

Perspective

Managing Treatment Failure

The International AIDS Society–USA presented an interactive symposium at the 2001 Interscience Conference on Antimicrobial Agents and Chemotherapy in Chicago in December. Daniel R. Kuritzkes, MD, discussed management of antiretroviral treatment failure, centering his discussion on 2 cases of drug failure encountered in clinical practice.

For a patient in whom an initial antiretroviral regimen has failed, a guiding principle in considering options is that ongoing viral replication in the setting of continued therapy selects for increasing drug resistance. Available data suggest that potentially half of patients on antiretroviral therapy have detectable plasma levels of HIV-1 RNA and that nearly all patients with detectable HIV-1 RNA have drug-resistant virus.

Case 1: Maintain, Switch, or Intensify Therapy After Initial Failure?

Case Presentation

A 21-year-old gay man presented 2 years ago with newly diagnosed HIV-1 infection. The patient was found to be HIV-1-infected by screening at a sexually transmitted disease clinic, and was referred for management of HIV-1 disease. At the time of initial evaluation, the patient was asymptomatic, with a normal physical exam, white blood cell count of 4300/ μ L, CD4+ count of 362 cells/ μ L, and a plasma HIV-1 RNA level of 33,000 copies/mL. After several additional visits and a repeat plasma HIV-1 RNA level that was 31,600 copies/mL,

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the patient was started on antiretroviral therapy with a twice-daily regimen of zidovudine/lamivudine/nelfinavir. A repeat plasma HIV-1 RNA test 4 weeks after initiating therapy showed a level of 249 copies/mL, but the patient complained of nausea and loose stools. The loose stools were controlled with loperamide, but nausea persisted, necessitating a switch from zidovudine to stavudine. A follow-up plasma HIV-1 RNA level was less than 50 copies/mL, and the CD4+ count was 451 cells/ μ L.

The patient continued to do well over the subsequent year with regular follow-up every 2 to 3 months. Plasma HIV-1 RNA levels remained below 50 copies/mL and the CD4+ cell count increased modestly over this interval. At a subsequent visit, the patient's plasma HIV-1 RNA level was 2300 copies/mL, with a CD4+ cell count of 511/ μ L; a confirmatory test 2 weeks later showed an HIV-1 RNA level of 7200 copies/mL. A genotype of the patient's plasma virus showed an M184V mutation in the reverse transcriptase gene, consistent with lamivudine resistance.

The possible treatment options discussed for this patient were:

1. Continue the patient on the current therapy
2. Change to abacavir/didanosine/efavirenz
3. Change to stavudine/didanosine/lopinavir/ritonavir
4. Change to stavudine/didanosine/nelfinavir
5. Intensify without removing drugs from the regimen
6. Discontinue antiretrovirals and monitor

Discussion

The discontinuation of all antiretrovirals has recently become more of a consideration in patients such as this one.

Upon initial presentation, the patient was at relatively low risk of near-term progression of disease based on CD4+ cell count and relatively low HIV-1 RNA level. It is now recognized that delaying initiation of treatment in early infection is not associated with increased risk of near-term progression, and in the past several years, many patients were started on antiretroviral therapy earlier than they would be under more current guidelines. Accumulating data from patients started early on therapy who have discontinued treatment suggest that CD4+ cell count gradually returns to pretreatment levels over several months, with such patients appearing to be at no increased risk of short-term progression. Likewise, plasma HIV-1 RNA levels gradually increase back to the pretreatment set point. Thus, supervised discontinuation of treatment with continued monitoring is an option in this case.

Among the other options, the least favorable is maintaining the current regimen. Factors in favor of changing the regimen include: (1) the potential for achieving maximum viral suppression with a compact regimen that minimizes the number of pills taken per dose, given the relatively limited viral resistance; and (2) the fact that clinical benefit of treatment is related to duration of viral suppression (primarily because such suppression is related to the overall magnitude of the CD4+ cell count increase).

Factors arguing against changing the regimen include the relatively low risk of clinical progression in this patient and the fact that CD4+ cell count appears to have been maintained in the presence of low-level viral replication. The factor that tips the balance in favor of changing therapy sooner rather than later in a patient in whom alternative treatment options exist is the concern that persistent virus replication in the setting of continued therapy will allow the accumulation of additional resistance mutations, leading eventually to a highly resistant virus. In such a patient, virus

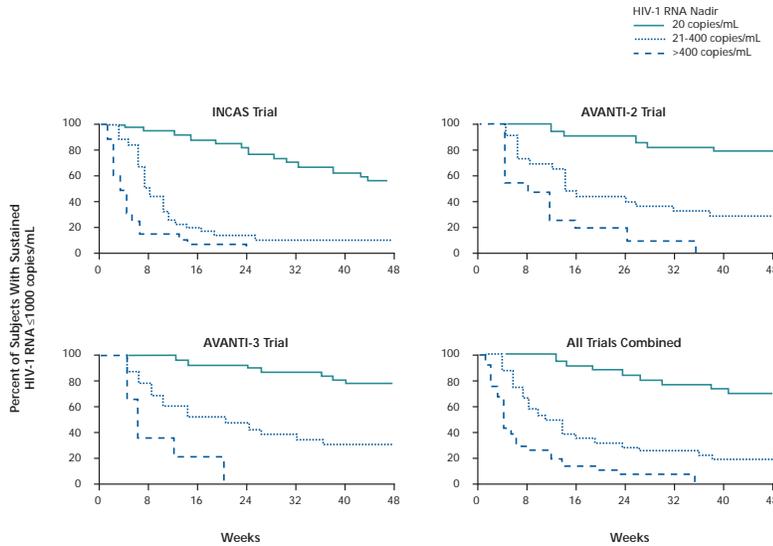


Figure 1. Proportions of patients with HIV-1 RNA level of 1000 copies/mL or less according to HIV-1 RNA nadir in INCAS, AVANTI-2, and AVANTI-3 studies and combined. Adapted from Raboud et al, *J Infect Dis*, 1999.

would likely accumulate additional nucleoside reverse transcriptase inhibitor (nRTI)-associated resistance mutations, eventually resulting in loss of utility of the whole nRTI class, and would begin to accumulate protease inhibitor resistance mutations as well. Although preservation of future treatment options has been considered a reason to avoid early switching, recent data suggest that early switching may in fact preserve treatment options by minimizing the development of broad cross-resistance.

A primary factor in treatment failure in many patients, and a primary factor to consider in selecting alternative regimens, is poor adherence to the drugs. A recent analysis by Paterson and colleagues (*Ann Intern Med*, 2000) showed that the virologic failure rate was 21.7% in patients with 95% or greater adherence and increased to 54.5% in those with 90% to 94.9% adherence. The failure rate was 66.7%, 71.4%, and 82.1% in patients with 80% to 89.9%, 70% to 79.9%, and less than 70% adherence, respectively. Other data have shown that increases in HIV-1 RNA can be detected in close temporal association with treatment interruptions, with eventual evolution of viral resistance being observed.

A variety of data support the notion that time to treatment failure is related to magnitude of viral suppression.

Studies from the potent antiretroviral therapy era demonstrate that risk of virologic failure, defined as plasma HIV-1 RNA level greater than 1000 copies/mL, is lowest among patients in whom the HIV-1 RNA nadir is less than 20 copies/mL compared with patients with higher HIV-1 RNA nadir values (Figure 1; Raboud et al, *J Infect Dis*, 1999). Data from these studies indicate that HIV-1 RNA nadirs in the 21 to 400 copies/mL range are associated with relatively little improvement in risk of failure compared with nadirs greater than 400 copies/mL.

A meta-analysis conducted by investigators from the US Food and Drug Administration, using data primarily from the era of dual nRTI therapy, showed that risk of clinical progression was related to duration of viral suppression, with viral suppression defined as an HIV-1 RNA decrease of 0.5 log₁₀ or greater from the pretreatment level (Murray et al, *AIDS*, 1999). Such data tend to support switching regimens with the intention of maximizing viral suppression.

Some direct evidence of the benefit of switching earlier rather than later comes from analyses of virologic outcome according to plasma HIV-1 RNA level at the time of switching. Tebas and colleagues (*AIDS*, 1999) conducted a study of patients in whom saquinavir/ritonavir was substituted for nelfinavir in a failing regimen. They reported that the likelihood of sustaining viral suppression at less than 500 copies/mL was significantly greater in those who switched drugs when plasma HIV-1 RNA level was less than 30,000 copies/mL than in those whose switched at a higher plasma HIV-1 RNA level (Figure 2). This difference in outcome was also related to the accumulation of drug resistance mutations.

In terms of evolution of resistance, the genotypic pattern in the virus in the patient described is characteristic of that in patients in whom a first protease inhibitor-based regimen including lamivudine is failing. Available data

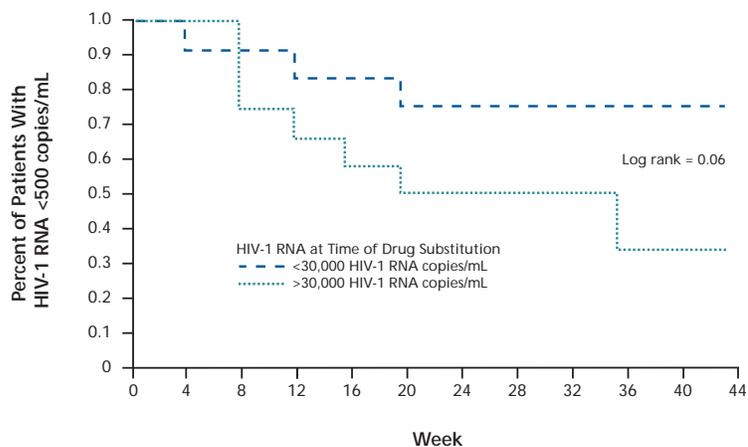


Figure 2. Proportions of patients maintaining virologic response after substitution of saquinavir/ritonavir for nelfinavir in a failing regimen according to whether HIV-1 RNA level was below or above 30,000 copies/mL at the time of substitution. Adapted from Tebas et al, *AIDS*, 1999.

indicate that the first resistance mutation to develop in patients receiving potent antiretroviral regimens tends to be the one that confers the highest level of resistance and is a single-step mutation. For protease inhibitor-based regimens and triple nRTI regimens containing lamivudine, it typically is lamivudine resistance that occurs first. In a study comparing zidovudine/lamivudine/abacavir and zidovudine/lamivudine/indinavir in treatment-naïve patients (Melby et al, 8th CROI, 2001), the only mutation present for 28 weeks in a patient with virologic failure on zidovudine/lamivudine/abacavir was the lamivudine M184V mutation. Other nRTI-associated mutations subsequently appeared. Examination of the evolution of resistance patterns in the entire study population showed that, over time, the proportion of patients with the M184V mutation plus any other nRTI-associated resistance mutation increased, and the proportion of patients with just the M184V mutation or wild-type virus decreased.

Among patients having first treatment failure while receiving protease inhibitor-based regimens, lamivudine resistance was found in 14 of 17 patients and indinavir resistance in 1 of 26 patients receiving zidovudine/lamivudine/indinavir or indinavir alone in one study (Havlir et al, JAMA, 2000). In another study, lamivudine resistance was found in 17 of 23 patients and indinavir resistance in 5 of 23 patients receiving zidovudine/lamivudine/indinavir (Boden et al, JAMA, 1999). In 16 patients in whom a regimen of zidovudine/lamivudine/amprenavir was failing, lamivudine resistance was found in 14, zidovudine resistance in 4, and amprenavir resistance in 2 (De Pasquale et al, *Antiviral Ther*, 1998). In studies of patients with plasma HIV-1 RNA levels greater than 400 copies/mL during weeks 24 to 60 of treatment that included lamivudine and lopinavir/ritonavir or nelfinavir, protease inhibitor resistance mutations were found in 0 of 40 and lamivudine resistance in 15 (38%) of 40 patients in the lopinavir/ritonavir arm. Nelfinavir resistance mutations were found in 31 (37%) of 84 patients and lamivudine resistance in 68 (81%) of 84 patients in the nelfinavir arm (Kempf et al, 1st IAS Conf, 2001).

A similar pattern has been observed

in patients receiving efavirenz in combination with a protease inhibitor, with efavirenz resistance being found in 10 of 14 patients and indinavir resistance in 3 of 14 patients receiving failing efavirenz/indinavir therapy (Holder et al, 6th CROI, 1999). With subsequent accumulation of protease inhibitor mutations, phenotypic susceptibility to the protease inhibitor being used decreases. These observations support earlier switching to prevent the predictable accumulation of mutations that will result in reduced effectiveness of alternative drugs, as well as to attempt to achieve resuppression of a viral population not yet characterized by accumulated mutations.

Although the patient in this case has a sustained elevation in viral load, there remain questions about whether “blips” in HIV-1 RNA level predict treatment failure. A study by Havlir and colleagues (JAMA, 2001) found that there was no significant difference in the rate of virologic failure, defined as sustained viremia greater than 200 copies/mL, in 97 patients with at least 1 episode of viremia of more than 50 copies/mL versus patients without blips (9.7% vs 13.9%). This result suggests that such intermittent viremia does not predict failure. Data presented recently by Di Mascio and colleagues support this conclusion (9th CROI, 2002). However, an analysis by Greub and colleagues (8th CROI, 2001) showed treatment failure rates of 5.1 per 100 person-years-of-observation in patients with no blips, 7.9 in those with 1 to 3 blips, and 21 in those with 4 or more blips. Blip was defined as an episode of viremia of 50 to 500 copies/mL. The 3.01 odds ratio for progression in the 4 or more-blip group versus the no-blip group was statistically significant. Ramratnam and colleagues (*Nat Med*, 2000) reported that viremia blips may be associated with a significant slowing of rate of decay of latently infected peripheral blood mononuclear cells or an increase in the viral reservoir of latently infected cells.

With regard to the option of intensification, a number of studies have shown benefit of the addition of abacavir or tenofovir to existing regimens. Katlama and colleagues (AIDS, 2000) found that the addition of abacavir to suboptimal background therapy pro-

duced a decrease in HIV-1 RNA of at least 0.5 log₁₀ copies/mL over 16 weeks compared with a slight increase in those continuing therapy. Rozenbaum and colleagues (6th CROI, 1999) found that the addition of abacavir to zidovudine/lamivudine therapy in patients with the M184V resistance mutation alone improved virologic response rates (<400 copies/mL) from 5 of 31 patients (16%) to 22 of 31 patients (71%) at 48 weeks, with 17 (55%) of these patients achieving HIV-1 RNA levels less than 20 copies/mL. Tenofovir produced maximal reductions in HIV-1 RNA in the treatment failure setting of 0.6 to 0.7 log₁₀ copies/mL, with smaller reductions being observed with decreased viral susceptibility to tenofovir at baseline. These effects were associated with the presence or absence of nRTI-associated resistance mutations. Although intensification is thus an option, there currently is relatively little information on this strategy in patients in whom initial antiretroviral regimens were failing.

Clinical Decision and Outcome

The available data indicate that the patient in this case, if he is not to have a supervised treatment discontinuation, should have his antiretroviral therapy changed and sooner rather than later. In fact, the patient opted to change from nelfinavir to lopinavir/ritonavir, and to change from lamivudine to didanosine. In this case, the need to change nelfinavir was based on issues related to tolerability rather than to drug resistance. Lopinavir/ritonavir was a good substitution because the patient was already taking a protease inhibitor-based regimen, and this change preserved the nonnucleoside reverse transcriptase inhibitors (NNRTIs) as a future option. The switch from lamivudine to didanosine was prompted by the presence of the lamivudine-associated M184V mutation.

Case 2: Options in the Setting of Complicated Treatment History

Case Presentation

A 49-year-old woman presented with heterosexually acquired HIV infection. She received initial therapy with zidovudine, lamivudine, and indinavir in 1995,

but was forced to discontinue zidovudine as a result of gastrointestinal intolerance. Substitution of stavudine led to development of severe peripheral neuropathy, which persisted despite discontinuation of stavudine and required methadone for pain management. During subsequent indinavir monotherapy, her HIV-1 RNA level was 12,650 copies/mL with a CD4+ count of 325 cells/ μ L. Abacavir/ritonavir/saquinavir was substituted and HIV-1 RNA level decreased to less than 50 copies/mL, but abacavir had to be discontinued because of apparently associated worsening of peripheral neuropathy.

Nevertheless, the HIV-1 RNA level remained suppressed to less than 400 copies/mL on ritonavir/saquinavir until ritonavir liquid replaced the capsule formulation, at which point the patient was unable to tolerate her medications and discontinued all antiretroviral therapy. The plasma HIV-1 RNA level increased to 47,320 copies/mL and the CD4+ count decreased to 283 cells/ μ L. A genotype assay demonstrated presence of the V32I, M46I, V82A, and L90M mutations in the protease gene and the M184V mutation in the reverse transcriptase gene. The patient was then started on zidovudine/lamivudine/efavirenz, but took her medications only intermittently because of the occurrence of numerous adverse effects. HIV-1 RNA level initially declined to 650 copies/mL and CD4+ count increased to 340 cells/ μ L, but the HIV-1 RNA level again increased to 43,520 copies/mL and the CD4+ count declined to 298 cells/ μ L when the patient discontinued her medications because of epigastric pain. Endoscopy revealed presence of a benign gastric ulcer, which was treated with omeprazole and ranitidine. A phenotype assay demonstrated resistance only to efavirenz, and sensitivity to all protease inhibitors and nRTIs.

The possible treatment options discussed for this patient were:

1. Start tenofovir/abacavir/ritonavir/amprenavir
2. Start zidovudine/lamivudine/ritonavir/indinavir
3. Start zidovudine/lamivudine/ritonavir/lopinavir

4. Start zidovudine/lamivudine/delavirdine/nelfinavir
5. Continue to monitor the patient off therapy

Discussion

At the time that this patient was seen, it was difficult to determine what the next step in management should be. She had experienced multiple toxicities with different agents. Lopinavir/ritonavir had just become available and tenofovir was not yet available. Although the patient showed phenotypic susceptibility to indinavir, the prior evidence of indinavir resistance argued against use of ritonavir-boosted indinavir in the context of other potential options, since it was reasonable to assume that the resistant virus remained present and would reemerge with reinstatement of indinavir. It was thought best to avoid the current formulation of amprenavir because of concern over gastrointestinal adverse effects.

In considering protease inhibitors in salvage therapy, it is important to note that there are greater differences among the resistance mutation patterns of these drugs than was initially believed. Data from the VIRA 3001 study, for example, show that virus with greater than 4-fold phenotypic resistance to indinavir is likely to be cross-resistant to nelfinavir and ritonavir but susceptible to amprenavir and saquinavir; virus with

greater than 4-fold resistance to nelfinavir is likely to remain susceptible in varying degrees to ritonavir, indinavir, saquinavir, and amprenavir (Figure 3) (Cohen et al, AIDS, 2002).

Lopinavir/ritonavir is a good choice in the case of the current patient. Responses to lopinavir/ritonavir have been observed even in patients with virus exhibiting 4 or 5 protease inhibitor resistance mutations. Kempf and colleagues (*Antivir Ther*, 2000) reported response rates of 67% and 50% in multiple protease inhibitor-experienced patients with virus having 20- to 40-fold and greater than 40-fold resistance to lopinavir at baseline, respectively. In NNRTI-naive, multiple protease inhibitor-experienced patients, Clumeck and colleagues (XIII Int AIDS Conf, 2000) observed a decrease in HIV-1 RNA level to less than 400 copies/mL in 92% of patients receiving lopinavir/ritonavir 533/133 mg twice daily plus efavirenz and 80% of patients receiving 400/100 mg twice daily plus efavirenz in on-treatment analysis (82% and 69%, respectively, in intent-to-treat analysis with missing data equal to failure).

Protease inhibitor inhibitory quotient (IQ) appears to be the best predictor of response to boosted protease inhibitor treatment. The IQ provides an integrated measure of resistance and drug concentrations in the individual patient. One way of measuring protease inhibitor IQ is to divide the trough plas-

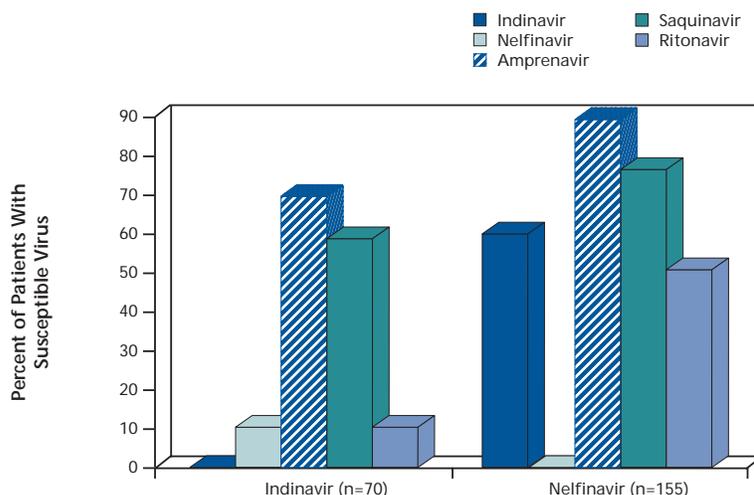


Figure 3. Distribution of susceptibility to protease inhibitors of virus with more than 4-fold phenotypic resistance to indinavir or nelfinavir. Adapted from Cohen et al, *AIDS*, 2002.

ma concentration by the 50% inhibitory concentration of the drug. The IQ of lopinavir has been shown to predict response to lopinavir/ritonavir plus efavirenz/nRTI therapy in multiple protease inhibitor-experienced, NNRTI-naive patients (Hsu, 5th Int Cong Drug Ther HIV Infect, 2000).

A virtual IQ can be derived from a phenotype database rather than from measurement of phenotypic susceptibility. Kempf and colleagues (8th CROI, 2001) used the virtual IQ in place of a phenotype determined by direct measurement in order to calculate the virtual IQ. In their study of 37 patients with HIV-1 RNA levels of 50 to 50,000 copies/mL on stable indinavir-containing therapy, use of indinavir virtual IQ showed that more than 80% of patients with indinavir IQ greater than 2 maintained virologic response to a ritonavir-boosted indinavir regimen at 48 weeks compared with no patients with indinavir IQ less than 2. (Virologic response was defined as a 0.5- \log_{10} decline in plasma HIV-1 RNA from baseline or plasma HIV-1 RNA below detection levels at week 24.) In this study, indinavir virtual IQ proved to be a better predictor of virologic response at week 3 than virtual phenotype, number of protease inhibitor mutations, or number of reverse transcriptase mutations (Figure 4).

Clinical Decision and Outcome

The patient in Case 2 was treated with the ritonavir-boosted lopinavir regimen (Option 3) and has done quite well on this treatment.

Conclusions

Management of treatment failure differs according to whether the failure emerges on the first or second regimen or after more regimens have been used. In all patients, treatment benefit is a function of immune reconstitution and viral suppression. For patients in whom initial regimens have failed, ongoing viral replication in the setting of continued treatment with a regimen to which resistance has emerged allows accumulation of additional resistance mutations and eventual emergence of highly resistant virus. In more advanced patients in whom options for achieving full viral suppression may be exhausted,

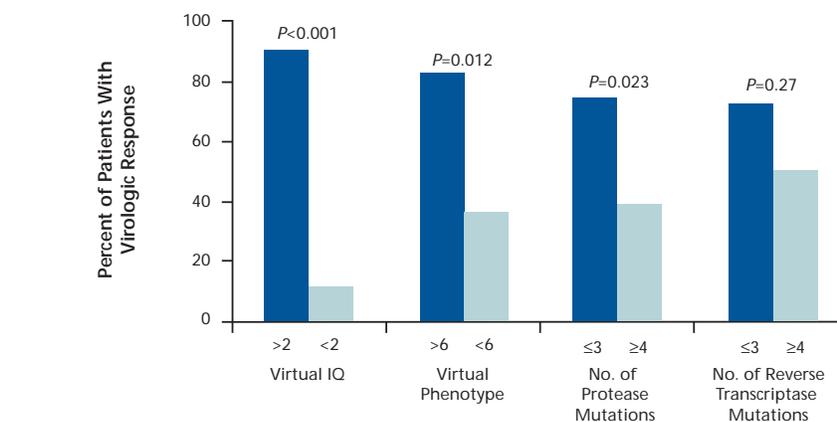


Figure 4. Ability of indinavir virtual inhibitory quotient (virtual IQ), virtual phenotype, number of protease inhibitor mutations, and number of reverse transcriptase mutations to predict virologic response to regimen containing indinavir/ritonavir at 3 weeks. Adapted from Kempf et al, 8th CROI, 2001.

residual virus suppression confers residual treatment benefit and persistent viral replication leads ultimately to immunologic decline; thus, some treatment is better than none in most such patients.

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