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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.

Viral 'blips' probably do not harm

Physicians dealing with HIV infection often have to interpret the meaning of 'blips' or transient episodes of detectable viral load in the range of 50 to 400 copies per ml during antiretroviral treatment. Two studies addressed this issue at the XIII International AIDS Conference held in Durban during the past July. Of patients experiencing blips, only 25% (8/32) in one study [Ward *et al*., abstract MoPpB1019] and 9.3% (9/97) in another [Havlir *et al*., abstract TuPeB3195], failed subsequently to contain viral load below 200-400 copies/mL. Viral blips occurred in 9% (32/342) and in 40% (97/241) of patients assessed in each of these studies, respectively. Interestingly, 25% (24/97) of patients included in Havlir's trial experienced more than one blip episode. In Ward's trial, the mean rebound in viral load and CD4+ counts were comparable between subjects who subsequently attained complete virus suppression compared to those who did not (96.4 copies/mL vs. 131 copies/mL, and 625 cells/mm^3 vs. 540 cells/mm^3, respectively).

Using a modified PCR viral load test with a detection limit of 2.5 copies/mL, Ward and colleagues found that the median viral load was significantly higher in subjects experiencing "blips" (23 copies/mL) compared with those without blips ($p < 0.001$). Moreover, a higher baseline viral load, as well as a longer time to reach less than 200 copies/mL after beginning therapy, were both independent predictors of blips. However, blips were not associated with a greater risk of viral rebound according to Havlir and colleagues; in fact, viral rebound occurred in 9.3% (9/96) of patients with blips and 13.8% (20/145) of those without blips. The authors from both studies concluded that blips of HIV viremia, while under successful antiretroviral therapy, do not necessarily anticipate virologic failure.

A third study presented at the Durban Conference assessed the clinical outcome in subjects experiencing blips compared to those who maintained HIV- RNA levels below 50 copies/mL [Greene *et al*. MoPeB2171]. The occurrence of AIDS-defining illnesses and mortality were comparable in both groups.

The clinical implications of these studies are remarkable. On the one hand, low-level viremia detected by "fourth generation" PCR assays (detection limit 2-5 copies/mL) does not seem harmful up to two years. On the other hand, there is a small subset of patients showing HIV-RNA rebound afterwards for whom there is no way to predict treatment failure based on viral load measurements. According to these data, the detection of HIV-RNA titers between 50 and 400 copies/mL most likely reflects a higher degree of residual HIV replication (which seems correlated with higher viral loads at baseline) rather than therapeutic failure of a given regimen. A caveat in these studies is that detectable samples were not re-tested to rule out laboratory errors (false positives) (De Mendoza *et al*. AIDS 1998; 12: 2076-7). Another unresolved issue is related to the presence of resistance mutations in these detectable samples, since reliable assessment at such low levels is very difficult. Lastly, the immunological implications of viral blips are not known. Studies evaluating HIV-specific immune responses in 'blippers' *vs*. 'fully-suppressed' patients are needed. After all, the immunogenicity triggered by low levels of HIV viremia might be of benefit. In the meantime, the detection of a "blip" should prompt to re-test the same sample or to call the patient back for repeating the test.

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Greater success of nevirapine than zidovudine for reducing mother-to-child HIV transmission

The XIII International Conference on AIDS took place in Durban during the past July. Among others, two major issues in therapeutics were widely discussed. One was the most appropriate strategy

for reducing the rate of perinatal transmission of HIV. Another referred to intermittent treatment interruptions. As expected, considerable interest arose when results of trials designed to prevent the vertical transmission of HIV were presented. In South Africa nearly one third of pregnant women are HIV-positive.

The final results of the Ugandan HIVNET 012 trial were presented (Owor, LbOr1). They showed that a single dose of NVP given to HIV+ women in labour and to the newborn within 72 hours of birth is safe and significantly reduces the perinatal transmission of HIV when compared with a short course of AZT.

In the SAINT trial, two short-course antiretroviral regimens previously demonstrated to effectively prevent mother-to-child HIV transmission, were compared (Moodley, Abstract LbOr2). There were 1306 HIV+ pregnant women assigned to one of two arms: i) NVP 200 mg during labour and 1 dose to mother and infant within 48 hours post-delivery, and ii) multiple dose AZT+3TC during labour and for one week to mother and infant post-delivery. There were no significant differences between arms (NVP 12.7% versus AZT+3TC 9.5%).

In the WITS trial (Blattner, LbOr4), the impact of different therapeutic regimens as well as mother viral load values at delivery were analysed. Overall, plasma viral load at delivery was a more important determinant of the rate of vertical HIV transmission, although the use of antiretroviral drugs provided an independent protective effect.

In the PETRA study (Gray, Abstract LbOr5), the negative impact of breastfeeding was pointed out. The combination of AZT+3TC was compared to placebo at 6 weeks and 18 months. Dual nucleosides were assigned to three different schedules (only intrapartum, intrapartum plus one week post-delivery, and intrapartum + one week post-delivery + since 36 weeks of pregnancy). There was a significant reduction in HIV transmission at 6 weeks of life for AZT+3TC compared to placebo, although the intrapartum-only arm was no different from placebo. Moreover, at 18 months of life, no significant differences were found between arms. This loss of efficacy of all AZT+3TC regimens over time is likely to result from a high number of HIV infections in breastfed children.

In summary, a single dose of NVP given to HIV+ women in labour and to the newborn within 72 hours of birth is safe and reduces significantly the perinatal transmission of HIV when compared with a short course of AZT. The combination of AZT+3TC did not significantly improve this benefit, and is much more expensive and difficult to fulfil by mothers and babies since multiple doses need to be given for longer periods. Breastfeeding impacts negatively, causing a substantial number of post-delivery infections.

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Vertical HIV transmission at the HIVNET 012 trial

	NVP (n=311)	**AZT** (n=308)
At birth	8.1%	10.3%
At 6-8 weeks	11.8%	20%
At 14-16 weeks	13.6%	22.1%

Mother-to-child HIV transmission at the WITS trial

Treatment	**Rate**		**Viral load**
Untreated	20.7%	30.1%	>100,000
ZDV before ACTG 076	19.4%	21.1%	40,000-100,000
ZDV after 076	7.7%	11.3%	3,000-40,000
Dual NRTI combinations	3.9%	6.4%	400-3,000
PI triple combinations	1.1%	0.9%	Undetectable

Mother-to-child HIV transmission at the PETRA study

	At 6 weeks	**At 18 months**
AZT+3TC since week 36 pregnancy + intrapartum + 1 week post-delivery	9.2%	20.7%
AZT+3TC intrapartum + 1 week post-delivery	12.6%	24.4%
AZT+3TC intrapartum	18.4%	25.7%
Placebo	19.2%	26.6%

What is the source of viral rebound after cessation of HAART?

The use of highly active antiretroviral therapy (HAART) has dramatically changed the clinical and virologic course of HIV-1 infection in a substantial proportion of infected individuals. HAART effectively controls the replication of HIV-1, and in many patients the virus becomes undetectable in plasma for extended periods of time. However, despite complete suppression of plasma viremia, evidence for residual viral replication has been demonstrated. Persistence of latent HIV reservoirs containing infectious proviruses integrated in resting memory $CD4^+$ T cells has also been shown. Therefore, it was not surprising to see that HIV-1 rebounds quickly in plasma after HAART cessation in patients who have had sustainable viral suppressions. A paper by Chun *et al*. in the July issue of Nature Medicine (6: 757-61) sheds new light on the relationship between the rebound virus and HIV-1 present within the resting memory $CD4^+$ reservoir. Using heteroduplex mobility and tracking assays, Chun *et al*. compared the genotype of the early rebounding virus with that in the latent reservoir. In six patients that had detectable latent reservoir, two had rebounding virus that was closely related to the latent reservoir. In contrast, four patients had genetically distinct viruses within both compartments. Chun *et al*. conclude that the viral rebound does not originate from resting memory $CD4^+$ T cells in most cases, and suggest the presence of an unidentified source. These results reiterate the importance of therapeutic interventions aimed at preventing the persistence and renewal of these viral reservoirs.

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High Stakes for Low Adherence

All clinicians are well aware that adherence to antiretroviral therapy is a critical determinant of outcome. While dosing regimens for current first line therapy represent a significant improvement from their predecessors, these therapies still provide enormous adherence challenges for the uninitiated patient. Ensuring adherence in patients embarking on salvage therapy poses an even more formidable task. Many patients require salvage therapy because of prior non-adherence. These patients are probably the least equipped to handle the generally more complex, more toxic regimens that are prescribed. Moreover, physicians appear to be particularly unskilled at estimating adherence among patients. How adherent do patients really need to be? What are the consequences of non-adherence? Some recent published reports and presentations shed light on these important, but complex questions.

Many current antiretroviral regimens are not forgiving for missed doses. Peterson *et al*. examined levels of HIV RNA in 99 subjects receiving protease inhibitor based regimens (Paterson *et al*. Ann Intern Med 2000;133:21-30) Adherence was measured by an electronic dose monitoring system. Virologic failure developed in 22% of patients with adherence of 95% or greater compared to 61% of patients with 80 to 95% adherence and in an astounding 80% of patients with less than 80% adherence.

The life and death consequences of non-adherence were highlighted in two presentations at the XIII International AIDS Conference in Durban (Carmona *et al*., Abstract; Braitson *et al*., Abstract). Carmona evaluated adherence and outcome in 736 subjects in Spain receiving antiretroviral regimens. Adherence was measured by pill counts and pharmacist history. "Poor" adherence was defined as taking less than 90% of prescribed medications. Poor adherence was associated with a 67% increase in mortality. In the second study, investigators correlated adherence to survival in a cohort of 950 individuals on antiretroviral regimens in Canada. Adherence was measured by tracking the number of prescriptions filled compared to the number of those prescribed. The limitations of this methodology notwithstanding, poor adherence was an independent risk factor for death.

While great strides have been made in improving the efficacy of antiretroviral therapy, it is clear that its overall effectiveness continues to be limited by poor adherence. Simpler regimens combined with behavioral approaches are needed to fully exploit the potential benefits of HIV therapies.

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Indirect impacts of Tat on HIV mRNA capping

The viral RNA expression of HIV-1 is greatly increased through the function of one of its regulator proteins, the transactivator Tat. It augments levels of viral RNA by increasing transcriptional elongation. For function, Tat requires a *cis*-acting RNA element, TAR, located at the 5' end of all viral transcripts. Through interaction with TAR, Tat recruits pTEFb, a cyclin T associated kinase (CDK9) complex, to the preinitiation transcription complex. The CDK9 kinase phosphorylates the C-terminal domain (CTD) of the RNA polymerase II complex, and processive elongation complexes are formed. Hyperphosphorylation of the serine residues in the CTD heptapeptide is associated with the transition of the promoter-bound transcription complex to a productive elongation

complex. Now, Zhou *et al*. (Mol Cell Biol 2000; 20: 5077-86) demonstrated that CDK9 (pTEFb) and CDK7 (TFIIH) are both associated with the HIV-1 preinitiation complex, and CDK9 and CDK7, respectiviely, phosphorylate serine 2 and serine 5 of the CTD. However, in HIV-1 Tat-activated transcription, CDK7 is released between positions +14 and +36, while CDK9 remains stably associated with the HIV-1 elongation complex. They showed that after depletion of the CDK7 from the transcription reaction, CDK9 is able to phophorylate serine 5 in the HIV-1 Tat transcription complex. In the absence of Tat, CDK9 phosphorylates only serine 2. It is suggested that Tat directly modifies the substrate specificity of CDK9. This is how Tat could indirectly stimulate translation. Capping is targeted to pre-mRNAs through binding of the guanyltransferase component of the capping apparatus to the phosphorylated CTD. Ho and Stewart (Mol Cell 1999; 3:405-11) reported that guanyltransferase binds CTD containing phophoserine at either position 2 or 5 and that phosphoserine 5 stimulates the enzyme activity. A CTD containing phosphorylated serine 2 has no effect on guanyltransferase activity. Taken together, Tat-directed phosphorylation of CTD serine 5 could add to the capping of the HIV pre-mRNA, which in turn is known to increase the translation of the mRNAs.

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