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Hot News

Welcome to «Hot News», a section of AIDS Reviews written by the editors and invited experts which focuses on recently reported information believed to be of both impact and higher interest to the readership.

Revision of the DHHS Guidelines for the Use of Antiretroviral Agents

Three major sections of the guidelines (http://www.aidsinfo.nih.gov/guidelines/) were revised on July 14th 2003 – (1) recommendations for the selection of antiretroviral drug combinations as initial regimen for treatment-naive HIV-infected patients; (2) recommendations for the use of resistance testing to guide therapy, and (3) recommendations on the management of patients who have experienced treatment failure.

Advances in research and knowledge in the use of antiretroviral therapy in the management of HIV infection has led to the licensing of 19 antiretroviral agents in the US. This allows for more flexibility in designing an individualized combination regimen consisting of 3-4 antiretroviral agents for treatment-naive patients.

Previous guidelines in table 12 divided a typical combination regimen into component A (1 or 2 protease inhibitors [PIs], or a non-nucleoside reverse transcriptase inhibitor [NNRTI], or abacavir [a nucleoside reverse transcriptase inhibitor or NRTI]) and component B (a 2-NRTI backbone). The prescribing clinicians had to select the regimen by combining the choices from each of the components. As the choices of which agents to use became more complex, it was obvious to the panel members that a change in the format of this table was necessary to make it a more useful guide for practicing HIV clinicians.

The new format divides the old "table 12" into three major tables. Table 12a provides a list of recommended "combination regimens" rather than two columns of components. The selection of "preferred" vs "alternative" regimens is primarily based on potency as well as tolerability of the regimens, using published or abstract data from clinical trials. In general, clinicians are recommended to initiate therapy with either a PI-based or an NNRTI-based combination regimen. Due to the virologic inferiority of a 3 NRTI-based regimen such as abacavir + zidovudine + lamivudine, this combination should only be used if there is a compelling reason not to use either an NNRTI-based or a PI-based regimen.

A newly created table 12b lists the known advantages and disadvantages of the different components, taking into account antiviral potency, side effect profiles, drug-drug and drug-food interaction potentials, pill burden, and dosing convenience. Prescribers are encouraged to refer to this table when selecting a specific initial regimen for an individual patient.

Lastly, another new table, table 13, lists the drug components not recommended to be prescribed and the rationale behind these recommendations.

As new knowledge becomes available and new drugs are being marketed, the guidelines need ongoing revision in a timely manner. The web-based "Living Document" allows for such revisions to occur. A new revision with recommendations for two new antiretroviral agents – namely, atazanavir and emtricitabine– will be available in the next couple of months.

Alice Pau
National Institute of Allergy and Infectious Diseases
National Institutes of Health, Bethesda, USA

Nevirapine reassessed by the WHO as the preferred drug to prevent mother-to-child transmission of HIV

The Division of AIDS of the National Institutes of Health (NIH) in Bethesda has recently released the final report (dated March 2003) from the reassessment of the trial procedures and results in the HIVNET 012 trial conducted in Uganda (www.niaid.nih.gov/daids/Prevention.htm). This trial, the first to demonstrate the safety and efficacy of nevirapine (NVP) to prevent mother-to-child transmission (MTCT) of HIV, was started in Uganda in 1997 and the results were published in 1999 (Guay, et al. Lancet 1999;354:795-802). A single dose of NVP given at onset of labor, plus a single dose to the newborn within 72 h of birth, reduced the risk of HIV transmission down to 13%, almost 2-fold lower than a short course of AZT started during labor. Concerns about the trial were raised when claims emerged that certain serious adverse events had not been properly reported. The Division of AIDS issued

a statement with the final report that concludes: "In summary, the re-monitoring of the study determined that NVP 200 mg orally given to the mother at delivery and 2 mg/kg given to the neonate within 72 h, is safe and effective".

NVP was the first non-nucleoside RT inhibitor approved by the FDA for the treatment of HIV infection. The drug is recommended by the US Public Health Service Task Force for MTCT prevention among women in labor who have had no prior therapy (http://AIDSinfo.nih.gov) and is included for both treatment and MTCT prevention purposes in the WHO Model List of Essential Medicines.

In October 2000, the WHO, in partnership with UNAIDS, UNICEF and UNFPA, convened a technical consultation to review all available evidence on the safety and effectiveness of short-course antiretroviral drug-based interventions to reduce the risk of MTCT (www.who.int/reproductive-health/rtis/MTCT_consultation.en.html). The consultation concluded that all regimens which had been shown to be safe and effective in controlled clinical trials could be used in MTCT prevention programs. These regimens included AZT alone or in combination with 3TC, as well as NVP. Since the consultation, further research conducted in South Africa has demonstrated the safety and efficacy of NVP.

Each year, about 800,000 infants become infected with HIV, mainly through vertical transmission. Scaling-up MTCT prevention programs in resource-limited settings to reach more HIV-positive mothers and prevent further infants being infected with HIV is a major challenge, to which many governments, non-governmental organizations, international agencies and the WHO are committed. While NVP is only one of several regimens which have been shown to be safe and effective, the low cost and simplicity of use of the regimen makes it particularly attractive and convenient. Therefore, the WHO and its partner United Nations agencies recommend that MTCT prevention using antiretroviral regimens such as NVP should be included in the minimum standard package-of-care for HIV-positive women and their children.

Pablo Barreiro
Hospital Carlos III
Madrid, Spain

New revised HIV treatment recommendations for women of reproductive age

The US Department of Health and Human Services (DHHS) released on July 14th 2003 new revised guidelines for the use of antiretroviral agents (http://www.aidsinfo.nih.gov). Special considerations in regimen selection were made for women of reproductive age. When initiating antiretroviral therapy, the indications for beginning therapy, and the goals of treatment, are the same as for other adults. For the woman who is pregnant, an additional goal of therapy is prevention of mother-to-child transmission (MTCT).

In women of reproductive age, regimen selection should allow for the possibility of planned or unplanned pregnancy. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity and reproductive plans should thus be discussed with the patient. As part of the evaluation for initiating therapy, women should be counseled about the potential risk of efavirenz-containing regimens, should pregnancy occur. These regimens should be avoided in women who are trying to conceive or who are not using effective and consistent contraception. This counseling should be provided on a routine basis after initiation of therapy as well.

Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to the prevention of MTCT and to maternal and fetal safety, timing of initiation of treatment and selection of regimens are different than for non-pregnant individuals.

Antiretroviral therapy is recommended in all pregnant women, regardless of virologic, immunologic, or clinical parameters, for the purpose of prevention of MTCT. Reduction of plasma HIV-RNA levels to below 1,000 copies/ml and use of antiretroviral therapy appear to have an independent effect on the reduction of perinatal transmission.

Standard combination antiretroviral therapy (HAART) is recommended for pregnant women who meet the clinical, immunologic, or virologic criteria for initiating therapy. HAART should also be recommended and offered to pregnant women who do not meet criteria outlined for initiation of therapy in non-pregnant adults, but who have HIV-RNA levels > 1,000 copies/ml. These regimens should be chosen from among those recommended for non-pregnant women. Whenever possible, AZT should be part of the combination, given that it has shown in PACTG 076 the greatest reductions in MTCT in clinical trial settings.

Stavudine-containing regimens are not recommended as initial regimens for antiretroviral-naive women in pregnancy because of pharmacological antagonism with AZT. However, regimens containing d4T may be considered in women unable to tolerate AZT (i.e., anemia). Regardless of the antepartum antiretroviral regimen, the intrapartum and neonatal components of the AZT chemoprophylaxis regimen are still recommended.

For pregnant women with plasma HIV-RNA levels < 1,000 copies/ml and on no therapy, acceptable options include standard combination therapy with HAART, dual NRTI therapy with AZT plus 3TC, or AZT monotherapy, all including the three-part AZT chemoprophylaxis regimen. Although use of less-than-standard therapy during pregnancy is controversial, possible advantages include further benefit in the reduction of MTCT and low expected rates of resistance due to low viral replication and time-limited administration of drug(s) during the second and third trimesters of pregnancy.

In antiretroviral-naive pregnant women, initiation of antiretroviral therapy may be delayed until after 10-12 weeks gestation, to avoid the period of greatest vulnerability of the fetus to potential teratogenic effects and because nausea and vomiting in early pregnancy may affect optimal adherence and absorption of antiretroviral medications. However, if clinical, virologic, or immunologic indications for initiation of therapy in non-pregnant individuals exist, many experts would recommend initiating therapy regardless of gestational stage.

There are insufficient data to support or refute the teratogenic risk of antiretroviral drugs in humans when administered during the first trimester of pregnancy. However, efavirenz-containing regimens should be avoided in pregnancy because significant teratogenic effects were seen in primate studies at drug exposures similar to those representing human exposure. In addition, a single case of myelomeningocele has now been reported after early human gestational exposure to efavirenz.

The combination of ddI and d4T should be avoided as first-line therapy during pregnancy because of reports of several maternal deaths secondary to lactic acidosis with prolonged use of regimens containing these two nucleoside analogues in combination. In general, this combination should be used during pregnancy only when other NRTI drug combinations have failed or have caused unacceptable toxicity or side effects. Lastly, the oral liquid formulation of amprenavir contains a high level of propylene glycol and should not be used in pregnant women.

Juan González-Lahoz
Hospital Carlos III
Madrid, Spain

Treatment guidelines revised: drugs to be excluded from initial regimens

The US Department of Health and Human Services (DHHS) updated its guidelines for the treatment of HIV Infection on July 14th 2003. Based on recent data, the Panel does not endorse a number of antiretrovirals as part of an initial regimen in an antiretroviral-naive patient. The reasons for not recommending their use as initial therapy are grouped in three categories.

First, drugs with modest antiviral activities. Affect delavirdine; and AZT plus ddC. Second, antiretroviral compounds requiring a high pill burden, such as amprenavir (16 capsules per day) and saquinavir soft gel capsule (18 capsules per day). The last category of drugs to be excluded from initial regimens are those with a proven high incidence of toxicity, like ritonavir used as single PI (due to gastrointestinal side effects) and d4T plus ddI (due to the increased risk of neuropathy and/or hyperlactatemia).

Marina Núñez
Hospital Carlos III
Madrid, Spain

New Guidelines on Antiretroviral Drug Resistance Testing

Antiretroviral (ARV) drug resistance is an important cause of treatment failure, and multiple studies have shown that such testing can result in improved virologic outcome in drug-experienced patients. It is noteworthy, in this regard, that four separate guideline documents, all published or posted on websites since June 2003, address the use of ARV drug resistance testing in clinical practice. These documents, including three from US governmental agencies and one from the International AIDS Society-USA (IAS-USA), are cited in the Guidelines Section of this issue of AIDS Reviews.

In general, these guidelines suggest a more aggressive use of ARV drug resistance testing than has been recommended previously. While testing has been recommended for patients who are failing or responding suboptimally to ARV therapy and for patients with acute HIV infection, testing is now proposed as an option for chronically infected patients initiating therapy, particularly for those thought to have been infected by a person receiving ARV drugs. The reasons for this change include an increasing body of information indicating a significant prevalence of drug resistance among treatment-naive persons, the knowledge that some drug resistance mutations can persist for two years or longer following seroconversion (and will therefore be detectable by current genotypic assays), and limited information that patients with baseline drug resistance respond suboptimally to ARVs not selected based on resistance testing. It also seems intuitive, and consistent with the approach to other infectious diseases, that testing for ARV resistance at baseline will be of value. However, it should be noted that prospective data supporting the use of baseline drug resistance testing in treatment-naive persons beginning therapy are currently lacking.

The guidelines differ slightly in their approach to testing in pregnant women. The IAS-USA guidelines are more aggressive, suggesting that all pregnant women with detectable virus be tested, to optimize therapy for the mother and for prevention of transmission to the child. The other documents suggest that testing should be used as for non-pregnant persons. Again, prospective data to support the utility of drug resistance testing in treatment-naive pregnant women, in terms of outcomes in mother and child, are currently lacking and would be of great value for future editions of these guidelines.

Jonathan E. Kaplan
Centers for Disease Control and Prevention
Atlanta, Georgia
USA

Tenofovir-related nephrotoxicity

Tenofovir disoproxil fumarate (TDF) is a novel nucleotide analog recently approved for the treatment of both naive and pre-treated HIV-infected individuals. *In vitro* comparisons with other nucleoside analogs indicate that the potential for mitochondrial dysfunction is low using TDF. However, concern exists about the risk of nephrotoxicity using this drug, given its similarities with adefovir. Although no significant kidney toxicity has been found in clinical trials conducted so far in humans exposed to TDF, abnormalities in renal function have been reported in studies performed in animal models using high doses of the drug.

In the last six months, at least 13 cases of TDF-related nephrotoxicity have been reported in the literature (see table). Mean age of these patients was 48 years. Interestingly, the weight of these patients tended to be low, suggesting a dose-related effect. In four cases, renal insufficiency was already present before TDF was initiated, although it worsened with TDF administration. Renal toxicity appeared with an average of 6.5 months (range, 1 to 11) after beginning TDF. Subjects developed either Fanconi's syndrome (proximal renal tubular acidosis, hypophosphoremia, hypouricemia, glucosuria and proteinuria) or nephrogenic diabetes insipidus, leading in some cases to acute renal failure. In patients in which a renal biopsy was performed, severe acute necrosis of the proximal tubular epithelium was found. In all cases, TDF discontinuation was followed by improvement in the renal function.

The mechanism by which TDF induces renal toxicity is not well known. This drug is structurally closed to adefovir and cidofovir, which are well-known nephrotoxic agents. As with these drugs, TDF is eliminated by glomerular filtration and mainly active tubular secretion through hOAT1 (human organic anion transporter-1). The hOAT1 is a transport system that internalizes nucleotide analogs (adefovir, cidofovir and TDF) into the proximal tubular epithelium by active secretion.

Table. *Case reports of tenofovir-related kidney dysfunction*

Case no.	Reference	Concomitant drugs	CD4 (cells/μl)	Creat (mg/dl)	[P]p	[U]p	Lactate	Metabolic Acidosis	[Prot]u	[hem]u	[P]u	[Glu]u
1	AIDS 2003;17:935-7	ddI + d4T + ATZ + RTV	318	↑	NA	↓	NA	+	+	+	+	+
2	Clin Infect Dis 2003;36:1070-3	LPV + RTV + ABC	<50	7.8	↓	NA	NA	+	+	–	NA	+
3	"	ddI + 3TC + RTV + APV + T20	<50	1.7	NA	NA	NA	NA	+	NA	NA	+
4	"	3TC + ABC + LPV + RTV	<50	2.7	↓	NA	NA	+	+	–	NA	NA
5	10th CROI, 2003 (P717)	3TC + EFV + LPV + RTV	822	1.13	↓	↓	N	NA	+	NA	NA	+
6	"	3TC + EFV + LPV + RTV	252	0.9	↓	↓	N	NA	+	NA	NA	+
7	"	3TC + ddI + APV + RTV	64	1.14	↓	↓	N	NA	+	NA	NA	+
8	10th CROI, 2003 (P718)	NA	NA	NA	↓	NA	N	NA	NA	NA	NA	NA
9	"	NA	NA	NA	↓	NA	N	NA	NA	NA	NA	NA
10	"	NA	NA	NA	↓	NA	N	NA	NA	NA	NA	NA
11	Am J Kidney Dis 2002;40:1331-3	ddI + LPV + RTV	NA	2.2	↓	NA	N	NA	+	NA	NA	NA
12	Clin Infect Dis 2003;36:1082-5	ddI + APV + RTV	35	↑	NA	NA	↑	+	NA	NA	NA	NA
13	Am J Med Sci 2002;324:342-4	NA	NA	↑	NA	NA	NA	NA	NA	NA	NA	NA

NA: not available; [P]p: plasma phosphorus levels; Creat: creatinine plasma levels; [U]p: uric acid plasma levels; [Prot]u: proteinuria; [hem]u: hematuria; [P]u: phosphaturia; [Glu]u: glucosuria

Once these drugs are accumulated within the tubular kidney cells, their high intracellular concentrations may interfere with cellular functions. In the particular case of adefovir, active metabolites interfere with mitochondrial function leading to mitochondrial toxicity. This kidney-specific susceptibility to the cytotoxic effect of both adefovir and cidofovir is mainly due to the high level of expression of hOAT1 in kidney cells. In contrast, *in vitro* studies have shown weak TDF cytotoxicity on proximal tubular cells (Cihlar T, et al. Nucleosides Nucleotides Nucleic Acids 2001;20:641-8). Another interesting finding is that nucleotide nephrotoxicity is not accompanied by hyperlactatemia, as often occurs when mitochondrial toxicity develops taking nucleoside analogs, such as stavudine (d4T) (Blanco F, et al. HIV Clin Trials 2003;4:11-9). This suggests that nucleotides may cause local rather than systemic mitochondrial dysfunction, which might be more often seen with some nucleoside analogs.

Physicians should be aware of the potential risk of nephrotoxicity using TDF, especially in patients with previous renal dysfunction. In TDF-treated individuals, urinoanalysis together with plasma measurement of phosphorus, lactate and uric acid should be added to the routine biochemical monitoring. More studies are warranted to clarify if other risk factors (age, weight, concomitant drugs, etc.) may predispose to renal dysfunction using TDF.

Teresa García-Benayas and Ana Barrios
Hospital Carlos III
Madrid, Spain

Clinically significant resistance mutations for abacavir unmasked

A recent report has proposed a new approach for the validation of clinically relevant scores for resistance to antiretroviral drugs. Initially it has been applied to abacavir (ABC) (Brun-Vézinet, et al. AIDS 2003;17:1795-802). The authors highlight the importance of appropriate interpretation of results of drug resistance testing. They propose a stepwise methodology for the development and validation of clinically relevant genotypic scores for antiretroviral drugs. After evaluating the impact of individual mutations on the virological response and the influence of the number of resistance mutations on the level of resistance (yes, possible and no evidence), a bootstrap resampling method was used to assess the robustness of the score obtained.

Six mutations were found to be associated with a reduced virological response to ABC. Four of the six Nucleoside Associated Mutations (NAMs) were involved; i.e. mutation at codons M41L, D67N, L210W, and T215Y/F. In addition, ABC resistance involved L74V and M184V/I. The genotypic score classifies the isolates as: with no evidence of resistance (0-3); with possible resistance (4); or with resistance (5-6). Whereas the introduction of changes at codons M184V/I and L74V in the set of mutations improved the genotypic score, mutations E44D and V118I, that had previously been associated with resistance to ABC (Walter, et al. AAC 2002;46:89-94), decreased the strength of the association between the number of mutations and the virological response.

Appropriate interpretation of drug resistance testing is an important tool for the design of rescue treatment interventions. Information available on drug resistance for individual drugs, especially for the new approved compounds, is often scarce. Studies examining the virological response in treatment-experienced patients according to the genotypic profile, like that performed for ABC, should be encouraged.

Carmen de Mendoza
Hospital Carlos III
Madrid, Spain

Are drug levels and susceptibility results enough to predict the virologic response to dual-PI combinations?

All protease inhibitors are competing with the HIV-1 encoded *gag-pol* polypeptide precursor at the enzyme substrate binding site. Therefore these compounds may also compete with each other. Merrill, et al. reported *in vitro* antagonism between saquinavir and indinavir at all doses (J Infect Dis 1997;176:265-8). In contrast, the *in vitro* combination of ritonavir and tipranavir showed synergistic antiviral effects against a ritonavir-resistant isolate (Chong, et al. Antimicrob Agents Chemother 1997;41:2367-73). The authors reported two different explanations for that observation.

Firstly, the viral isolate may contain viral populations with different levels of sensitivity to ritonavir. In the presence of drug mixtures, the virus variants less sensitive to ritonavir would be readily inhibited by tipranavir, thus exposing the more sensitive variants to a greater concentration of ritonavir. In this case the same effect could also be achieved with tipranavir alone in higher concentrations (ritonavir/tipranavir was used in a 1:50-75 ratio).

Secondly, the high drug concentrations may saturate protein binding leading to greater free-drug levels of both agents in the culture medium. But the authors took into consideration that ritonavir and tipranavir are known to bind to human plasma albumin and alpha-1 acid glycoprotein, and that it is not known whether these drugs exhibit competitive binding in mixtures or whether one drug displaces the binding of the other. Therefore, it is possible that the free-drug

level of the less effective drug might be higher in dual-PI combinations.

The second explanation clearly reveals that pharmacokinetic interactions of two PIs could be more complicated and that the inhibitory quotient (IQ) may not be sufficient to predict the virologic response to dual-PI combinations. This limitation was ignored in a recent comment that appeared in the journal (Vandamme A. AIDS Rev 2003;5:62).

Dieter Schake
Düsseldorf, Germany

Evidence for recombination at different stages of SIV evolution

Simian immunodeficiency viruses (SIVs) have been described in several species of African primates. Full-length sequences, derived from different SIV variants, have been phylogenetically classified into six main lineages, including the human HIV-1 lineage with groups M, O, and N together with SIVcpz from chimpanzees, as well as the HIV-2 lineage that clusters with SIVsm from mangabeys.

Recent findings (Salemi, et al. J Virol 2003; 77:7202-13) have shown that the six major primate lentivirus lineages from any simian species have a recombinant origin, caused by events that occurred relatively close to the root of the tree. Thus, there are no pure lineages of SIVs and it is difficult to say what the original virus was. These results suggest that during the early stages of SIV evolution, possibly when the original virus was still infecting a single species, different strains recombined. After cross-species transmission events among different simian species, the virus lineages could have evolved independently into the current lineages. This recombinant origin of SIVs, as discussed by Salemi and co-workers, makes the co-speciation hypothesis of SIVs and their hosts less likely.

Interestingly, recombination events between SIVrcm and SIVgsn infecting red-capped mangabeysand greater spot-nosed monkeys, respectively, must have been at the origin of SIVcpz (Courgnaud, et al. J Virol 2002;76:8298-309; Bailes, et al. Science 2003;300:1713). This would imply that SIV in chimpanzees also arose by cross-species transmissions. The only difference between recombination events in the various primate lentivirus lineages and the recombination creating SIVcpz, was the time frame. Recombination between SIVrcm and SIVgsn resulting in SIVcpz was much more recent.

One step further, recent findings (Paraskevis, et al. Mol Biol Evol 2003;20(11) show evidence of discordant phylogenetic relationships between the HIV-1 and SIVpcz lineages, caused by recombination or altered rates of evolution, or a combination of these factors. According to those results, SIVcpz from *P.t.troglodytes* rather than from *P.t.schweinfurthii* still remains the most plausible origin of HIV-1 for both HIV-1 group M and group O. Interestingly, in partial gp120 fragments, including the V3 region, the human viruses HIV-1 groups M and O cluster together. The grouping of HIV-1 groups M and O in this region may be caused by convergent evolution during the adaptation process to the human host.

Taking all these findings together, they show evidence about the complexity of SIV evolution, which was driven by recombination and cross-species transmission events at different stages of its evolution. Recombination events occasionally reported before (between SIVrcm, SIVgsn and SIVcpz in Courgnaud, et al. J Virol 2002;76:8298-309; Beer, et al. J Virol 2001; 75:12014-27; between SIVmnd type 2, SIVrcm and SIVsun in Hu, et al. J Virol 2003;77:4867-80; and between SIV_{AGM} lineages in Jin, et al. EMBO J 1994;13:2935-47) cannot be considered sporadic events any more. SIV evolution seems mainly driven by recombination and cross-species transmission events between and within different species, resulting in a network-like evolution. Additionally, recombination events between currently divergent lineages occurred close to the root of the tree, when these lineages were still very similar. Similarly, the more recent recombination events occurred between currently more similar sequences. This means that recombination events might not occur between highly divergent genomes, suggesting a threshold similarity above which lineages continue to evolve independently. These may be confounding factors to detect recombination, such that we are not able any more to estimate the true level of recombination. How this affects our ability to reconstruct the evolutionary histories of SIV and HIV is not yet clear.

Dimitrios Paraskevis
Rega Institute for Medical Research
Katholieke Universiteit
Leuven, Belgium