Long-term Management of the HIV-infected Patient – Tailoring Highly Active Antiretroviral Therapy to Optimise Therapeutic Outcome

a report by

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The introduction of highly active antiretroviral therapy (HAART) regimens has dramatically changed the prognosis of HIV-infected patients, as reflected by the sustained declines in the incidence of opportunistic infection and AIDS-related mortality that have occurred over the last decade.[1] For those HIV-infected patients who achieve CD4 cell counts in excess of 500 cells/mm^3 on long-term HAART, life expectancy now approaches that of the general population.[2] However, the transformation of HIV/AIDS into a chronic disease requiring continuous, lifelong treatment with potent antiretroviral drug combinations presents the clinician with new challenges. HAART regimens are subject to various limitations, including inconvenience of dosing, acute and chronic toxicity and drug interactions that have a negative impact on patient compliance and the ability to achieve adequate viraemic control. A major factor for the long-term management of HIV infection is how to minimise the evolution of antiretroviral drug resistance and prevent virological failure. All effective antiretroviral agents will select for drug-resistant virus, and this risk is substantially increased in the presence of persistent low-level viraemia.[3] Uncontrolled HIV replication and immune activation raises not only the prospect of progression to AIDS but also an increased risk of non-AIDS-defining diseases, such as non-AIDS cancers[4,5] and cardiovascular, renal and hepatic end-organ dysfunction.[6,7]

Management of HIV infection is continuously evolving with the development of new antiretroviral drug classes, improved formulations of existing drugs and better understanding of how to use these drugs in combination, and most patients can now achieve sustained suppression of HIV replication with an acceptable level of convenience and tolerability. However, it is increasingly recognised that no single antiretroviral drug combination is best suited for all patients or even for the same patient during different stages of the disease. The marked inter-individual variability in antiretroviral drug exposure, virological response and tolerability underlines the need for an individualised approach to antiretroviral therapy.

The term 'personalised medicine' has to some extent been appropriated by the field of pharmacogenetics, where it describes the tailoring of treatment according to an individual patient's genetic background. This approach to drug prescribing certainly has a role in HIV medicine. For example, pre-therapy screening for human leukocyte antigen (HLA)-B*5701 and avoiding abacavir in patients who are HLA-B*5701-positive has been shown to significantly reduce the incidence of abacavir hypersensitivity reaction (HSR). However, in this article personalised medicine assumes a broader definition, recognising that each HIV-infected patient presents with unique virus-specific characteristics (drug sensitivity, replication fitness, syncytium/non-syncytium-inducing phenotypes) and host-specific characteristics (concurrent disease, adherence to medication, HLA status, pharmacokinetic disposition) that, together with drug-specific characteristics (drug interactions, tolerability, cross-resistance), are likely to influence the outcome of HAART. A personalised, patient-focused approach considers all of these factors in selecting the optimal antiretroviral drug regimen for a given patient (see *Figure 1*).

Considerations for Patients Initiating Antiretroviral Therapy

Recommendations for initiating antiretroviral therapy in HIV-infected adults are provided in standard treatment guidelines. However, there is an increasing need for these initial treatment regimens to be tailored towards individual patients not only to improve efficacy, but also to reduce the side effects of long-term therapy.

Patient Considerations

It has long been recognised that individuals vary in their response to drug treatments and, as such, pharmacogenetic testing is being increasingly used in all branches of medicine, where studies have linked differences in drug efficacy and tolerability to differences in genes that code for the production of drug-metabolising enzymes, drug transporters and drug targets.[8–10] Identification of these genetic factors provides the opportunity to use molecular screening to select optimal therapy from the outset rather than relying on the more usual empiric approach.

Host Genetic Factors

The field of HIV therapeutics is particularly well suited to pharmacogenetic investigation since molecular diagnostic methods are already used in routine clinical management, and treatment outcomes – whether related

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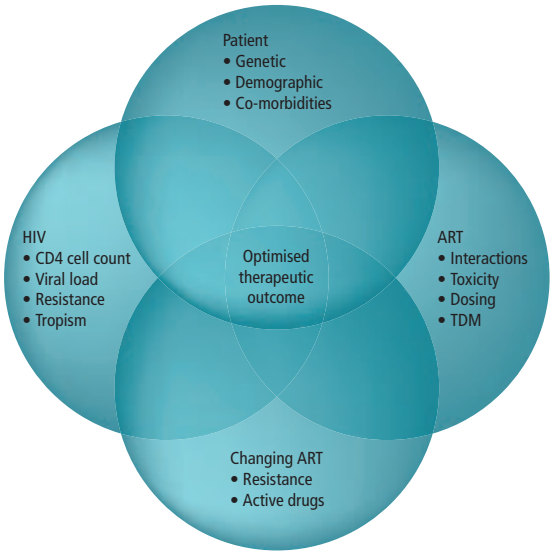
to drug efficacy or toxicity – are closely monitored and are often readily identifiable. The most extensively studied genetic marker in HIV therapeutics is the HLA-B*5701 allele, which has been linked with predisposition to abacavir hypersensitivity. Abacavir is generally well tolerated, but therapy is sometimes limited by the appearance of an HSR. Abacavir HSRs usually occur within the first six weeks of treatment, are characterised by fever, rash and gastrointestinal symptoms and are thought to affect up to 8% of patients.[11,12] Following a number of retrospective and prospective cohort studies that demonstrated the utility of HLA-B*5701 screening in reducing the incidence of abacavir HSR, a randomised controlled study, Prospective Randomized Evaluation of DNA Screening in a Clinical Trial (PREDICT-1), was established to formally investigate this association in a large multinational study population (n=1,956).[13] In this study, patients were randomly assigned to undergo prospective HLA-B*5701 screening (n=980) or to undergo the standard-of-care approach involving use of abacavir without screening (n=976). The study utilised two co-primary end-points: clinically and immunologically confirmed abacavir HSRs. All clinically identified cases ceased abacavir immediately. A subsequent diagnosis of 'immunologically proven' abacavir hypersensitivity required a positive epicutaneous patch test performed six to 10 weeks after the onset of the reaction (abacavir patch testing was additionally validated among the first 100 abacavir-tolerant patients, revealing no false-positive test results). Overall, the prevalence of HLA-B*5701 carriage in each study arm was 5.6%. Screening for HLA-B*5701 eliminated immunologically confirmed HSRs (0 versus 2.7% in the control group) with a negative predictive value of 100%, and reduced the rate of clinically suspected HSRs (3.4 versus 7.8% in the control group).

Until recently, data on the usefulness of HLA-B*5701 screening in non-Caucasian populations have been limited. The Study of Hypersensitivity to Abacavir and Pharmacogenetic Evaluation (SHAPE) utilised a case-control design to evaluate the sensitivity and specificity of the HLA-B*5701 allele as a marker for abacavir hypersensitivity in both black and white populations in the US.[14] This study involved retrospective identification of clinically suspected cases among white (n=130) and black patients (n=69), and revealed 42 immunologically confirmed cases among white patients (32%) compared with five cases within the black patient group (7%). Of these 47 patch-test-confirmed cases, 100% carried the HLA-B*5701 allele. Based on these findings, treatment guidelines now recommend that abacavir should not be used without prior HLA-B*5701 screening, and abacavir use should be avoided in persons testing positive for this allele (International AIDS Society [IAS],[15] the British HIV Association [BHIVA],[16] the European AIDS Clinical Society [EACS][17] and the US Department of Health and Human Services [DHHS][18]).

A number of other genetic polymorphisms associated with drug-related adverse events have been identified for several antiretroviral agents. Nevirapine-associated hypersensitivity has been linked with carriage of the HLA-Cw8-B14 and HLA-DRB1*0101 alleles,[19–21] although in this case HLA testing does not have the predictive value observed for the HLA-B*5701/abacavir association, and the clinical utility of genetic screening prior to nevirapine prescription therefore remains uncertain. Unconjugated hyperbilirubinaemia related to treatment with atazanavir and indinavir is more commonly observed in patients with Gilbert's syndrome, which itself is associated with the UGT1A1*28 allele.[22] Efavirenz-related neurotoxicity is frequently associated with increased plasma exposure of the drug due to various polymorphisms in the CYP2B6 enzyme.[23,24] Protease inhibitor (PI)-related severe hypertriglyceridaemia has been linked to the presence of

Figure 1: Aspects of Personalised HIV Medicine that can be Used to Optimise Therapeutic Outcomes



ART = antiretroviral therapy; TDM = therapeutic drug monitoring.

polymorphisms in the APOC3 and APOE alleles in Caucasian patients,[25–27] while some APOE variants are thought to provide protection against hypertriglyceridaemia in Hispanic patients.[28] Finally, tenofovir-related renal proximal tubulopathy is associated with the 1249G→A variant in the ABCC2 gene encoding the MRP2 transporter.[29] Although screening patients for the selected polymorphisms described above would undoubtedly lead to a more personalised approach to treatment initiation, large-scale, prospective, controlled studies such as those seen with HLA-B*5701 are required before their introduction into routine clinical practice. Indeed, in some cases (e.g. efavirenz) it may be that therapeutic drug monitoring (TDM) provides a superior alternative for monitoring and managing neurotoxicity.

Host Demographic Factors

Patient demographics are another important consideration for the personalisation of HIV medicine. In general, gender does not greatly influence the efficacy of antiretroviral therapy, although female gender is reportedly an independent predictor of HIV RNA response to saquinavir.[30] A literature review by Nicastri and colleagues found little evidence of differences between the genders during antiretroviral therapy, although the authors noted that the majority of studies were not powered to detect gender differences.[31] Recent results from clinical studies examining the efficacy of treatment regimens with regard to gender (Antiretroviral Therapy with TMC114 Examined in Naive Subjects [ARTEMIS], Atazanavir-Ritonavir vs Lopinavir-Ritonavir in Antiretroviral-Naïve HIV-1 Infected Patients: 96 Week Efficacy & Safety [CASTLE] and the Phase III, Randomized, Open-Label Study of Lopinavir/ritonavir (LPV/r) Tablets Once Daily (QD) versus Twice Daily (BID), Co-Administered with Tenofovir DF (TDF) + Emtricitabine (FTC) in Antiretroviral-Naive (ARV) HIV-1 Infected Subjects [M05-730]) have also reported no gender differences, although women represented only approximately 20–30% of the total population in these studies.[32–34]

Among women of reproductive age, discussion of the options for contraception is necessary and treatment choices should be modified in women who are actively trying for a child; efavirenz should be avoided in these circumstances. With regard to antiretroviral drug toxicity, the effect of

Table 1: Summary of Patient Considerations for Optimising Therapeutic Outcome

	Ma or igni icance	Minor igni icance
Genetic actors		
HLA genotype	B*5701: abacavir HSR	HLA: nevirapine HSR
Cytochrome P450		CYP2B6: efavirenz toxicity
Lipid metabolism		APOC3: hypertriglyceridaemia
Other		UGT1A1*28: atazanavir hyperbilirubinaemia
Demographic actors		
Gender	Female: increased toxicity potential/pregnancy	
Behavioural	Risk of non-adherence/ lifestyle considerations	
Age		Elderly: slower immune recovery
Co-morbidities		
HBV, HCV, TB	Early treatment initiation; drug interactions	
Opportunistic infection	Consider ART choice; ensure optimised therapy	
Metabolic, cardiovascular	Early treatment initiation	

HLA = human leukocyte antigen; HSR = hypersensitivity reaction; HBV = hepatitis B virus; HCV = hepatitis C virus; TB = tuberculosis; ART = antiretroviral therapy.

gender appears to be significant, with increased rates of adverse events and discontinuations observed among women treated with nucleoside reverse transcriptase inhibitors (NRTIs), non-NRTIs and PIs (reviewed in Umeh and Currier 2006).[35] The disparity in the rates of observed drug toxicity is potentially due to differences in pharmacokinetics, with women often achieving higher drug exposures than men.[36] Women also appear to be more susceptible to didanosine-induced pancreatic toxicity[37] and to nevirapine-associated rash and hepatotoxicity.[38,39] There is a striking association between female gender and risk of lactic acidosis with certain NRTIs (e.g. stavudine and didanosine).[40] For example, a US Food and Drug Administration (FDA) report of 60 cases of NRTI-associated lactic acidosis found that 83% occurred in women, including 85% of fatal cases.[41]

The increasing age of patients diagnosed with HIV infection poses a potential challenge to initiating treatment. Virological responses to antiretroviral therapy appear similar in the elderly compared with younger patients; however, immune recovery may be somewhat slower.[42,43] Other considerations for treatment initiation in older patients are dose adjustment for impaired renal or hepatic function and increased risk of cardiovascular disease and lipodystrophy, which may influence drug selection.

Behavioural factors must be considered before the initiation of antiretroviral therapy. An assessment of the risk of poor adherence is important, since low adherence is linked with detectable viraemia, disease progression and death.[44–47] A number of important steps can be taken to improve adherence, such as providing education on medication, improving low mood, reducing levels of substance abuse, reviewing and anticipating drug side effects and providing an accessible, trusting healthcare team.[16,18] Simplification of treatment regimens has also been shown to significantly improve adherence.[48,49] Lifestyle factors, work and family situations should be considered before treatment initiation, as these can also influence adherence.[50]

Effects of Co-morbidity

Infectious co-morbidities, such as hepatitis B and C and tuberculosis, and non-infectious co-morbidities, such as metabolic, cardiovascular, liver, kidney and central nervous disease, may influence the choice of initial antiretroviral therapy. Antiretroviral therapy may be deferred until treatment for the co-morbidity has been initiated and/or completed, but this clearly needs to be balanced against the risks associated with drug–drug interactions, overlapping toxicities, immune reconstitution disease and unopposed viral replication. Faced with the realisation that progressive liver disease makes a substantial contribution to long-term morbidity and mortality in patients co-infected with HIV and hepatitis B and/or hepatitis C, and that effective HIV treatment reduces the risk of hepatic complications,[51–53] international guidelines now recommend HIV treatment in co-infected patients, irrespective of the CD4 cell count.[15] This is particularly important for hepatitis B management, where tenofovir + lamivudine or emtricitabine NRTI combinations allow for effective long-term treatment of both HIV and hepatitis B infection.

With regard to HIV-associated opportunistic infections, results from the AIDS Clinical Trials Group (ACTG) 5164 study have demonstrated the benefit of the early introduction of antiretroviral therapy in patients with AIDS-related opportunistic infection.[54] In this study, patients who received immediate antiretroviral therapy after a median of 12 days of starting acute opportunistic infections treatment benefited from fewer deaths/AIDS progressions, longer time to death/AIDS progression and shorter time to achieving increase in CD4 cell count compared with those who started after a median of 45 days. Obviously, any choice of initial antiretroviral drugs should take into account known interactions with concomitant non-antiretroviral drugs. *Table 1* summarises the recommendations concerning patient considerations.

HIV Disease Considerations

The findings from a number of prospective analyses have demonstrated that the initiation of antiretroviral therapy in patients with low CD4 cell counts (<200 cells/mm^3) is associated with a significantly increased risk of disease progression and death.[55–57] However, in many cases a significant proportion (up to 50%) of HIV-infected patients initiating treatment have CD4 cell counts <200 cells/mm^3.[58] In general, guideline recommendations on initiating treatment are based on CD4 cell counts. All guidelines recommend that antiretroviral treatment is started in all patients with CD4 cell levels <350 cells/mm^3 (IAS,[15] BHIVA,[16] EACS,[17] DHHS[18]). However, there are subsets of patients who may benefit from earlier initiation of treatment, even when CD4 cell counts exceed 350 cells/mm^3. These groups include patients with a high viral load (>100,000 copies/ml), hepatitis B or C co-infection, HIV-associated neuropathy, a high cardiovascular risk or rapidly declining CD4 counts (>50–100 cells/mm^3/year). The initiation of antiretroviral therapy should not constitute an emergency since time needs to be allowed for completion of pre-treatment assessments such as viral resistance and HLA-B*5701 testing.

The choice of initial antiretroviral therapy in treatment-naïve patients should take into account baseline viral load levels, since virological efficacy for most antiretroviral combinations is generally inversely related to baseline viral load. Potent regimens with proven efficacy should be administered in patients with high viral load levels. An interim analysis of data from the ongoing study ACTG 5202 comparing the NRTI backbones abacavir/lamivudine and tenofovir/emtricitabine given in combination with either efavirenz or atazanavir/ritonavir has shown that time to virological failure was significantly shorter among patients with baseline viral load levels >100,000 copies/ml in the abacavir/lamivudine arm.[59] In addition, the completed Abacavir/Lamivudine Versus

Emtricitabine/Tenofovir Both In Combination With Lopinavir/ Ritonavir For The Treatment Of HIV (HEAT) study has shown that both regimens resulted in similar proportions of patients achieving <50 copies/ml in those with >100,000 copies/ml at baseline.[60] The manufacturers of abacavir, GlaxoSmithKline, have presented a *post hoc* analysis of pooled data from six previous clinical trials, one of which was HEAT, which did not identify any significant differences between patients with viral loads above or below 100,000 copies/ml.[61] Until further data are available, it is recommended that abacavir/lamivudine should be used cautiously in patients with viral loads >100,000 copies/ml.[15–17] There is also some evidence to suggest that regimens containing boosted lopinavir administered once daily rather than twice daily may be less effective in patients with viral levels >100,000 copies/ml,[62,63] although other studies have shown no difference in efficacy.[64] A recent study comparing darunavir/ritonavir with lopinavir/ritonavir has shown that treatment with lopinavir/ritonavir resulted in significantly fewer patients achieving <50 copies/ml than treatment with darunavir/ritonavir in patients with baseline viral load >100,000 copies/ml.[65] Finally, evidence is emerging that the combination of tenofovir with nevirapine in treatment-naïve patients may be associated with a higher risk of virological failure.[66,67] There is concern that this may reflect a broader risk of 'synergistic' resistance profiles for tenofovir in combination with NNRTIs;[68] however, follow-up data from Gilead study 903 do not appear to indicate increased rates of resistance with tenofovir in combination with efavirenz.[69]

Transmission of drug-resistant HIV has been documented in developed countries, and the prevalence of clinically relevant baseline drug resistance is ~10%.[70,71] Generally, patients infected with drug-resistant strains have a delayed response to therapy and an increased risk of treatment failure.[71,72] Therefore, pre-treatment initiation of HIV-resistance testing is considered to be essential, unless pre-existing results are available or an earlier stored serum sample is available for testing. Initial treatment choices should be amended according to these results. It is also recommended that resistance testing be performed during primary infection or during the initial evaluation of chronic HIV infection, since it is possible that wild-type virus may replace drug-resistant virus in patients who do not receive immediate treatment.[73] These results may be useful for making treatment initiation decisions years later because archived resistant virus can emerge in cases of suboptimal therapy.

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Maraviroc is the first of a new class of chemokine (C-C motif) receptor (CCR)-5 co-receptor antagonists designed to interfere with the so-called R5 variants of HIV, which use the CCR-5 co-receptor to enter cells.[74] As it is also possible for HIV variants to use the alternative CXCR-4 co-receptor – particularly in more advanced HIV infection – and thus become relatively resistant to CCR-5 antagonists, it is recommended that all patients undergo tropism testing before initiating therapy with this agent.[75,76] Currently, the only licensed test for determining HIV-1 tropism is the cell-based assay (Trofile™, Monogram Biosciences, San Francisco) that was used in the pivotal clinical trials.[77] The assay is able to detect the presence of CXCR-4-tropic virus in 85% of samples when the virus comprises at least 5% of the total viral population, although the sensitivity of the assay does vary with viral load level.[78] Thus, tropism testing should be performed before treatment initiation, since low viral load levels in patients already receiving treatment may reduce the sensitivity of the assay. However, practical difficulties and the fact that the test is performed only in central laboratories may preclude its widespread use.

Table 2: Summary of HIV Disease Considerations for Optimising Therapeutic Outcome

	Ma or igni icance	Minor igni icance
CD4 cell counts		
<350 cells/mm3	Initiate treatment	
>350 cells/mm3	Consider treatment depending on co-morbidities	
aseline viral load		>100,000 copies/ml: cautious use of abacavir/lamivudine and regimens containing once-daily boosted lopinavir
Resistance testing		
Pre-treatment	Ideally performed during primary infection, but always pre-treatment (genotypic)	
Change of ART	Genotypic/phenotypic testing if regimen suboptimal or failing	
CCR- co-receptor tropism		Perform before initiation of CCR-5 antagonist

ART = antiretroviral therapy; CCR-5 = chemokine (C-C motif) co-receptor 5.

Uncontrolled HIV replication is associated with certain cardiovascular, hepatic and renal co-morbidities, as most notably shown in the landmark Strategies for Management of Anti-Retroviral Therapy (SMART) study, which unequivocally demonstrated the detrimental effects of interrupting effective antiretroviral therapy.[52,56,79] Identification of such co-morbidities usually indicates the need to initiate antiretroviral therapy; however, consideration should also be given to optimising treatment choice accordingly. For example, in patients with central nervous system (CNS) manifestations of HIV infection, consideration should be given to using agents with optimal CNS penetration.[80] *Table 2* summarises the recommendations concerning HIV disease considerations.

Antiretroviral Therapy Considerations

Potential drug–drug interactions must be considered before initiating antiretroviral therapy. Drug–drug interactions may occur between antiretroviral therapies themselves and between antiretroviral therapies and concomitant medicines. Both scenarios have the potential to induce life-threatening reactions, as well as to allow development of resistance in cases where suboptimal antiretroviral drug concentrations are achieved. In general, drug–drug interactions are more common and potentially more severe with NNRTIs and PIs than with NRTIs.[81] Since the information on drug–drug interactions is extensive and is frequently updated, it is recommended that physicians consult a pharmacist or suitable resource, e.g. www.hiv-druginteractions.org. Patients may also need to be counselled with regard to potential interactions between their antiretroviral therapy and common over-the-counter medicines.

Table 3: Summary of Antiretroviral Therapy Considerations for Optimising Therapeutic Outcome

	Ma or igni icance	Minor igni icance
Drug interactions	Consider other antiretroviral therapies and concomitant medications (risk greater with NNRTIs and PIs than NRTIs)	Consider interactions with over-the-counter medications
Toxicity	Avoid exacerbating pre-existing conditions Consider individual drug toxicity profiles rather than drug 'class effects'	
Dosing schedules		Simple, improved compliance
Therapeutic drug monitoring		Dependent on availability/ individual patient need
Failing regimen	New regimen should contain at least two (preferably three) active drugs	

NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

All antiretroviral therapies have the potential to cause toxicity and this should be taken into account when initiating antiretroviral therapy. This is especially the case when patients have pre-existing conditions that may be exacerbated by antiretroviral therapy. The NRTIs have a well-established toxicity profile on account of their extensive use and long-term clinical experience. They are generally well tolerated, although some have more distinct toxicities, including abacavir (rash, HSR), tenofovir (nephrotoxicity, bone toxicity), didanosine (peripheral neuropathy), stavudine (lipoatrophy, neuropathy) and zidovudine (bone marrow suppression, lipoatrophy).[82,83] Among the NNRTIs, efavirenz is associated with CNS side effects such as insomnia, vivid dreams, irritability and less commonly, psychosis.[81] Thymidine NRTIs (stavudine more than zidovudine) have been associated with lipoatrophy, dyslipidaemia and insulin resistance. Nevirapine is associated with rash and hepatotoxicity.[39] Although not currently indicated for treatment-naïve patients, etravirine was well tolerated in clinical trials, with rash being the only adverse effect to occur more frequently with active drug than with placebo.[84] The use of PIs – particularly those from the first generation – has been associated with dyslipidaemia, insulin resistance and increased cardiovascular risk.[82]

Evidence from cohort studies suggests that cumulative exposure to PIs and recent exposure to the NRTIs didanosine and abacavir are associated with an increased risk of myocardial infarction (~1.5–2.0-fold).[85,86] These associations are not causally proved, although the effect of PIs seems to be mediated at least in part by their lipid effects. However, the clinical significance of this antiretroviral-related risk varies from patient to patient, being determined by the individual's underlying (i.e. pre-existing) cardiovascular risk profile (reviewed in Mallon and Sattar[87]). Accordingly, an individualised pre-treatment assessment of the patient's absolute risk of vascular events, as calculated using the Framingham equation or similar risk tool,[88] should be performed before prescribing PIs, abacavir and didanosine.

Dosing schedules should also be considered when initiating antiretroviral therapy. Complex dosing regimens that negatively influence work or other routine activities may lead to lower rates of adherence. Indeed, reductions in dosage frequency and the number of pills afforded by fixed-dose combinations and boosted PIs have been shown to improve rates of adherence.[48,49] In addition, once-daily medications with long elimination half-lives are less likely to be affected by late or missed doses.[89]

Finally, consideration should also be given to incorporating TDM into patient management if local facilities are available. TDM is likely to be most valuable for optimising treatment in certain patient populations, including patients with significant drug–drug or drug–food interactions, patients with impaired gastric, hepatic or renal function, treatment-naïve patients with a lack of expected treatment response, paediatric patients and pregnant patients.[90] In addition, TDM may also be of use in assessing adherence, concentration-dependent toxicities and alternative regimens where no clinical trial data exist. The recommendations concerning antiretroviral therapy considerations are summarised in *Table 3*.

Considerations for Patients Changing Antiretroviral Therapy

The management of the treatment-experienced patient is an important challenge facing the HIV clinician. Patients may experience a relatively high level of antiretroviral drug resistance despite receiving potent drug regimens from the outset.[91,92] There is a high degree of cross-resistance within drug classes, and today's highly treatment-experienced patients typically have high-level resistance to NNRTIs, varying degrees of PI resistance and extensive NRTI resistance, resulting in reduced treatment options in the event of virological failure.[93–95] It is estimated that up to one-third of heavily treatment-experienced HIV patients experience viral rebound within the first year of initiating HAART.[96,97] In addition, drug tolerability has become a major concern, especially mitochondrial toxicity, which is the cause of most, if not all, of the medium- and long-term adverse effects with NRTIs.[98,99] As a further complication, cardiovascular, hepatic and renal sequelae in the HIV-infected patient can be a consequence of uncontrolled HIV replication as well as drug toxicity.[79]

Options for constructing effective antiretroviral regimens for treatment-experienced patents are often limited. In most cases, choosing three fully active antiretroviral drugs is unfeasible because of cross-resistance or tolerability concerns. In situations in which significant cross-resistance has emerged, adherence counselling and the use of resistance testing to select an optimised background regimen to complement newly available antiretroviral drugs with novel mechanisms of action (e.g. enfuvirtide) or distinctive resistance profiles (e.g. tipranavir and darunavir) is a crucial first step. TDM may be useful in assessing virological failure in the absence of resistance when adherence is thought to be excellent.[15]

> All antiretroviral therapies have the potential to cause toxicity, and this should be taken into account when initiating antiretroviral therapy.

HIV Disease Considerations

Effective antiretroviral therapy should generally result in suppression of HIV-1 RNA to <50 copies/ml within six months of initiating treatment, depending on pre-treatment viral load.[15] Virological failure, defined as the inability to achieve or maintain virological suppression at this level, may be caused by pre-existing (transmitted) drug resistance, poor treatment adherence due to the complexity of the dosing regimen or intolerable drug effects and suboptimal pharmacokinetics, each of which can promote viral replication. When patients have detectable HIV RNA levels while receiving

antiretroviral therapy, the clinician should seek to establish the reason for the lack of virological response and review the therapeutic goal in line with the patient's treatment history. Subsequent antiretroviral regimens need to be individualised with the help of resistance testing and consideration of factors such as regimen tolerability, drug interactions and previous adherence with therapy.

For the patient with limited or intermediate treatment experience (e.g. the patient whose first antiretroviral regimen fails), the therapeutic goal should be to restore an HIV RNA level of <50 copies/ml in order to prevent selection of additional resistance mutations.[100] Provided that medication adherence matters have been addressed, the antiretroviral regimen should be changed promptly: the likelihood of achieving undetectable HIV RNA after virological failure is greater when treatment is changed before the accumulation of multiple resistance mutations.[101,102] For the patient with extensive treatment experience, achievement of undetectable HIV RNA may prove unrealistic; instead, the therapeutic goal should be partial suppression of HIV RNA to below the pre-treatment level in order to preserve immune function and prevent disease progression.

Two types of resistance test are available: genotypic assays and phenotypic assays, of which the former are more widely used.[103] Genotypic resistance tests identify actual mutations that develop in response to antiretroviral drug exposure. In phenotypic testing, a laboratory recombinant virus derived from the patient's virus is exposed to various concentrations of antiretroviral drugs, and the ability of the recombinant virus to replicate *in vitro* in the presence of the individual drugs is determined. Genotypic testing has several advantages over phenotypic testing, including a more rapid turnaround time, lower cost and greater sensitivity to the presence of resistance in the absence of therapy. A 'virtual phenotype' test is also commercially available, and this correlates the patient's genotype with a database-matched genotype for which a phenotypic profile is available to predict the actual phenotype.[103,104] Phenotype testing is more complex than genotype testing; the results are expressed as a fold-change in drug susceptibility, which can then be correlated to clinical results to define susceptible or resistant virus. Although clinical cut-offs are increasingly being applied to phenotype interpretation, these correlations have not been defined for all antiretroviral drugs.

For both genotype and phenotype testing the patient must generally have an HIV RNA level of ≥500–1,000 copies/ml. The plasma sample should be taken while the patient is taking the failing regimen, as wild-type virus may outgrow drug-resistant virus once treatment ceases.[73] Previously selected resistant viral strains may re-appear on treatment re-initiation and failure of subsequent treatment regimens,[105,106] and the cumulative results of previous resistance tests are useful in selecting subsequent antiretroviral regimens. Resistance testing should also be considered after introducing a new drug regimen if the trajectory of HIV RNA reduction is suboptimal.[15]

Antiretroviral Treatment Considerations

Current guidelines recommend that virological failure of an initial NNRTI- or PI-based regimen should be treated early with at least two (ideally three) fully active drugs; the replacement regimen should, in general, contain NRTIs (one being lamivudine or emtricitabine) and a boosted PI, and the number of new drugs and new drug classes included in the regimen should be individually determined.[15] In the setting of multidrug (including NNRTI and PI) resistance, three active drugs, including new classes of agent where possible, should be used. However, it is important to bear in mind that treatment options are also dictated by the choice of initial antiretroviral therapy. High-level NNRTI resistance may occur with single mutations in the reverse transcriptase gene, and any NNRTI exposure with virological failure reduces subsequent response to a second NNRTI.[93] The patient whose NNRTI-based regimen fails frequently displays cross-resistance between nevirapine and efavirenz. A Phase II Randomized, Active-Controlled, Open Label Trial to Investigate the Efficacy and Tolerability of TMC125 in HIV-1 Infected Subjects (TMC125-C227) comparing etravirine with boosted PI after first-line NNRTI failure was prematurely discontinued after a poor response in the etravirine arm in comparison with the PI arm.[107] Subsequently, high levels of both NNRTI and NRTI resistance were found, which was thought to explain the poor etravirine response. Accordingly, first-line NNRTI failure should be detected promptly so that additional mutations to the NNRTI and dual NRTI components do not emerge to compromise other compounds in the class. Typically, replacement therapy comprises two active NRTIs plus a boosted PI, but if such a regimen cannot be constructed, an agent in a new class (maraviroc, raltegravir) may be considered if adequately supported by other active drugs.[15] Cross-resistance to NRTIs also occurs, although to a lesser extent than with NNRTIs. As most initial antiretroviral regimens contain lamivudine or emtricitabine, the signature M184V mutation to these agents commonly develops with treatment failure, although this is less common when a boosted PI is used.[108] Of the major antiretroviral drug classes, boosted PIs have the highest barrier to resistance, and single mutations in the viral protease gene are usually insufficient to produce a significant loss of phenotypic susceptibility. The patient whose initial regimen contains ritonavir-boosted PIs rarely shows PI resistance when virological failure is identified.[109] Nevertheless, for the patient who fails boosted PI therapy and has evidence of partial PI resistance, boosted lopinavir, darunavir or tipranavir should be considered. Where possible, two fully active NRTIs should be included in the replacement regimen, together with an NNRTI (if not previously used).

When modifying a drug regimen that has proved successful in suppressing HIV, replacing single agents to reduce toxicity or drug interactions or to improve convenience and adherence is acceptable, provided the regimen potency is maintained and subsequent adverse drug interactions are avoided. Close monitoring of plasma HIV RNA levels after such a switch can help ensure that virological suppression is maintained.

Conclusion

Patient non-compliance with treatment regimens leads to adverse health effects and increased costs. When personalised therapies prove more effective or confer fewer adverse effects, it can be assumed that patients will more likely comply with their treatments. The benefits of personalised medicine may well outweigh any drawbacks or challenges. Advocates of personalised medicine stress its potential to: detect disease at an earlier stage, when it is easier to treat effectively; enable the selection of optimal therapy and reduce trial-and-error prescribing; reduce adverse drug reactions; increase patient compliance with therapy; improve the selection of targets for drug discovery; reduce the time, cost and failure rate of clinical trials; revive drugs that failed in clinical trials or were withdrawn from the market; avoid withdrawal of marketed drugs; shift the emphasis in medicine from treatment to prevention; and reduce the overall cost of healthcare. ■

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