

Clinical issues

in HIV/AIDS

This is the fourth in a series of bulletins focusing on advances in therapy for HIV/AIDS, particularly developments in triple therapy employing protease inhibitors.

This bulletin looks at HIV drug resistance testing and considers the

availability, uses and interpretation of phenotypic and genotypic assays.

There is also an update to the article on drug interactions in HIV therapy, which appeared in the last bulletin.

Watch out for further update bulletins in the coming months.

In this issue ...

1 Commentary

Simon Barton BSc MD MRCCOG HIV/GUM
Consultant, Chelsea & Westminster
Hospital, London

David Hicks FRCOG MFFP DipVen HIV/GUM
Consultant Physician, Department
of Genitourinary Medicine, Royal
Hallamshire Hospital, Sheffield

2 Clinical utilities of HIV drug resistance testing

Deenan Pillay BSc PhD MRCPATH
Consultant Virologist, Head of PHLS
Antiviral Susceptibility Reference
Unit, Division of Immunity and
Infection, University of Birmingham
Medical School

7 Update on drug interactions

David J Back BSc PhD Professor,
Sara E Gibbons BSc MPhil Research
Assistant, Department of
Pharmacology and Therapeutics,
University of Liverpool

Commentary

Uncertainty, and how we cope with it, continues to be a major challenge in the management of HIV infection. Despite significant reductions in the number of people dying from AIDS or developing opportunistic infections that have been achieved by combination antiretroviral therapies, major uncertainties continue to exist about the longer-term side-effects of these therapies and the reason for virological failure with specific antiretroviral combinations. In addition, as therapies move from research trials through compassionate release to become licensed products, we become increasingly aware of drug interactions with both other licensed therapies and recreational drugs.

Continued over

Commentary continued

The articles in this issue are up to date and extremely clearly written, and will go some way towards ameliorating the areas of uncertainty that currently exist in the questions and dilemmas that we daily face with patients in our clinics. It is vital, however, that we continue to strive to bridge the knowledge gap that can easily develop between specialist clinicians and the patients for whom we care.

Because clinical guidelines on antiretroviral therapy are drawn up reflecting data that is often only available in abstract form from specialist clinical meetings, it is important that the reasoning behind the choice of those specific options is discussed and conveyed to patients in a coordinated and coherent manner by all members of the multidisciplinary care team. This places a responsibility for remaining up to date and well informed on all medical practitioners caring for individuals with HIV, as well as on their colleagues in nursing, dietetics, pharmacy, health advising and other important areas of liaison. Furthermore, it is essential that communication with GPs is maintained and

enhanced, particularly to avoid drug interactions from concomitant medications for patients on antiretroviral therapy.

However, as we struggle with these important clinical issues, the uncertainty is worsened by a lack of clear policy on the continuation of a national funding system for HIV care provision and the absence of a national AIDS or sexual health strategy. Within this framework the challenge of caring for people with HIV infection has never been greater. To rise to this challenge we must look to the historical basis of our success in partnership with our patients, collaboration with other statutory and voluntary bodies, and our belief that combining clinical research with excellence in clinical service will be rewarded with support and proper provision of resources from politicians and health planners.

Simon Barton ^{BSc MD MRCOG} HIV/GUM Consultant, Chelsea & Westminster Hospital, London

David Hicks ^{FRCOG MFFP DipVen} HIV/GUM Consultant Physician, Department of Genitourinary Medicine, Royal Hallamshire Hospital, Sheffield

Clinical utilities of HIV drug resistance testing

Deenan Pillay ^{BSc PhD MRCPATH} Consultant Virologist, Head of PHLS Antiviral Susceptibility Reference Unit, Division of Immunity and Infection, University of Birmingham Medical School

Biological basis of resistance

Within the HIV-infected individual, the virus exists as multiple variants, termed quasi-species. These variants are generated through high level viral replication in conjunction with the inherent error rate of the viral reverse transcriptase. Within this population, in the untreated individual, will exist minority populations of virus with reduced drug susceptibility. Thus, when a selection pressure is imposed (drug therapy), these viruses will preferentially replicate and further evolve,

and will become the dominant species. Reduced drug susceptibility is defined as an increase in the concentration of drug required to inhibit virus replication – in other words, a raised IC_{50} or IC_{90} compared with pretreatment virus. It follows that drug resistance is not ‘all or none’, but rather a quantitative measure of the degree of reduced drug susceptibility. Assays that measure this aspect of drug resistance are known as phenotypic assays. Underpinning the phenotypic change are alterations in the genes coding for reverse transcriptase and/or protease. The

underlying genetic changes associated with resistance are termed the viral genotype, and this is what is detected by genotypic assays.

Available assays

Phenotypic assays

Cell culture-based assays, such as the peripheral blood mononuclear cell (PBMC) assay, have hitherto been regarded as the gold standard for determining drug susceptibility of virus isolates. However, this assay is extremely time consuming and (therefore) expensive, and is not suitable for routine clinical use.¹ In addition, concern has been expressed that the process of *in vitro* cultivation of viruses from infected individuals may select for a species that is not reflective of the original sample. To some extent, these problems have been circumvented by the development of a recombinant virus assay, whereby polymerase chain reaction (PCR) amplified products of reverse transcriptase and/or protease genes from plasma virus are recombined with a HIV clone lacking the relevant genes.¹ This clone is infectious and can be used to undertake a drug susceptibility assay. Such assays are undertaken on a commercial basis, but remain expensive with a long turnaround time (more than three to four weeks). Some laboratories undertake this assay for research purposes; however, it remains unclear whether the routine use of currently available phenotypic assays as a first line test is practicable.

Genotypic assays

The methods for detection of resistance-associated mutations fall into two categories:

1. Detection of specific mutations – these include the line probe assay,² which allows for detection of mutations at specific positions in the gene of interest by hybridisation against specific probes covering the relevant areas of the genome. This assay is commercially available, but is currently limited to the detection of nucleoside analogue resistance mutations. An updated assay incorporating non-nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor resistance mutations is in development.
2. Nucleic acid sequencing – new resistance associated mutations are continually being identified, and many laboratories therefore prefer to undertake sequencing of a large portion of the reverse transcriptase gene and of the protease gene in order to capture as much information as possible. This is a more demanding technique than the line probe assay, not least because of the

large amount of nucleotide (gene) sequence data generated. This has fuelled the commercial development of software systems linked to sequencing assays, which will assist in the identification of known resistance associated mutations. It is also of note that sequencing-based technologies are able to identify novel insertion changes within the genome, whereas hybridisation-based assays are not. An example is the insertion recently noted around position 69 of the reverse transcriptase gene.³

For a laboratory with trained staff and the sequencing hardware, it should be possible for results to be obtained within two weeks of the specimen being received. This methodology is also cheaper than the phenotypic assays described above. For these reasons, it is likely that genotypic resistance tests will represent first-line analysis in the near future.

There is limited information on the comparison of genotypic and phenotypic data. The group from VIRCO identified a good correlation between the two methods for phenotypically-resistant virus; however, there was less concordance for phenotypically-sensitive samples.⁴ In other words, phenotypic assays are probably better at documenting reduced drug susceptibility than sensitivity. These data also imply that early development of resistance may be easier to detect by genotypic analysis.

Interpretation of genotypic-resistance assays

A number of limitations of genotypic analysis must be considered before such data are used to guide treatment in a patient failing therapy.

Relationship of resistance mutations to drug resistance

There is now a large body of data relating specific mutations and sets of mutations within reverse transcriptase and protease genes to reduced susceptibility to antiretroviral drugs. This data set is continually increasing in the light of studies of new drugs and combinations of drugs. In some instances, there is a very clear association between a single amino acid change and drug resistance; examples are the M184V mutation change coding for 3TC resistance, and the K103N mutation coding for resistance to NNRTIs.

For other drugs, a larger number of amino-acid changes are required to generate high level resistance, such as for zidovudine and

some of the protease inhibitors. In these instances, the significance of just one mutation in a patient failing on therapy may be unclear. Finally, there are some drugs for which virological failure may not be associated with any specific mutations. Stavudine is a case in point – only a minority of patients failing on this drug have mutations or insertions associated with reduced drug susceptibility.⁵ It is possible that specific d4T resistance mutations *in vivo* have been ‘hidden’ by the co-existence of resistance to other nucleoside analogues. It is also possible that cellular factors may play a role in reducing the virological effect of this drug.

Thus the utility of genotypic changes in guiding therapy is, to some extent, drug specific – for example, genotyping is far more likely to guide decisions on the use of 3TC and NNRTIs than for DDI and d4T, for which failure is variably associated with mutations for which the associated reduction in susceptibility is rather modest. With regard to protease inhibitor resistance, there appears to be considerable cross-resistance within the class as a whole,⁶ which is especially the case for multiple protease mutations.⁷

A number of retrospective studies have now demonstrated that the presence of resistant virus (by genotypic and phenotypic testing) at time of failure is predictive of subsequent short-term virological success on switching therapy.⁸⁻¹² These data relate to reverse transcriptase and protease inhibitor resistance. Prospective studies are required to demonstrate the clinical utility of testing in the routine clinic setting (see below).

Minority species

Plasma virus consists of a quasi-species in which a large number of variants will be represented as minority species. Sequencing or hybridisation based assays have a limit of sensitivity for detection of these species. Sequencing can detect variants represented at 25% of the total population but rarely those at 10%,¹³ with the line-probe assay having an increased sensitivity coping with variants at 2% to 8% representation.² Thus, these technologies may not detect the emergence of a drug resistance associated mutation early in failure.

Significantly improving this level of sensitivity is technically demanding, and it is unlikely that such modifications will be available to routine testing laboratories in the near future.

Reversion of mutations

Many drug resistance-associated mutations generate viruses with a reduced ‘fitness’ compared with wild-type virus. Of course, in the presence of the drug selection pressure, these variants are better able to replicate compared with drug-sensitive virus; however, when this drug pressure is removed (switching therapy) wild type virus at that specific position may re-emerge over a variable period of time.¹⁴ It follows that genotypic sequencing undertaken on plasma virus from a patient failing therapy will only represent the virus that is escaping from current therapy. Nevertheless, drug resistant viruses will continually infect susceptible cells, some of which will be long-lasting. Thus, archival drug resistant virus may be represented within proviral DNA but not necessarily within plasma virus at a detectable level. It follows that, for example, the absence of the M184V mutation in a patient previously but not currently on 3TC does not necessarily imply that 3TC could be successfully used.

Interaction of mutations

Much of the data regarding drug resistance-associated mutations have been gleaned from drug monotherapy studies. However, we are increasingly aware of the impact of interactions between mutations. For instance, the development of 3TC resistance in a background of existing high-level zidovudine resistance leads to a resensitisation of the virus to zidovudine.¹⁵ It is also apparent that drug resistance mutations emerging on combination therapy are different from those emerging on monotherapy – for example, nevirapine resistance is encoded within reverse transcriptase amino acid 181 on monotherapy, whereas other nevirapine drug resistance mutations emerge in a patient receiving zidovudine in addition.¹⁶ We are likely to witness many new examples of these interactions as patients are treated for longer on new combinations of drugs, and we must be aware of this when interpreting genotypic sequence data.

Clinical utilities of HIV drug resistance assays

There are several scenarios within which HIV drug resistance assays could guide the management of patients:

- In patients failing on therapy.
- Prior to initiation of therapy.
- Testing the ‘donor’ after a needlestick injury.
- During pregnancy in order to guide maternal and neonatal therapy/prophylaxis.

Resistance assays in patients failing therapy

Resistance assays are most widely requested in these circumstances. The interpretation of genotypic data generated is based on our prior knowledge of resistance and cross-resistance properties of viruses containing specific mutations. These data are perhaps easiest to interpret following first-line therapy failure, whereas reversion back to wild type of previously dominant resistance mutations may have occurred when genotyping is undertaken on a virus from a very highly drug experienced patient. It is essential, therefore, that drug history is taken into account when interpretation of a resistance assay is made. This begs the question as to whether resistance assays can provide information additional to a good drug history.

In order to address this issue, 21 patients with virological failure to their current drug regimen were tested for reverse transcriptase resistance mutations by the line-probe assay.¹⁷ Decisions on therapy were made in the absence of resistance data, and then reviewed in the light of genotypic information.¹⁷ In this highly antiretroviral drug experienced group, knowledge of resistance data altered therapeutic decisions in 40% of cases.¹⁷ It is of interest that in half of this 40% there were no drug resistance-associated mutations.¹⁷ This suggests that poor compliance may be an important component of virological failure.

The more important question is whether changes in therapy based on genotypic changes lead to improved virological and clinical outcomes. This issue has been investigated in two studies. The VIRADAPT study randomised 108 patients failing on reverse transcriptase and protease inhibitors to genotypic resistance testing or standard of care, with subsequent therapeutic decisions made accordingly.¹⁸ The GART study randomised 153 patients with a viral load rebound after more than 16 weeks of triple therapy to genotypic resistance testing or standard of care.¹⁹ In both, the short-term HIV viral load reduction in patients with resistance testing was greater than in those in whom therapy was decided in the absence of resistance testing.^{18,19}

These data provide good evidence for a virological utility of resistance testing. Nevertheless, it may be that this benefit is relatively short-lived in the type of multi-drug experienced patients entered into these studies. As discussed above, it is possible that resistance testing will yield greater benefits following failure of first-line therapy. Indeed, even in patients failing second- or third-line therapy, it may be

more appropriate to undertake genotypic testing on a stored sample from the time of an earlier virological failure in order to identify the presence of mutations that may subsequently have reverted within plasma virus to wild type.

This underlines the importance of ensuring that specimens taken for routine viral load monitoring are stored at -70°C for as long as possible. It is also important that testing is undertaken on samples taken while the patient is receiving therapy, rather than, for example, at the end of a 'drug holiday' during which time reversion may have occurred.

Resistance testing prior to initiating therapy

The presence of resistance-associated mutations in drug-naïve patients is well established. This provides circumstantial evidence for the transmission of such viral variants from one individual to another. With the recent demonstration of the sexual transmission of multi-drug resistant virus,²⁰ it is now important to consider the possibility of pre-existing drug resistance before initiating therapy. In some areas of the USA, the prevalence of any level of genotypic or phenotypic resistance is around 20% in drug-naïve individuals.^{21,22}

Surveillance for 'primary' resistance should be undertaken within different communities in order to provide the justification for introducing routine pretreatment resistance testing. Nevertheless, it seems very reasonable from a clinical and cost-effectiveness viewpoint to routinely test all patients prior to therapy initiation. This is especially the case before treatment of primary infection, in which the plasma virus is more likely to be a true representation of the infecting viral species.²³

Resistance testing to guide prophylaxis

Following a needlestick injury involving blood from a known HIV-infected individual, post-exposure prophylaxis is a priority. It is prudent to consider the drug history of the donor in order to guide suitable therapy. It is also appropriate to undertake an urgent genotyping assay (if available) that can be used to modify therapy within two to three days of starting treatment.

Pregnancy

Drug-resistant HIV can be transmitted from mother to neonate, and the presence of zidovudine resistance within the mother predicts the presence of resistant virus in her infected

offspring following initiation of therapy.²⁴ On this basis, resistance testing of pregnant women should be considered before deciding on optimal therapy for her and prophylaxis for her neonate.

Conclusion

The recent demonstration of a virological benefit in undertaking genotypic resistance testing in patients failing antiretroviral therapy will lead to an increase in demand for these assays. There are a number of scenarios in which resistance assays could be requested, but, currently, the biggest demand is for patients failing salvage therapy. As for any diagnostic test, clinicians should aim to answer some specific questions through requesting an assay. It may be useful to test stored samples, obtained at virological failure to previous drug regimens. It is important to appreciate that genotypic resistance information is merely one component of the complex decision-making process involved in formulating appropriate and effective antiviral therapy.

References

1. Hertogs K, de Béthune MP, Miller V et al. A rapid method for simultaneous detection of phenotypic resistance to inhibitors of protease and reverse transcriptase in recombinant human immunodeficiency virus type 1 isolates from patients treated with antiretroviral drugs. *Antimicrob Agents Chemother* 1998;42:269–276.
2. Stuyver L, Wyseur A, Rombout A et al. Line probe assay for rapid detection of drug-selected mutations in the human immunodeficiency virus type 1 reverse transcriptase gene. *Antimicrob Agents Chemother* 1997;41:284–291.
3. de Jong JJ, Goudsmit J, Lukashov VV et al. Insertion of two amino acids combined with changes in reverse transcriptase containing tyrosine-215 of HIV-1 resistant to multiple nucleoside analogs. *AIDS* 1999;13:75–80.
4. Pauwels R, Hertogs K, Kemp S et al. Comprehensive HIV drug resistance monitoring using rapid, high-throughput phenotypic and genotypic assays with correlative data analysis. *Antiviral Therapy; 2nd International Workshop on HIV Drug Resistance and Treatment Strategies 1998. (Abstracts 51;35–36).*
5. Lin P-F, González CJ, Griffith B et al. Stavudine resistance: an update on susceptibility following prolonged therapy. *Antiviral Therapy* 1999;4:21–28.
6. Winters MA, Schapiro JM, Lawrence J, Merigan TC. Human immunodeficiency virus type 1 protease genotypes and in vitro protease inhibitor susceptibilities of isolates from individuals who were switched to other protease inhibitors after long-term saquinavir treatment. *J Virol* 1998;72:5303–5306.
7. Zolopa AR, Shafer RW, Warford A et al. Predictors of antiviral response to saquinavir/ritonavir therapy in a clinical cohort who have failed prior protease inhibitors: a comparison of clinical characteristics, antiretroviral drug history and HIV genotype. *Antiviral Therapy; 2nd International Workshop on HIV Drug Resistance and Treatment Strategies 1998. (Abstracts 54;37).*
8. Leigh Brown AJ, D'Aquila RT, Johnson VA et al. Baseline sequence clusters predict response to combination therapy in ACTG 241. *Antiviral Therapy; 2nd International Workshop on HIV Drug Resistance and Treatment Strategies 1998. (Abstracts 50;35).*
9. Harrigan PR, Montaner JS, Hogg RS et al. Baseline resistance profile predicts response to ritonavir/saquinavir therapy in a community setting. *Antiviral Therapy; 2nd International Workshop on HIV Drug Resistance and Treatment Strategies 1998. (Abstracts 55;38).*
10. Deeks SG, Parkin N, Petropoulos CJ. Correlation of baseline phenotypic drug susceptibility with 16 week virologic response in a pilot combination therapy study in HIV-infected patients who failed indinavir therapy. *Antiviral Therapy; 2nd International Workshop on HIV Drug Resistance and Treatment Strategies 1998. (Abstracts 53;36–37).*
11. Patick AK, Zhang M, Hertogs K et al. Correlation of virological response with genotype and phenotype of plasma HIV-1 variants in patients treated with nelfinavir in the US expanded access program. *Antiviral Therapy; 2nd International Workshop on HIV Drug Resistance and Treatment Strategies 1998. (Abstracts 57;39).*
12. Lanier R, Danehower S, Daluge S et al. Genotypic and phenotypic correlates of response to abacavir (ABC, 1592). *Antiviral Therapy; 2nd International Workshop on HIV Drug Resistance and Treatment Strategies 1998. (Abstracts 52;36).*
13. Larder BA, Kohli A, Kellam P et al. Quantitative detection of HIV-1 drug resistance mutations by automated DNA sequencing. *Nature* 1993;365:671–673.
14. Boucher CA, van Leeuwen R, Kellam P et al. Effects of discontinuation of zidovudine treatment on zidovudine sensitivity of human immunodeficiency virus type 1 isolates. *Antimicrob Agents Chemother* 1993;37(7):1525–1530.
15. Larder BA, Kemp SD, Harrigan R. Potential mechanism for sustained antiretroviral efficacy of AZT-3TC combination therapy. *Science* 1995;269:696–699.
16. Richman DD, Havlir D, Corbeil J et al. Nevirapine resistance mutations of human immunodeficiency virus type 1 selected during therapy. *J Virol* 1994;68:1660–1666.
17. Pillay D, White D, Taylor S et al. Genotypic HIV drug resistance assays alter clinical decision making in patients failing therapy. 4th International Congress on Drug Therapy in HIV Infection, 8–12 November 1998, Glasgow, UK. (Abstract OP3.1).
18. Durant J, Clevenbergh P, Halfon P et al. Can HIV genotype determination be useful for individualised adaptation of antiretroviral therapy: the VIRADEPT French Study. 4th International Congress on Drug Therapy in HIV Infection, 8–12 November 1998, Glasgow, UK. (Abstract OP7.1).
19. Baxter JD, Mayers DL, Wentworth DN et al. A pilot study of the short-term effects of antiretroviral management based on plasma genotypic antiretroviral resistance testing (GART) in patients failing antiretroviral therapy. 6th Conference on Retroviruses and Opportunistic Infections, Chicago 1999. (Abstract LB8).
20. Hecht FM, Grant RM, Petropoulos CJ et al. Sexual transmission of an HIV-1 variant resistant to multiple reverse transcriptase and protease inhibitors. *N Engl J Med* 1998;339:307–311.
21. Little S, Daar E, Keiser P et al. The spectrum and frequency of reduced antiretroviral drug susceptibility with primary HIV infection in the United States. 6th Conference on Retroviruses and Opportunistic Infections, Chicago 1999. (Abstract LB10).
22. Wegner S, Mascola J, Barile A et al. High frequency of antiretroviral drug resistance in HIV-1 from recently infected therapy naive individuals. 6th Conference on Retroviruses and Opportunistic Infections, Chicago 1999. (Abstract LB9).
23. Yerly S, Rakik A, Kinloch de Loes S et al. Switch to unusual amino acids at codon 215 of the human immunodeficiency virus type 1 reverse transcriptase gene in seroconvertors infected with zidovudine-resistant variants. *J Virol* 1998;72:3520–3523.
24. Colgrove R, Pitt J, Japour A et al. Zidovudine resistance after vertical transmission of HIV-1. 6th Conference on Retroviruses and Opportunistic Infections, Chicago 1999. (Abstract 265).

Update on drug interactions

David J Back BSc PhD Professor, Sara E Gibbons BSc MPhil Research Assistant, Department of Pharmacology and Therapeutics, University of Liverpool

Since the publication of the original article,¹ key new data have emerged.

Antiretroviral therapy

Data on the interaction of protease inhibitors (PIs) were presented at the 12th World AIDS Conference.² Amprenavir caused a 38% decrease in the area under the plasma concentration time–curve (AUC) of indinavir, an 18% decrease in saquinavir AUC and a 15% increase in nelfinavir AUC. Indinavir increased amprenavir AUC by 26% but saquinavir reduced AUC by 36%.

Further information is now available for the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz with the PIs saquinavir and ritonavir. Fiske *et al*³ reported a 17% increase in AUC of ritonavir (500 mg twice daily) when administered with efavirenz (600 mg once daily), and suggested that, in cases of intolerance attributed to ritonavir, a ritonavir dosage reduction may be considered. When efavirenz was administered with saquinavir, there was a 62% decrease in the AUC of saquinavir. Therefore it is recommended that efavirenz is not administered when saquinavir is the sole PI.⁴

There is increasing interest in exploiting the metabolic interaction profile of a drug and thereby reducing the frequency of dosing. Co-administration of ritonavir with indinavir enhances indinavir's systemic availability and means indinavir does not need to be taken on an empty stomach. A combination of ritonavir 400 mg and indinavir 400 mg, both twice daily, gave higher and more sustained indinavir levels than 800 mg indinavir every eight hours, and was not affected by food.⁵ A twice-daily regimen of indinavir 800 mg with ritonavir 100 mg has also been investigated.⁶ This regimen showed a decrease in peak levels of indinavir and an increase in trough levels when compared with indinavir 800 mg alone every eight hours.⁶ These increased trough levels of indinavir may give superior and more sustained efficacy.⁶

Another approach to improving the indinavir dosing regimen has been to divide the daily dose into 1,200 mg every 12 hours. Administration of this dose with nelfinavir (1,250 mg twice-daily) resulted in peak and trough concentrations and

AUCs of indinavir comparable to a regimen of 800 mg every eight hours.⁷

When more than two drugs are administered, the nature of the interactions becomes less clear. The ACTG 359 study investigated saquinavir/ritonavir or saquinavir/nelfinavir with delavirdine and/or adefovir.⁸ The addition of delavirdine alone increased the AUC of saquinavir, ritonavir and nelfinavir as anticipated. However, the addition of adefovir with delavirdine appeared to decrease the AUC of delavirdine, which in turn caused a decrease in the AUC of saquinavir.⁸ These results are surprising given that adefovir is cleared by renal excretion and delavirdine by hepatic metabolism.

ABT-378 is a very potent inhibitor of HIV-1 protease.⁹ As with many other PIs, oral dosing results in low levels of ABT-378 in plasma; however, co-administration of a low dose of ritonavir enhances ABT-378's pharmacokinetic properties. In healthy volunteers, co-administration of a single 400 mg dose of ABT-378 with 50 mg of ritonavir enhanced the AUC of ABT-378 in plasma by 77-fold compared with ABT-378 alone, and mean concentrations of ABT-378 exceeded the EC₅₀ for more than 24 hours.⁹ The combination is well tolerated and the sustained plasma levels may delay the emergence of resistance.⁹

Other drug interactions

Methadone

Interactions with methadone are difficult to predict. Methadone is metabolised by CYP3A4 (mainly), CYP1A2 and glucuronyl transferase. *In vitro* ritonavir is more potent than saquinavir or indinavir at inhibiting the metabolism of methadone.¹⁰ However, in healthy volunteers methadone plasma concentrations are significantly reduced in the presence of ritonavir.¹¹ The authors suggest that for low intrinsic clearance CYP3A substrates, especially those with other inducible non-CYP3A pathways, the net effect of ritonavir co-administration can be inductive rather than inhibitory.¹¹

Similarly, nevirapine appears to induce the metabolism of methadone. Seven cases of methadone-maintained patients who developed symptoms of opiate withdrawal within four to eight days of starting nevirapine have been

Further information is available at <http://www.liv.ac.uk/hivgroup>

described.¹² Of the PIs, saquinavir and indinavir appear the least likely to interact with methadone.¹³ The nucleoside analogues zidovudine (ZDV)¹⁴, ddI and d4T¹⁵ have shown no significant alteration of methadone concentrations. However, co-administration of methadone resulted in an increase in the AUC of ZDV¹⁴ and decreases in the AUCs of ddI and d4T.¹⁵

'Ecstasy'

A fatal interaction between ritonavir and ecstasy (MDMA) has been reported,¹⁶ with a plasma ecstasy level approximately ten times greater than anticipated detected post-mortem in a 32-year-old man who had taken MDMA while receiving ritonavir 600 mg twice daily. Ritonavir is a potent inhibitor of CYP2D6, the enzyme principally responsible for MDMA metabolism.

Viagra

Sildenafil (Viagra[®], Pfizer Limited, UK) is metabolised by CYP3A4 and, to a lesser extent, by CYP2C9; it is also a weak inhibitor of CYP2D6. Thus there is the potential for interaction between sildenafil and PIs (and possibly NNRTIs). Pfizer recently released data from two interaction studies. There is a marked pharmacokinetic interaction; sildenafil AUC was increased fourfold and elevenfold by saquinavir and ritonavir respectively. These results have important dosage implications for sildenafil for patients on PIs.

References

1. Back DJ, Barry MG, Gibbons SE. Drug interactions in HIV infection. *Clinical Issues in HIV/AIDS* 1999;3:3-7.
2. Sadler BM, Gillotin C, Chittick GE, Symonds WT. Pharmacokinetic drug interactions with amprenavir. 12th World AIDS Conference, Geneva, Switzerland, June/July 1998 [Abstract 12389].
3. Fiske W, Benedek IH, Joseph JL et al. Pharmacokinetics of efavirenz (EFV) and ritonavir (RIT) after multiple oral doses in healthy volunteers. 12th World AIDS Conference, Geneva, Switzerland, June/July 1998 [Abstract 42269].
4. Summary of Product Characteristics for efavirenz. DuPont Pharmaceuticals Ltd, 1999.
5. Saah AJ, Winchell G, Seniuk M, Deutsch P. Multiple-dose pharmacokinetics and tolerability of indinavir (IDV) ritonavir (RTV) combinations in healthy volunteers. 6th Conference on Retroviruses and Opportunistic Infections, Chicago, February 1999 [Abstract 362].
6. Burger DM, Hugen PWH, Prins JM et al. Pharmacokinetics of an indinavir/ritonavir 800/100 mg bid regimen. 6th Conference on Retroviruses and Opportunistic Infections, Chicago, February 1999 [Abstract 363].
7. Squires K, Riddler S, Havlir D et al. Co-administration of indinavir (IDV) 1200 mg with nelfinavir (NFV) 1250 mg in a twice daily regimen: preliminary safety, PK activity. 6th Conference on Retroviruses and Opportunistic Infections, Chicago, February 1999 [Abstract 364].
8. Acosta EP, Gulick R, Katzenstein D et al. Pharmacokinetic (PK) evaluation of saquinavir soft gel capsules (SQV)/ritonavir (RTV) or SQV/nelfinavir (NFV) in combination with delavirdine (DLV) and/or adefovir dipivoxil (ADV) - ACTG 359. 6th Conference on Retroviruses and Opportunistic Infections, Chicago, February 1999 [Abstract 365].
9. Sham HL, Kempf DJ, Molla A et al. ABT-378, a highly potent inhibitor of the human immunodeficiency virus protease. *Antimicrob Agents Chemother* 1998;42:3218-3224.
10. Iribarne C, Berthou F, Carlhant D et al. Inhibition of methadone and buprenorphine n-dealkylations by three HIV-1 protease inhibitors. *Drug Metab Dispos* 1998;26:257-260.
11. Hsu A, Granneman GR, Carothers L et al. Ritonavir does not increase methadone exposure in healthy volunteers. 5th Conference on Retroviruses and Opportunistic Infections, Chicago, February 1998 [Abstract 342].
12. Altice FL, Cooney E, Friedland GH. Nevirapine induced methadone withdrawal: implications for antiretroviral treatment of opiate dependent HIV infected patients. 6th Conference on Retroviruses and Opportunistic Infections, Chicago, February 1999 [Abstract 372].
13. Beauverie P, Taburet A-M, Dessalles M-C et al. Therapeutic drug monitoring of methadone in HIV-infected patients receiving protease inhibitors. *AIDS* 1998;12:2510-2511.
14. McCance-Katz EF, Rainey PM, Jatlow P, Friedland G. Methadone effects on zidovudine disposition (AIDS Clinical Trials Group 262). *J Acq Immune Defic Syndr Hum Retrovirol* 1998;18:435-443.
15. Rainey PM, McCance EF, Mitchell SM et al. Interaction of methadone with didanosine (ddI) and stavudine (d4T). 6th Conference on Retroviruses and Opportunistic Infections, Chicago, February 1999 [Abstract 371].
16. Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. *Lancet* 1998;352:1751-1752.

The data, opinions and statements appearing in the articles herein are those of the contributor(s) concerned; they are not necessarily endorsed by the sponsor or publisher. Accordingly, the sponsor and publisher, and their respective employees, officers and agents, accept no liability for the consequences of any such inaccurate or misleading data, opinion or statement.

Published by Hayward Medical Communications, a division of Hayward Group plc, Rosemary House, Lanwades Park, Kentford, Newmarket CB8 7PW. Tel: (01638) 751515. Fax: (01638) 751517. email: admin@haywardmedical.co.uk
Art & Editorial Office Hayward Medical Communications, 44 Earlham Street, Covent Garden, London WC2H 9LA.
Tel: (0171) 240 4493. Fax: (0171) 240 4479. email: edit@hayward.co.uk
Copyright © 1999 Hayward Group plc. All rights reserved.

Sponsored by an educational grant from



Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU