

Managing the patient on antiretroviral therapy

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8.1 Monitoring, adherence and therapeutic failure

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Success of initial combination antiretroviral therapy (cART), especially in the treatment-naïve person, is based on adherence. It is important to ensure that the person comprehends the concept of adherence and its overall relevance. Education is essential regarding the need for adherence, administration (dosing, timing, food), drug interactions (including recreational drugs), and side-effects (acute and chronic) of cART. Discussion of side-effects needs to include reference to the expected timing of these events. For example, a person starting nevirapine needs to be aware of the possibility of rash, the likely time of its development, and the approach to dealing with rash. Incomplete understanding of the logistics of therapy may compromise therapy or, at worst, place the person at risk. The psychological aspects of treatment initiation need to be addressed early on and revisited over time.

8.1.1 Monitoring

Monitoring of therapy includes clinical assessment and laboratory testing aimed at documenting efficacy of therapy (initially a fall in plasma HIV RNA and subsequently a rise in CD4 cell count) and detecting toxicity (clinical and laboratory). While currently recommended first-line antiretroviral regimens generally have a more favourable toxicity profile than that of earlier regimens, it is still important to assess and manage side-effects which may potentially have an impact on adherence if not addressed.

Factors associated with a favourable outcome include:

- high potency of the antiretroviral regimen
- excellent adherence
- lower baseline viraemia
- higher baseline CD4 cell count
- rapid reduction of viraemia after initiation of therapy.

The key measure for assessing efficacy of an antiretroviral regimen is the plasma HIV RNA level. Typically the viral load is measured four weeks after commencing therapy at which point a fall of 1 log should be observed; by 24 weeks the viral load should be below the limit of detection (i.e. <50 copies/mL).¹ Where the latter does not occur, consideration should be given to problems with adherence, potential drug interactions and the possibility of resistance. The CD4 cell count increment after commencement of therapy is variable. Some people with HIV infection may have a rapid initial rise in CD4 cells with a subsequent plateau, reaching an average increment of 100-200 CD4 cells/μL in the first year of treatment. Other people (especially older individuals and those with a low baseline CD4 cell count) may experience slow CD4 cell rises. Monitoring of immune recovery is also important in terms of decisions regarding cessation of opportunistic infection prophylaxis.²

Table 8.1 outlines an approach to monitoring the person with HIV infection who has just commenced antiretroviral therapy. It should be emphasised that this is a guide only. Frequency of review and laboratory testing should be directed by the needs of the individual and clinical progress.

8.1.2 Adherence

Adherence is increasingly recognised as the critical factor in treatment success in most people with HIV infection. There are significant correlations between adherence to medication and virological suppression,^{3,4} plasma HIV RNA levels, CD4 cell count and mortality.⁵ In addition the possibility of transmission of drug-resistant virus is a public health concern.⁶

Table 8.1 Clinical and laboratory follow-up of the person who has commenced combination antiretroviral therapy

Visits	Pre-commencement: 2–3 visits to discuss therapy Subsequent: review at two weeks, monthly for 2–3 months, then 2–3 monthly
History	New symptoms Side-effects Adherence Psychosocial issues
Examination	Baseline: full examination, including weight and BP Subsequent: weight, BP, body shape changes, peripheral neuropathy, rash Targeted: If CD4 cells <350/μL – mouth and skin If CD4 cells <50/μL – retinal examination by fundoscopy
Laboratory	Baseline, 1 month, 3 months and then 1–3 monthly: Plasma HIV RNA, CD4 cell count, FBE, liver function test, electrolytes Fasting lipids and glucose at baseline and 6 monthly Genotype if virological failure occurs Lactate if symptomatic (nausea, vomiting, fatigue)
Assessment of co-morbidity	Depression Recreational drug use, especially in those on ritonavir Sexually transmitted infections
Assessment of toxicity	Peripheral neuropathy Cardiovascular risk factors Lipodystrophy

BP = blood pressure; FBE = full blood examination.

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Suboptimal adherence is associated with loss of virological control, development of resistance to antiretroviral drugs (often with cross-resistance) and ultimately progression of HIV disease. While early reports⁴ suggested greater than 95% adherence (i.e. missing no more than one or two doses per month of a twice-daily regimen) was required for optimal virological control, more recent data demonstrate that lower adherence rates may be sufficient.⁷ The latter notwithstanding, the goal for every person on cART should be maximal adherence.

Many studies have identified factors (summarised in the US guidelines)¹ associated with poor adherence, however many of these have been hampered by study design (assessment of a single time point, small sample size) and short follow-up. More recently, longitudinal data regarding changes in adherence have been published.⁸ A five-year follow-up of two large prospective cohorts in the USA (the Multicentre AIDS Cohort Study and the Women's Interagency HIV Study) investigated predictors of poor versus good adherence. In these cohorts women and African-American men were found to have lower levels of adherence at baseline. Independent predictors of increasing adherence for men included increasing age and increasing number of antiretroviral medications, while for women there were only negative predictors for improving adherence (binge drinking and use of recreational drugs). On the other hand, predictors for decreasing adherence included symptomatic disease, depression, treatment-related factors and alcohol use. These data serve to reinforce the concept that the dynamics of human behaviour are complex; strategies adopted must be tailored to the individual and reviewed over time.

The following methods have been used in practice and clinical trials to measure adherence:

- self-report over the previous four, seven and 28 days
- electronic pill-cap devices
- pharmacy pill counts
- pharmacy record/prescription monitoring
- directly observed therapy.

Most of these methods are indirect and results do not necessarily correlate with pills taken. In clinical practice, self-report is the most convenient method. It is reasonably accurate and ideally promotes a candid exchange between clinician and the treated person.

Before adopting specific interventions to improve adherence, potentially reversible factors associated with poor adherence should be investigated. Factors include recreational drug or alcohol use, depression, social instability including insecure housing, lack of understanding of the consequences of poor adherence, and psychological barriers to antiretroviral therapy. With some individuals, these factors may necessitate deferral of therapy or modification of the regimen chosen. Cultural factors may impact on adherence for people with HIV infection from non-English speaking backgrounds. The use of an interpreter may be required to explain these issues.

A number of strategies can be used to improve adherence. These strategies include: education; simplification of regimen in regard to timing, pill burden and food requirements; avoidance of side-effects; implementation of a plan to support adherence; involvement of the health care team and family/friends; appropriate referral and treatment for people with co-morbidities (psychiatric, drug-related); and staff training.

Specific interventions that have been investigated in clinical trials and shown to be associated with improved adherence are listed in Table 8.2.

8.1.3 Failure of therapy

The goals of therapy for HIV infection are maximal and durable suppression of HIV replication (i.e. HIV RNA to undetectable levels <50 copies/mL), and restoration or preservation of immune function to improve quality of life and reduce HIV-related morbidity and mortality.¹ Response to therapy may be measured by changes in viral load and CD4 cell count. Broadly, therapeutic failure can be defined as failure to attain the goals of therapy; in practice this may be considered in terms of virological failure, immunological failure and clinical progression.

Table 8.2 Interventions associated with improved adherence

Pharmacist-based adherence clinics
Adherence encounters at each visit
Reminders, pagers, alarms, timers
Patient education aids
Clinician education aids

Case Study 8.1 Adherence and advanced HIV infection

John is a 56-year-old man with HIV infection diagnosed more than ten years ago. He commenced therapy early in the cART era. However, he was lost to follow-up for a number of years, following relocation to a rural area. He re-presented three years ago and was diagnosed with disseminated *Mycobacterium avium* complex infection. Following treatment of his presenting illness and initiation of antiretroviral therapy he has been well and returned to part-time work.

John presents to the clinic without an appointment, seeking a prescription for two of his antiretroviral drugs. He is adamant that he has an appointment for that day although none was booked. He states he has missed a number of appointments in recent months due to the illness of his partner for whom he is the principal carer. Various doctors have written prescriptions for him in the intervening period. On questioning, John states he has plenty of the third drug left. He claims 100% adherence with his medication.

His surrogate markers are assessed and reveal a falling CD4 cell count (currently 30 cells/ μ L) and a viral load of 57 000 copies/mL. Discussion with the dispensing pharmacist reveals he has not collected supplies of the third drug in his regimen over the past five months, although continuing to collect the others. The clinic nurse indicates she has significant concerns regarding John's cognition following her discussion with him while he is waiting.

Upon receipt of the results a genotype is requested. Further evaluation including a neuropsychological assessment is deemed necessary. It is suggested to John that he should consider hospital admission to change regimen and arrange other necessary investigations. He declines, citing his partner's ill-health as the reason, but agrees he should change his medication in the near future.

Virological failure

Virological failure is generally defined as the inability to achieve or maintain suppression of viral replication below the limits of detection i.e. <50 copies/mL. This may manifest as one of the following:

- reduction in plasma HIV RNA of less than 1 log₁₀ four weeks after initiation of therapy
- failure to suppress plasma HIV RNA to undetectable levels within six months of treatment initiation
- confirmed rebound viraemia after initial reduction to undetectable levels.

Immunological failure

Immunological failure is generally defined as failure to achieve or maintain an adequate CD4 cell response in the setting of virological suppression. There is no agreement regarding a specific definition however one of the following may be observed:

- CD4 cell decline e.g. decline greater than 30% of absolute count or drop of 3% when considering percentage (especially in asplenic people where the absolute CD4 cell count is elevated)
- failure to increase above a threshold e.g. >200 cells/μL.

While in practice the cause of immunological failure often remains uncertain, a number of associated factors are known, including:

- increasing age
- low baseline CD4 cell count (<200 cells/μL)
- co-infections e.g. hepatitis C virus
- drugs e.g. zidovudine, tenofovir co-administered with didanosine, chemotherapy
- malignancy.

Clinical progression

Defined as the occurrence of HIV-related events after at least three months on cART, excluding immune reconstitution (see Chapter 22).

Many factors are potentially associated with treatment failure (Table 8.3); treatment failure should prompt a thorough re-evaluation of the person's history and current clinical context. A detailed discussion of the approach to treatment failure may be found in the USA guidelines.¹

Table 8.3 Factors associated with an increased risk of treatment failure

Baseline factors	Outdated, potentially less potent regimen Unfavourable surrogate markers (high VL, low CD4 cell count) Prior AIDS illness Comorbidities e.g. depression Unrecognised drug resistant virus Prior treatment failure with resistant virus
On therapy	Incomplete adherence Drug side-effect and/or toxicity Pharmacokinetic issues (metabolism, absorption, drug interactions) Less potent regimen

VL = viral load.

Reference: Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. November 3, 2008; 1-139. Available at: <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. (cited February, 2009)

8.2 Resistance testing and changes to antiretroviral regimen

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8.2.1 Resistance testing

Resistance testing (see Section 4.1) is indicated in a number of clinical settings to aid the clinician in selecting the most appropriate antiretroviral regimen and is now standard of care in the United States, Europe and Australia.^{1,9,10} The results of resistance testing should always be considered in conjunction with the person's antiretroviral treatment history. Resistance may be determined by either a genotypic or phenotypic resistance assay however the latter is only available in Australia via clinical research studies. There is a role for genotype testing both at baseline and on therapy (see below).

8.2.2 Genotypic assays

Genotypic assays are based on the determination of the nucleotide sequence of HIV and the presence of drug resistance mutations in specific gene sequences e.g. the reverse transcriptase and protease genes. Interpretation of results is complex and requires knowledge of the range of mutations

selected by various antiretroviral drugs. Interpretation includes not only the effect of each mutation on drug susceptibility, but also interactions among mutations that can increase or decrease drug susceptibility.

The results of a genotypic assay list identified resistance mutations, and should include an interpretation of the significance of the mutation, i.e. whether a particular mutation has a known effect on drug susceptibility. Examples of resistance interpretation algorithms include those from the Stanford HIV resistance database (www.hivdb.stanford.edu) and the International AIDS Society–USA (IAS–USA) Drug Resistance Mutations.¹¹

Nucleoside reverse transcriptase inhibitors mutations

There is now increasing evidence that the pattern of resistance to nucleoside reverse transcriptase inhibitors (NRTIs) is similar to

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that of protease inhibitors (PI) with substantial cross-resistance conferred by the presence of multiple mutations. The mutations (M41L, D67N, K70R, L210W, T215Y/F, K219E/Q) associated with resistance to thymidine analogues (zidovudine and stavudine) have been defined for many years¹² and are known as thymidine analogue mutations (TAMs) (a subset of nucleoside analogue mutations (NAMs)). The presence of these mutations has implications for resistance to other drugs in the NRTI class with the exception of lamivudine and emtricitabine. A study evaluated the fold change in NRTI susceptibility as a function of the number of nucleoside analogue mutations and the presence of M184V or other reverse transcriptase substitutions. This study identified that many NAMs are associated with decreased susceptibilities to all NRTIs. In particular, mutations at positions 41 and 210 (TAM 1 pathway) have been associated with an increased likelihood of cross-resistance to other NRTIs, including to tenofovir. Other amino-acid substitutions that have not previously been recognised as NAMs have also demonstrated high levels of cross-resistance.¹³ The M184V mutation (conferring up to 1000-fold increases in resistance to lamivudine) not only enhances susceptibility to zidovudine, but also improves susceptibility to stavudine and tenofovir.¹³

TAMs are also important in the development of resistance to tenofovir. Initially the K65R mutation was noted to develop in a small proportion of patients treated with tenofovir. It has also been shown that virological response to tenofovir is diminished in patients with three or more TAMs that include either the M41L or L210W mutations or, alternatively, the presence of the L210W mutation in any context.^{14,15}

Non-nucleoside reverse transcriptase inhibitors mutations

High-level resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) develops quickly, often within a few weeks of initiating monotherapy. Single-point mutations confer high-level resistance and the degree of cross-resistance in this class is high. For example, the presence of the K103N mutation alone precludes the use of other first generation NNRTIs. Resistance to the second generation NNRTI, etravirine, is more complex, with reduction in drug activity being observed as mutations accumulate.¹⁶

Protease inhibitors mutations

Interpretation of protease inhibitors (PI) mutations is complex as PI display multiple, overlapping patterns of resistance, and there is widespread cross-resistance within the class. In the protease gene, resistance mutations are classified as either major or minor. Major mutations are usually selected first and have an independent effect on phenotype. Minor mutations usually appear later and do not have a significant effect on phenotype alone. Multi-protease inhibitor resistance is likely to occur with the accumulation of four or more of these mutations.¹⁷ New generation PIs including tipranavir and darunavir have different resistance profiles, and virological response depends on both the protease-specific mutations and the number of mutations at baseline.^{18,19}

New classes of antiretroviral drugs

Antiretroviral agents targeting the HIV-1 gp41, HIV-1 integrase or CCR5 require genotypic tests that detect relevant mutations. No commercially available mutation detection kits are presently available. Many laboratories are developing and evaluating

their own in-house assays for this purpose. Tropism testing to determine the effectiveness of CCR5 antagonists is currently not routinely performed in Australia, although the analysis can be requested from specialty research laboratories.

8.2.3 Phenotype assays

Phenotypic assays measure the susceptibility of a patient's viral isolates to specific antiretroviral drugs. The concentrations of drug needed to inhibit 50% and 90% of viral replication (IC50 and IC90) are calculated. The ratio of the IC50 of the test and reference viruses is reported as the fold-increase in IC50. An increase in IC50 (decreased susceptibility) means that more drug is required to inhibit the patient's virus *in vitro*. The major limitation of the phenotypic assay is the interpretation of the IC50 i.e. what fold-change in IC50 predicts therapeutic failure *in vivo*.

Another test is the virtual phenotype which is an estimate of the real phenotype, derived from a patient's genotype. A phenotypic prediction is made possible by comparison with a database with thousands of clinical isolates in which both the genotype and phenotype are recorded. The virtual phenotype is determined by matching a patient's genotype with genotypes in the database. The virtual phenotypes have shown a high degree of concordance with the actual phenotype.²⁰ Phenotypic assays and virtual phenotypes are only accessible in Australia via clinical studies. These assays are performed in the USA.

8.2.4 Utility of resistance assays

Resistance assays are unable to detect minor viral species (less than 10-20% of the circulating virus population). This is particularly important when interpreting results in regard to the susceptibility to a drug that a patient has taken in the past, but which is no longer part of the current antiretroviral regimen. The drug-resistant virus may have become a minor species owing to the lack of selective pressure, and it is therefore not detected.²¹ In addition, neither genotypic nor phenotypic resistance tests take into account the effect of drugs used in combination on viral replication.

There have been a number of prospective, randomised, controlled trials to examine the benefit of genotypic and phenotypic analysis in assisting drug selection. Studies using genotypic testing have consistently demonstrated an improvement in short-term virological outcome following a change of therapy when guided by the genotype result as well as recommendations from an expert panel.²²⁻²⁴ In particular, in the Havana study, patients were randomised to one of four arms: no genotype/no expert advice; genotype alone; expert advice alone; or genotype/expert advice.²⁴ The group that received both genotypic testing and expert advice demonstrated the best response. A recent randomised controlled trial examined salvage antiretroviral therapy guided by rules-based genotype interpretation versus virtual phenotype with or without therapeutic drug monitoring.²⁵ No major differences were found according to the method of resistance testing, when combined with expert opinion. A number of studies comparing phenotype testing with genotype testing indicate that there is no additional benefit from performing a phenotype in addition to a genotype.^{26,27} Additionally, a randomised trial comparing genotypic and virtual phenotypic interpretation of HIV drug resistance did not demonstrate any clear benefit from the use of virtual phenotype interpretation.²⁸

Despite the results supporting the addition of resistance testing to treatment strategies, there are many unresolved issues and challenges, including cost, availability and laboratory issues pertaining to standardisation and reproducibility. Interpretation of the results of resistance testing is difficult and is rapidly evolving as new drugs are introduced and new resistance mutations recognised. A number of algorithms are available to aid interpretation of test results.²⁹ Clinicians with little experience in genotype interpretation are advised to seek the advice of other colleagues. Table 8.4 outlines some key points in genotype interpretation.

8.2.5 Indications for resistance testing

The current guidelines for resistance testing are summarised in Table 8.5. As this remains an evolving area it is suggested that clinicians periodically review the guidelines, especially after significant updates occur.

8.2.6 Changing antiretroviral therapy Indications

There are a number of reasons why a change in antiretroviral therapy may be required. Decisions regarding changes in antiretroviral therapy should be guided by HIV viral load, CD4 cell count and clinical status. Toxicity caused by antiretroviral drugs as well as significant drug interactions with other necessary medications may also warrant a change to the current antiretroviral regimen. A change in therapy is often prompted by treatment failure, which is discussed above.

The changes made to a regimen will depend upon the reason for the change. It is important that the recent clinical history, remaining potent treatment options, potential resistance patterns from prior therapy, and potential for adherence are all taken into account. For those failing third or subsequent regimens, the choice of available agents may be limited, and the decision to change therapy may further limit future treatment options. The patient must also be prepared for the implications of a new regimen, including new side-effects, drug interactions, dietary requirements, and the possible need to alter concomitant medications.

Therapeutic failure

The types of therapeutic failure (clinical, immunological and virological) have been discussed above. Although the aim of cART is to suppress HIV RNA to undetectable levels, this is not always achievable or sustainable. Once viraemia recurs, the possibility of virological failure needs to be considered. Alternative explanations include a temporary increase in viral load in the context of intercurrent infection (e.g. syphilis) or vaccination or a viral load blip. The viral load should be repeated at least two to four weeks later (and not temporally related to intercurrent infection or vaccination). A viral load increase also represents an opportunity to revisit adherence.

The HIV RNA nadir achieved with antiretroviral therapy is an important predictor of long-term virological suppression.³⁰ Durable viral suppression is critical for preventing the emergence of drug-resistant virus and subsequent virological

Table 8.4 Ordering and interpreting a genotype test: key points

Issues to consider	Rationale
Initial questions	
Does the indication for genotype fit within the current guidelines?	Clinical utility of the test
If pre-treated with cARTs, is the person still on therapy?	Off treatment, the virus reverts to wild-type and mutations may be archived
Is the viral load sufficiently high to do a genotype?	Generally needs to be >1000 copies/mL
Important history	
cART treatment history	Genotype must be interpreted in the context of prior treatment in order to make informed treatment decisions
Previous genotype result(s)	May be archived resistance from previous regimens e.g. loss of NNRTI mutations when NNRTI ceased
HBV co-infection	Mandates continuation of cART with anti-hepatitis B virus activity – refer to chapter 21.1 (HBV-HIV co-infection)
Interpretation of the test	
Is there a single mutation conferring high level resistance?	M184V - 3TC K103N - NVP/EFV I50L - ATV
Are there mutations which confer partial loss of activity, with increasing resistance as mutations accumulate?	Protease inhibitors – commonly
Are there mutations conferring cross-resistance within the class?	K103N – NVP and EFV
Are there mutations conferring hypersusceptibility?	M184V – resistance to 3TC and increased susceptibility to ZDV and TDF
Is it possible to choose a regimen with at least two and preferably three fully active drugs?	
ATV= atazanavir; PI = protease inhibitor; ZDV = zidovudine; TDF = tenofovir disoproxil fumarate; NVP = nevirapine; cART = combination antiretroviral therapy; EFV = efavirenz; 3TC = lamivudine; NNRTI = non-nucleoside reverse transcriptase inhibitor; M = methionine; V = valine; K = lysine; N = asparagine; HBV = hepatitis B virus.	

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Case Study 8.2 Therapeutic failure due to lack of adherence

Tom, a 45-year-old man, known to be HIV-infected since 1992, presents for review. He is currently taking his fourth antiretroviral regimen of Trizivir and ritonavir-boosted atazanavir. Tom started antiretroviral therapy in 1996 with zidovudine, lamivudine and saquinavir. Over the ensuing years he had multiple treatment breaks and a number of regimen changes; other regimens included stavudine/lamivudine/nevirapine and stavudine/didanosine/nelfinavir. At the time of the latter regimen he moved interstate. A genotype taken during this time demonstrated K103N, M184V and a number of TAMs, however, no PI mutations.

Approximately two years ago he re-presented to hospital having moved back to his city of origin. He was dishevelled and disorientated; following assessment a diagnosis of HIV encephalopathy was made. After reinstatement of antiretroviral therapy and intensive multidisciplinary support he improved slowly and was able to be discharged to the community. At this time he had an undetectable viral load and neuropsychological testing revealed considerable improvement although some deficits in judgement and impulse control were noted.

Although Tom states he is currently well, repeat testing shows he now has a viral load of 57 000 copies/mL and his CD4 cell count has fallen from 230 (16%) to 120 (11%) cells/mL. Upon discussion of these results he is adamant that he has not missed any of his medications. A genotype is requested.

Following this, it is discovered that about two months ago, the community nurse supporting Tom's care and adherence resigned and he was not able to sustain a relationship with the replacement nurse. The genotypic test shows the presence of the primary mutation K103N only. Because of the lack of resistance mutations and increasing viral load, the question of adherence to therapy is raised. The plasma drug level of atazanavir is measured and found to be undetectable, adding further weight to the suggestion that the patient is not actually taking the antiretroviral therapy, and that the K103N mutation has persisted after the earlier period of nevirapine treatment.

The clinician decides to work with Tom, the community nurse and his social worker in developing a new care plan aimed at improving adherence. It is decided to continue current therapy but implement adherence interventions, then repeat the viral load and genotype test.

Case Study 8.3 Development of non-nucleoside reverse transcriptase inhibitor resistance

David, a 50 year-old man with a long history of HIV, presented for review. He has Kaposi's sarcoma for which he had required a number of courses of chemotherapy. His nadir CD4 cell count is 60 (14%). David commenced antiretroviral therapy in 1996, initially with zidovudine and zalcitabine and, subsequently, with the addition of saquinavir. When testing became available he is found to have a viral load of 70 000 copies/mL and his regimen is changed to lamivudine, stavudine and nevirapine. Over the next five years, due to ongoing virologic failure, he had a number of regimen changes using various protease inhibitors as they became available and a second trial of an NNRTI-based regimen. His first genotype test, performed at the time he was failing an indinavir-based regimen showed the M184V mutation and a number of PI mutations. His clinician at that point chose a new regimen of zidovudine, lamivudine, tenofovir, nevirapine and lopinavir/ritonavir. David is very pleased when his viral load quickly dropped to below the level of detection and remained there, apart from a couple of blips, for the next five years.

David presented for review again in 2007, at which time his health was stable. Routine monitoring revealed a viral load of 6400 copies/mL (previous test was 350 copies/mL) and CD4 cell count of 286 (16%) which was a significant drop from his level of 380 (22%). A genotype test showed the following mutations: D67N, K70R, M184V, T215I and K219EQ (NRTI) and G190A (NNRTI) in the reverse transcriptase gene and V32I, M46I, I47V, I50V, I54L, L10F and A71V in the protease gene. These mutations conferred high level resistance to first generation NNRTIs, most NRTIs (tenofovir and didanosine low level resistance only) and high or medium level resistance to all PIs apart from tipranavir. In retrospect it was likely that he had archived NNRTI resistance from his two earlier treatment periods on nevirapine, which was not demonstrated by his first genotype taken on a PI-based regimen. Given his extensive NRTI exposure with less potent and unboosted PIs it was surprising that he had achieved an undetectable viral load for five years. Upon receipt of these results his clinician initiates discussion regarding various new agents available to him as part of a salvage regimen.

failure. Viral load blips (or transient low level viraemia) occur frequently in patients on cART and have been variously defined as increases up to 500 copies/mL³² or 1000 copies/mL³³ in recent studies. A Spanish study, in which a blip was defined as an increase to 500 copies/mL, found that, in most instances, blips were transient; however plasma HIV RNA level at the time of the blip was predictive of subsequent virological failure.³¹ Another recent study of this phenomenon has shown that a transient increase to less than 1000 copies/mL was not

associated with clinical events or resistance while increases above 1000 copies/mL were commonly associated with resistance and subsequent therapy change.³² In practice, the viral load should be repeated to determine whether the initial increase represents transient low-level viraemia or not. Situations where low-level viraemia is continuous but the viral load is too low for genotype testing pose a challenge to clinicians.

The development of drug resistance is a significant contributory factor to therapeutic failure. However, other factors such as drug intolerance, drug toxicity, poor adherence, malabsorption and drug-drug interactions must be considered and eliminated.

Toxicity

If treatment failure is due to drug intolerance or toxicity, a single drug switch may be deemed appropriate. In this instance the viral load should be repeated and confirmed to be below the level of detection (<50 copies/mL) before the single drug switch is made.

First antiretroviral regimen change

After failure of first and second regimens, the objective of changing therapy is to achieve undetectable viral load. It is recommended that at least two and preferably three drugs in the regimen should be changed to achieve this goal. Resistance testing, if available, should be used to guide the choice of next regimen. However, as discussed above, the absence of resistance to a specific drug does not mean drug resistance is not present in a minority of viral species.

The first regimen is most likely to consist of two NRTIs plus either a PI or an NNRTI. At first virological failure, a genotype analysis is recommended to guide the choice of a second regimen. In general, the NNRTI is swapped to a ritonavir-boosted PI and vice versa, with a change in the NRTI backbone. In situations where the only NRTI mutation is M184V some clinicians would retain lamivudine and change the other NRTI while others would advocate changing both NRTIs. There is a paucity of evidence in regard to this approach.

Subsequent changes: salvage therapy

For patients where second and subsequent regimens have failed, the choice of new regimens is not simple, and the optimal therapeutic approach is not well defined. In recent times a number of new agents (Table 8.6),³³⁻⁴⁰ have been demonstrated to be highly effective in treatment-experienced patients and thus the goal of salvage therapy is now the same as for

earlier regimens i.e. complete virological suppression. Drugs are available from a number of classes including PIs, second generation NNRTI, integrase inhibitor and an entry inhibitor (CCR5 inhibitor). Clinical studies have demonstrated that when two new fully active drugs are used 70% of the study population will achieve an undetectable viral load (<50 copies/mL). There is little further improvement in outcome when three fully active drugs are used. Important points to consider when choosing a salvage regimen:

- Avoid addition of a single fully active drug, even if there is no other option, as resistance will quickly develop
- two or three fully active new drugs should be included, based on treatment history, genotype and new class of drug
- where it is not possible to identify two new fully active drugs, continuing current cART in the face of virologic failure is associated with both clinical and survival benefit⁴²
- web-based genotype interpretation algorithms are only as accurate as the data entered – discuss genotype results for new agents with the laboratory or a colleague
- NRTIs will usually maintain partial activity; most experts promote retaining NRTIs, based on genotype and toxicity minimisation
- optimal sequencing of new agents is not known
- when using new agents remember to check drug interactions, including ARV-ARV interactions as these may be significant e.g. etravirine and tipranavir should not be used together.

In this population of patients, it is important to distinguish between virological failure due to drug resistance and low blood levels of drugs. Resistance testing in conjunction with therapeutic drug monitoring can be used to clarify the reasons for virological failure. CD4 cell counts initially remain elevated in patients who fail to achieve and maintain an undetectable plasma viral load while receiving a PI-based regimen. Immunological progression does occur, but only after prolonged periods. Change in viral load from pre-therapy levels, rather than the absolute level of viraemia achieved, is the most important determinant of these CD4 cell changes.

In those who fail to achieve complete virological suppression, discontinuation of antiretroviral therapy results in increased

Table 8.5 Indications for resistance testing

Clinical setting	Rationale
Genotype recommended	
Prior to cART therapy <ul style="list-style-type: none"> • Acute HIV infection • Chronic HIV infection, undetermined duration • Chronic HIV infection, about to commence cART, no baseline genotype 	Possibility of transmitted drug resistance; virus may revert to wild-type over time. In Australia the risk of transmitted drug resistance in a person with recently acquired HIV is of the order of 10%
On antiretroviral therapy <ul style="list-style-type: none"> • Virological failure (rebound viraemia) • Suboptimal VL suppression after cART initiation 	Elucidate the role of resistance in treatment failure Guide choice of new active regimen
Ceased cART therapy <ul style="list-style-type: none"> • Within 4 weeks of cessation 	Document development of resistance mutations prior to reversion to wild-type
Pregnant women <ul style="list-style-type: none"> • All, prior to cART initiation • On therapy with detectable viraemia 	Optimise treatment for maternal infection Prevention of mother-to-child transmission Guide choice of effective safe regimen
cART = combination antiretroviral therapy; VL = viral load.	
Reference: Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. November 3, 2008; 1-139. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf . (cited February, 2009)	

Table 8.6 New antiretroviral agents available for salvage therapy

Agent	Mode of action	Status (2008)	Comment
darunavir	PI	Section 100	Active against PI-resistant virus
tipranavir	PI	Section 100	Multiple mutations required for loss of activity Toxicities evolving
raltegravir	Integrase inhibitor	Section 100	Triple-class experienced patients or those intolerant of licensed drugs
etravirine	NNRTI (2nd generation)	Special Access Scheme	3 or more NNRTI resistance mutations associated with significantly less activity; K103N has no effect
maraviroc	CCR5 inhibitor	TGA approved Expanded access safety study and Special Access Scheme	Only if R5 tropic virus (NB advanced HIV infection – mostly X4 or dual tropic virus); tropism assay required Multiple drug interactions requiring dose modification

PI = protease inhibitor; TGA = Therapeutic Goods Administration; NNRTI = non-nucleoside reverse transcriptase inhibitor; CCR5 = chemokine receptor 5; Section 100 = a section of the Pharmaceutical Benefits Scheme which provides access to highly specialised drugs.

plasma HIV RNA levels, decreased CD4 cell counts and predominance of virus with 'wild type' genotype.³³ Despite viral drug resistance, continuation of antiretroviral therapy in this setting appears to have some degree of activity. *In vitro* measurements of replicative capacity suggest that wild-type (drug-sensitive) virus has greater replicative capacity than drug-resistant virus, thus providing evidence for continuing a well tolerated regimen despite ongoing viral replication.

There is no role for structured treatment interruptions in patients with multidrug-resistant HIV and who are failing their current regimen, with the aim of replacing drug-resistant virus with wild-type virus. In a randomised study comparing immediate change of cART with a four month treatment interruption prior to changing cART, there was a statistically significantly greater rate of disease progression and death in the group who underwent a treatment interruption. In addition, the treatment-interruption group had significantly lower CD4 cell count for the duration of the study. Structured interruption of treatment did not confer immunological or virological benefits or improve the overall quality of life.⁴¹

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