



## **INFECTIOUS DISEASES NEWS AND VIEWS\***

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### **WHO guidelines for antiviral treatment for H1N1 and other influenza, 2009**

The World Health Organization (WHO) has recently issued guidelines for antiviral treatment of novel influenza A (H1N1) and other influenza. The purpose of the new recommendations, which were posted online recently, is to provide a basis for advice to clinicians regarding the use of the currently available antivirals for patients presenting with illness caused by influenza virus infection, as well as considerations regarding potential use of these antiviral medications for chemoprophylaxis.

H1N1 influenza infection transmitted person to person was first detected by WHO in April 2009. Although the first cases were limited to Mexico and the United States, subsequent spread overseas resulted in WHO declaring on June 11, 2009, the first influenza pandemic to occur in 41 years.

On the basis of a review of data collected with previously circulating strains, and treatment of human H5N1 influenza virus infections, the new guidelines expand on recommendations published in May 2009, titled «Clinical management of human infection with new influenza A (H1N1) virus: Initial guidance.» These new guidelines do not change recommendations in the WHO rapid advice

guidelines on pharmacological management of humans infected with highly pathogenic avian influenza A (H5N1) virus.

In April 2009, sustained person to person infections with H1N1 virus in Mexico and the United States have been reported to WHO. Although the first cases were limited to these two nations, subsequent international spread led WHO to declare on 11 June 2009 that the first influenza pandemic in 41 years had occurred. This 2009 pandemic H1N1 influenza virus has now spread worldwide, with confirmed cases of pandemic H1N1 virus infection reported in more than 100 countries in all 6 WHO regions. This has led to the need to add to the existing guidance on the use of antivirals.

The new recommendations highlight oseltamivir and zanamivir, which are neuraminidase inhibitors, and amantadine and rimantadine, which are M2 inhibitors. Suggestions are also provided regarding the use of some other potential pharmacological treatments, such as ribavirin, interferons, immunoglobulins, and corticosteroids.

Management of patients with pandemic influenza (H1N1) 2009 virus infection is the primary focus of the statement, although it also includes guidance regarding the use of the antivirals for treatment of other seasonal influenza virus strains, as well as for infections resulting from novel influenza A virus strains.

The guidelines urge country and local public health authorities to issue local recommendations for clinicians periodically, based on epidemiological and antiviral susceptibility data on the locally circulating influenza strains. As the prevalence and severity of the current pandemic evolves,

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WHO anticipates that additional data will be forthcoming that may require revision of the current recommendations. WHO therefore plans to review the guidance no later than September 2009 to determine whether modifications to the recommendations are needed.

### **Recommendations for Antiviral Treatment of H1N1**

For patients with confirmed or strongly suspected infection with influenza pandemic (H1N1) 2009, when antiviral medications for influenza are available, specific recommendations regarding use of antivirals for treatment of pandemic (H1N1) 2009 influenza virus infection are as follows:

- Oseltamivir should be prescribed, and treatment started as soon as possible, for patients with severe or progressive clinical illness (strong recommendation, low-quality evidence). Depending on clinical response, higher doses of up to 150 mg twice daily and longer duration of treatment may be indicated. This recommendation is intended for all patient groups, including pregnant women, neonates, and children younger than 5 years of age.
- Zanamivir is indicated for patients with severe or progressive clinical illness when oseltamivir is not available or not possible to use, or when the virus is resistant to oseltamivir but known or likely to be susceptible to zanamivir (strong recommendation, very low-quality evidence).
- Antiviral treatment is not required in patients not in at-risk groups who have uncomplicated illness caused by confirmed or strongly suspected influenza virus infection (weak recommendation, low-quality evidence). Patients considered to be at risk are infants and children younger than 5 years of age; adults older than 65 years of age; nursing home residents;

pregnant women; patients with chronic comorbid disease including cardiovascular, respiratory, or liver disease and diabetes; and immunosuppressed patients because of malignancy, HIV infection, or other diseases.

- Oseltamivir or zanamivir treatment should be started as soon as possible after the onset of illness in patients in at-risk groups who have uncomplicated illness caused by influenza virus infection (strong recommendation, very low-quality evidence).

### **Recommendations for Chemoprophylaxis of H1N1**

Specific recommendations regarding the use of antivirals for chemoprophylaxis of pandemic (H1N1) 2009 influenza virus infection are as follows:

- When risk for human-to-human transmission of influenza is high or low, and the probability of complications of infection is high, either because of the influenza strain or because of the baseline risk of the exposed group, use of oseltamivir or zanamivir may be considered as postexposure chemoprophylaxis for the affected community or group, for individuals in at-risk groups, or for healthcare workers (weak recommendation, moderate-quality evidence).
- Individuals in at-risk groups or healthcare personnel do not need to be offered antiviral chemoprophylaxis if the likelihood of complications of infection is low. This recommendation should be applied independent of risk for human-to-human transmission (weak recommendation, low-quality evidence).

For treatment of mild to moderate uncomplicated clinical presentation of infection with multiple cocirculating influenza A subtypes or viruses with different antiviral susceptibilities, patients in at-risk groups should

be treated with zanamivir or oseltamivir plus M2 inhibitor (noting that amantadine should not be used in pregnant women). Otherwise-healthy patients with this presentation need not be treated.

When the clinical presentation of infection with multiple cocirculating influenza A subtypes or viruses with different antiviral susceptibilities is severe or progressive, all patients should be treated with oseltamivir plus M2 inhibitor, or zanamivir.

For treatment of mild to moderate uncomplicated clinical presentation of infection with sporadic zoonotic influenza A viruses including H5N1, the at-risk population should be treated with oseltamivir or zanamivir, and the otherwise-healthy population with oseltamivir. All patients, regardless of risk status, with severe or progressive presentation of infection with sporadic zoonotic influenza A viruses including H5N1 should be treated with oseltamivir plus an M2 inhibitor.

## REFERENCES

1. WHO guidelines for pharmacological management of pandemic (H1N1) 2009 Influenza and other influenza viruses, 2009. <http://www.who.int/csr/swineflu/2009>
2. <http://cme.medscape.com/viewarticle/708032?src=cmenews&uac=62320HK>

### **Antiretrovirals reduce the risk of non-HIV illnesses at lower CD4 cell counts**

HIV treatment guidelines in Europe and North America have recently been changed to recommend the initiation of HIV therapy once a patient's CD4 cell count declines to around 350 cells/mm<sup>3</sup>. One of the main reasons for this recommendation was the realisation that patients with CD4 cell counts below this level had an increased risk of developing a number of illnesses not traditionally regarded as being related to HIV, such as heart, kidney and liver

diseases as well as some cancers.

Antiretroviral treatment reduces the risk of serious non-HIV-related illness for patients with a CD4 cell count below 350 cells/mm<sup>3</sup>, according to a study conducted by investigators at Johns Hopkins University in the US and published in the October 15th edition, 2008 of *Clinical Infectious Diseases*. The findings of this study broadly reflect those of the SMART study which found that patients taking a break from HIV treatment with a CD4 cell count below 350 cells/mm<sup>3</sup> were more likely to develop both HIV and non-HIV-related illnesses.

Investigators from the Baltimore University studied the medical records of 2824 patients between 1997 and 2006. They looked at rates of non-HIV-related liver, kidney, heart, lung and neurological diseases as well as non-HIV-related cancers in these patients. They then examined individuals' medical records to see if they could establish a link between these illnesses and the non-use of antiretroviral therapy and CD4 cell count. A total of 817 serious non-HIV-related illnesses were observed. These illnesses were more common at lower CD4 cell counts, and were also more common amongst patients not receiving HIV treatment than those receiving anti-HIV drugs ( $p = 0.001$ ).

Furthermore, not receiving antiretroviral therapy (compared to HIV treatment) was associated with a higher risk of such illnesses for patients with a CD4 cell count below 200 cells/mm<sup>3</sup> (incidence rate, 2.7 per 100 person years vs. 1.2 per 100 person years,  $p = 0.001$ ), and for patients with CD4 cell counts below 350 cells/mm<sup>3</sup> (incidence rate 1.3 per 100 person years vs. 0.6 per 100 person years,  $p = 0.002$ ). Patients with CD4 cell counts above 350 cells/mm<sup>3</sup> were slightly more likely to develop serious non-HIV-related illnesses than if they were not taking HIV treatment, but the difference with patients taking anti-HIV drugs was not significant (0.8 per 100 person years vs. 0.5 per 100 person years,  $p = 0.18$ ). Other

factors associated with an increased risk of non-HIV-related illnesses were age over 50, injecting drug use, and black race.

“This analysis provides evidence from clinical practice that HAART use is associated with a decreased risk of comorbidities not related to HIV infection...amongst patients with CD4 cell counts below 350 cells/mm<sup>3</sup>”, conclude the investigators, adding “HAART may have a protective effect on the occurrence of comorbidities not related to HIV infection or AIDS and may reduce the risk of AIDS-defining illness.”

## REFERENCE

Moore R.D. et al. Rate of comorbidities not related to HIV infection or AIDS among HIV-infected patients, by CD4 cell count and HAART use status. *Clin Infect Dis* 47: 1102 – 1104, 2008.

## Switching to AZT from d4T poses challenges in resource-limited settings

Investigators in rural Cambodia have found while substituting AZT for d4T maintains immune health and adherence to therapy, the increased monitoring needed to identify and treat AZT-associated anaemia that burdens both patients and local healthcare systems. Their report, published in the September 1st issue, 2008 of the *Journal of Acquired Immune Deficiency Syndromes*, cautions that any decisions to switch large numbers of patients in resource-limited settings should carefully weigh these challenges.

d4T (stavudine, Zerit) has several features that made it the drug of choice for first-line antiretroviral therapy regimens in many resource-limited settings: it is effective, inexpensive and has a relatively mild short-term toxicity profile, meaning patient adherence is high and the need for expensive laboratory monitoring tests, low. Unfortunately, long-

term d4T use has been associated with mitochondrial toxicity leading to serious side-effects including lipodystrophy and peripheral neuropathy, and for these reasons its use is limited in developed countries where other options are available. In settings where it is available AZT (zidovudine, Retrovir) often replaces d4T in antiretroviral combinations due to its more advantageous long-term tolerability profile. However, in the short-term, AZT use is associated with an increased risk of anaemia. Additional laboratory monitoring of blood cell levels is required to ensure patient safety. This poses little problem in resource-rich settings, but in resource-limited settings, clinical and laboratory services may already be scarce and overloaded.

To reduce the long-term toxicity of d4T while maintaining its advantages of being easy to adapt to and easy to administer, researchers have proposed a strategy of starting people with HIV on d4T then switching them to AZT after six months of therapy. Clinical evidence is very limited, but one trial reported fewer cases of anaemia than expected.

In early 2006, based on the promising results, clinicians at a rural hospital in Takeo, Cambodia instituted a treatment protocol in which patients were switched to AZT after having been on d4T for at least six months. The current report is a retrospective, observational analysis of data collected from patients' records.

Overall, the switch was successful, with almost all patients, 503 of 527 (95.4%), remaining on antiretroviral therapy at the end of the study. Records showed that HIV treatment had a beneficial effect on CD4 counts, and the switch to AZT provided continuing benefit. Median CD4 cell count gains were 180 cells/mm<sup>3</sup> at twelve months.

However, 156 patients (29.8%) demonstrated a drop in CD4 cell counts after switching to AZT. This finding, seen in at least one other study of AZT substitution, may indicate a

possible negative impact of the switch strategy, the investigators write. However, a lack of routine viral load testing in the clinic made it impossible to determine whether or not the declines were due to treatment failure.

Investigators then looked for cases of anaemia among the patient records. They found that within one year of switching to AZT, 114 (21.9%) of the 527 patients developed anaemia of any grade; 7.1% developed severe anaemia. They attributed most of the cases to anti-HIV drugs, since there were few other concomitant infections that might have caused the drop in blood cell levels. Drug-related anaemia was cited as the reason for switching among 38 of the 51 patients who switched from AZT within one year, and one of the four deaths during the study was due to severe anaemia.

The investigators found no evidence supporting the earlier finding of fewer than expected cases of anaemia. Incidence of the condition was in agreement with other studies of AZT and was particularly notable given that many of the factors for HIV-related anaemia—advanced disease, female gender, African origin, low body mass index (BMI) and increasing age—were not prevalent in the study: 75% had CD4 cell counts above 200 cells/mm<sup>3</sup>, 57% were female, 81% had a BMI over 18 kg/m<sup>2</sup> and the median age was 35 years.

The investigators went on to analyse the impact of the regimen switch on the patients' daily life and on the healthcare system. They noted that introducing the switch regimen and its associated need for increased monitoring involved several significant changes in the clinic. In addition to ensuring an adequate supply of test reagents and improving the clinic's capacity to manage the increased patient load, there was a need to provide more patient counselling regarding the switch in pill-taking habits and in identifying signs of drug toxicity.

In summing up their results, the investigators plant their findings firmly in the reality that faces the majority of HIV programmes around the world. While it may provide adequate clinical results, they write, "if a strategy for substituting [AZT] for d4T-based HAART is to be applied in resource-limited settings, then [AZT]-associated adverse events and context-specific programmatic challenges need to be weighed against the expected benefit of decreased long-term d4T toxicity."

## REFERENCE

1. Isaakidis P et al. Evaluation of a systematic substitution of zidovudine for stavudine-based HAART in a program setting in rural Cambodia. *J Acquir Immune Defic Syndr* 49:48 – 54, 2008.