HIV resistance testing: value for money

Human immunodeficiency virus (HIV)-related morbidity and mortality has declined dramatically with the introduction of highly active antiretroviral therapy (HAART) into routine HIV care (Palella et al, 1998). Nevertheless, many health authorities continue to struggle with the excessive health-care costs for HIV infection (Perdue et al, 1998). With the emergence of viral resistance testing as a potentially useful adjuvant to standard HIV care, budget pressures will certainly increase.

WHAT IS HIV-1 RESISTANCE TESTING?

Resistance to antiretroviral therapy (ART) is determined by mutations in the genes that encode the HIV-1 reverse transcriptase and protease enzymes. Those mutations result in alteration of drug binding to its target and therefore increase the amount of drug required to inhibit the enzyme (Hirsch et al, 1998).

Genotypic assays use polymerase chain reaction (PCR)-based techniques to determine the nucleotide sequence of the HIV-1 reverse transcriptase and protease enzymes. This is compared with a consensus ('wild type') sequence to identify specific mutations that are associated with ART resistance. They are relatively simple to perform, widely available and have shorter times to results. However, these tests lack standardization (Schuurman et al, 1999), and the results need expert interpretation in line with treatment history, longitudinal changes in plasma HIV-1 RNA levels and likelihood of adherence to medication (Hirsch et al, 1998).

Furthermore, the proportion of ART resistance that can be explained by a specific mutation varies with different antiretroviral agents (Schinazi et al, 1997).

On the other hand, phenotypic assays detect drug-resistant HIV-1 phenotype by measuring the 50% or 90% inhibitory concentration (IC50 or IC90) of a drug in vitro. Individual tests give highly reproducible results (Hellmann et al, 1999) with a significant interassay variation. They involve an expansive, mostly time-consuming, multistage procedure. Both genotypic and phenotypic assays may not detect minority drug-resistant species contributing to drug failure or transmission of resistant virus (Hirsch et al, 1998).

IS HIV RESISTANCE TESTING USEFUL IN CLINICAL PRACTICE?

HIV-1 resistance testing could be useful in guiding choice of initial treatment regimen, explaining and managing treatment failure and tracking the prevalence of primary drug resistance. The routine use of testing is supported by current British HIV Association antiretroviral therapy guidelines (Pozniak et al, 2000).

Before starting ART

Transmission of drug-resistant HIV-1 has been reported in several parts of the world (Boden et al, 1997; Yerly et al, 1999). Therefore, screening for the presence of drug resistance before initiating therapy is sensible, particularly in areas of high prevalence (Hirsch et al, 1998) or when postexposure prophylaxis has failed.

Change of ART

It is important to realize that resistance is only one possible cause of ART failure. Other causes include incomplete adherence (Paterson et al, 1999), suboptimal plasma drug levels (Garraffo et al, 1999), limited penetration of drug to sanctuary sites (Overbaugh et al, 1996), and suboptimal intracellular active drug levels (Sammadossi et al, 1998).

In patients failing ART, several retrospective studies have shown that the only independent predictor of viral suppression was the number of drug-resistance mutations present at baseline (Lorenzi et al, 1999; Zolopa et al, 1999). Data from two, controlled, randomized, prospective studies confirmed that genotypic testing may help improve the outcome of salvage therapy (Baxter et al, 1999; Durant et al, 1999).

Similarly, retrospectively determined phenotypic susceptibility to drugs in the new regimen was the best predictor of sustained virological suppression in a cohort of ART-experienced HIV-infected individuals (Saag et al, 1999). There are no prospective data suggesting that phenotypic resistance testing has clinical utility in determining effective salvage regimens for patients failing current regimens.

Resistance testing is likely to be most useful in detecting the presence of resistance mutations to drugs which can then be avoided. The absence of apparent drug resistance mutations does not exclude the presence of minority resistant variants, which would rapidly predominate under selective drug pressure.

WHAT ARE THE COST IMPLICATIONS?

Genotypic resistance assays cost approximately £200–300. This contrasts with an annual antiretroviral drug cost of up to £10 000–15 000 per patient receiving triple therapy. Economic evaluation of drug resistance genotyping for the adaptation of treatment in HIV-infected patients in

the VIRADAPT study showed no significant difference in total cost between the standard of care group and the genotyping group. However, there was a nearly significant (P=0.06) decrease in drug cost in the genotyping arm. In other words, the savings in drug costs offset the cost of genotyping (Chaix et al, 1999). There are no data available on the cost implications of HIV-1 resistance testing in antiretroviral therapy-naïve patients.

DISCUSSION AND CONCLUSION

Genotypic HIV-1 resistance testing could be beneficial in guiding antiretroviral therapy and improving clinical outcome in HIV-1 infected patients. The increased cost incurred seems to be marginal in the context of antiretroviral drug costs, and the consequent improvement in standard of care.

At present, there is no evidence to support routine use of phenotypic assays in clinical care on HIV-infected individuals. Further studies are required to clarify the cost-effectiveness of resistance testing in ART-naïve and experienced HIV-infected patients. HM

AS Omrani

Specialist Registrar in Genitourinary Medicine

Department of Sexual Medicine

Birmingham Heartlands Hospital

Birmingham B9 5SS

D Pillay

Head

PHLS Antiviral Susceptibility Reference Unit

Department of Infection

University of Birmingham Medical School

Birmingham B15 2TT

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KEY POINTS

- Despite the continuing decline in human immunodeficiency virus (HIV)-related morbidity and mortality, HIV care remains very costly.
- Genotypic resistance assays detect resistance-associated mutations in the viral genome, while phenotypic assays determine the inhibitory concentration of a drug in vitro.
- In treatment-naïve patients, HIV resistance testing can be useful where prevalence of transmission of resistant HIV variants is high.
- In change of therapy, HIV resistance testing helps explain treatment failure and choice of new therapy.
- Evidence suggests that HIV resistance testing in addition to expert interpretation may improve clinical outcome in patients failing an initial antiretroviral therapy regimen.
- Limited data suggest that savings in drug costs probably match extra costs incurred as a result of genotypic testing.