fluid and seminal fluid HIV screening. Those who have detectable viral loads in their cervical or seminal fluid and were CCR5 positive at the initiation of therapy should undergo intensification with maraviroc; those who were CCR5 negative should receive Truvada (tenofovir with emtricitabine).

A recent study demonstrated that in individuals receiving triple therapy and who are fully viral load suppressed, 2.8% still had a positive seminal viral load.33 It is important therefore that such potential sanctuary sites are targeted, due both to the possible risk of virological failure within the compartment, with possible ‘leaching’ back into the plasma, and to the issues of potential sexual transmission. Maraviroc is actively secreted in the cervical vaginal fluid (although there are no data for seminal fluid). Potential sexual transmission. Maraviroc is actively secreted in the cervical vaginal fluid (although there are no data for seminal fluid), being 410% above the mean plasma load. In the male genital tract, both tenofovir and emtricitabine have shown similar rates of active secretion into this compartment.

Finally, one of the issues concerning PI mono-therapy, as shown by several studies with lopinavir/r, is the relatively high rate of ‘blipping’ with this approach (whereby viral load briefly becomes detectable and then falls back below the limit of detection). In individuals who have currently ‘blipped’, then success has been achieved by adding in nucleosides; this approach could continue but perhaps the use of maraviroc, with its low toxicity, may replace the role of nucleosides.

Conclusions

The guidelines for the treatment of HIV should be based on published, high quality data. All current guidelines suggest that initial therapy should be with two nucleosides and either a non-nucleoside or a PI. Studies are ongoing of nucleoside-sparing regimens and this approach may be warmly welcomed in the future by both HIV-infected individuals and the physicians who treat them. It is paramount, however, that we do not just treat numbers, counting viral load undetectability as success, but rather also consider the individual patient, particularly with regards to drug-associated toxicity. The advent of pharmacogenomics to identify individuals at risk of adverse effects should be embraced and encouraged. It is only by treating both the individual and the virus that we can hope for the long-term virological suppression that many of the agents discussed here are capable of achieving.

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