AIDS Brief

Nevirapine and co-trimoxazole prophylaxis safe in HIV-exposed, uninfected infants

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Use of nevirapine with co-trimoxazole prophylaxis in HIV-exposed, uninfected (HIV-EU) infants until 6 months of age in Zimbabwe and Uganda was safe with no immediate or long-term adverse effects, researchers on behalf of the HIV Prevention Trials Network (HPTN) 046 protocol trial report in the advance online edition of *AIDS*.

The findings from this secondary data analysis have important policy implications for HIV-EU infants in resource-poor settings.

The HPTN 046 protocol, a prospective, randomised placebo-controlled trial looked at the safety and efficacy of nevirapine prophylaxis against HIV transmission in breastmilk, with infants followed up for 18 months.

Policy makers can now make informed decisions regarding the WHO 2010 prevention of mother-to-child transmission (PMTCT) guidelines and the combined use of nevirapine and co-trimoxazole prophylaxis for extended periods of time. Such use is critical in these settings where frequent monitoring is challenging, and where the difficulties of travelling long distances and the high costs of transportation make regular clinic visits difficult.

The guidelines are based on evidence of the effectiveness of the extended use of daily nevirapine in reducing breastmilk transmission of HIV. Daily use of nevirapine prophylaxis in HIV-EU infants for PMTCT from birth until 1 year of age, or until the stopping of breastfeeding (whichever comes first), is recommended.

The WHO also recommends that HIV-EU infants get co-trimoxazole prophylaxis from the age of 4 - 6 weeks until they are no longer exposed to HIV and have confirmation of being HIV negative. Co-trimoxazole is a highly effective antibiotic against pneumonia and other opportunistic infections.

Side-effects with the extended use of nevirapine have included some reports of rash and a decrease in white blood cells (neutropenia); these side-effects in addition to anaemia are frequently seen with the use of co-trimoxazole.

However, the safety of the combined use in HIV-EU is not well understood. The authors note that there are no studies assessing the risks in HIV-EU infants and that safety data are based on HIV-infected individuals, notably adults. Without such data effective public health implementation is handicapped.

So the authors chose to determine the risk and severity of neutropenia and/or anaemia and severe rash in HIV-EU infants randomised to one of two study arms: 6 months of getting daily nevirapine and co-trimoxazole prophylaxis from 6 weeks until breastfeeding stopped compared with those getting co-trimoxazole alone.

Following the release in August 2007 of the Six Week Extended Nevirapine (SWEN) trial that showed a 50% reduction in MTCT through breastmilk, recruitment into HPTN-043 stopped. Analysis was based on a fixed sample size of infants enrolled between February and August 2007.

Among the 293 mother-infant pairs the randomised incidence of neutropenia and/or anaemia and skin rash, regardless of the study arm, was highest during the first 6 weeks of life; then from 6 weeks to 6 months, and lowest in the 6 - 12-month period.

Most (96%) infants had at least one episode of neutropenia and/or anaemia and about half had the most severe form, with relatively few (13%) experiencing skin rash. The authors suggest that this may reflect a high background of neutropenia and/or anaemia in this study population. Or, it may reflect an overestimation bias since the ranges used to determine potential toxicity in what is

a primarily black African population are white-based norms.

After 6 weeks the time to any adverse event was similar in both arms for neutropenia and/or anaemia (all grades); for neutropenia and/or anaemia (grade 3 or above); and skin rash (grade 2 or above: HR, 95% CI: 1.26 (0.96 - 1.66); 1.27 (0.80 - 2.03); and 1.16 (0.46 - 2.90)), respectively.

An adverse event in this trial was defined as 'any unfavourable or unintended symptom, sign (including an abnormal laboratory finding) or disease temporally associated with the use of the study product (onset after enrolment), regardless of relatedness'.

There were no statistically significant differences in the immediate (6 weeks to 6 months) or long-term (6 - 12 months) adverse event risks among infants on nevirapine and co-trimoxazole compared with those on co-trimoxazole alone.

The authors note that the potential for drug-drug interactions resulting in an increased risk of patient illness and death is well documented; taking nevirapine may alter the amount of other drugs absorbed into the bloodstream and vice versa.

The authors note that the placebo design of this trial within a setting with routine co-trimoxazole prophylaxis 'provided a unique opportunity to assess the immediate and long term adverse events risk associated

with concurrent nevirapine and co-trimoxazole use'.

Adjustments to eliminate potential confounders (variables such as infants who got zidovudine tail and maternal ARVs found in breastmilk) were made in the time to adverse event and adverse event risk assessments.

The authors conclude that 'extended nevirapine and cotrimoxazole prophylaxis until six months of age among HIV-EU did not appear to increase the immediate or long-term risk of neutropenia, anaemia or skin-rash. However, the safety of concurrent use beyond six months, among HIV-EU breastfed infants, as is currently recommended by WHO needs further evaluation.'

Aizire J, et al. Extended prophylaxis with nevirapine and co-trimoxazole among HIV-exposed uninfected infants is well tolerated. Advance online edition of AIDS 25, doi:10.1097/QAD.0b013e32834e892c, 2011.

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SINGLE SUTURE

Breathing new life into lung repair

There's new hope for heavy smokers, people with asthma and those with chronic lung scarring. Stem cells have been discovered that naturally rebuild alveoli.

Frank McKeon of the Genome Institute in Singapore and his team infected mice with flu. The virus quickly destroyed over half of the alveolate tissue – but within three months it had repaired itself.

The team found that stem cells in the lungs had multiplied rapidly, creating hundreds of times their original number within a week. Then they had migrated to sites of damage and formed pod-like structures before becoming new air sacs.

The team have isolated similar stem cells from human lung tissue. They are now searching for the chemicals that activate them, which could be harnessed to boost the lung's self-repair mechanism.

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