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Using HAART to Decrease Peri-operative HIV-1 Transmission Risk: Response to Papendorp and van den Berk

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We read with interest the novel strategy described by Drs. Papendorp and van den Berk in the March 27 issue of AIDS [1] of instituting a standard HAART regimen (tenofovir, emtricitabine, and efavirenz) plus raltegravir to reduce HIV-1 viral load rapidly in order to decrease peri-operative infectious risk. While raltegravir-containing HAART affords a more rapid viral load decline compared to other antiretroviral regimens [2], there remains a period of several weeks before virions are cleared from the plasma. This may represent an unacceptably long time to wait for urgent surgery. Building upon Drs. Papendorp and van den Berk's innovative concept of using the pharmacodynamic properties unique to particular classes of antiretrovirals to reduce peri-operative risk, we describe an alternative strategy that theoretically offers the same benefit within a much shorter time period.

Raltegravir, the first integrase inhibitor approved for clinical use, blocks incorporation of HIV-1 reverse transcripts into the host cell genome. Infected cells that have already undergone HIV-1 DNA integration at the time raltegravir is initiated will not be blocked from producing infectious virions. The rapid viral load decay seen in patients taking raltegravir may be the result of the blockade of a later stage of viral replication than other currently available antiretroviral drugs [3]. For example, it is likely that a larger population of infected cells can continue to produce virus in patients starting an efavirenz-based regimen than in patients starting a raltegravir-based regimen. With efavirenz initiation, all infected cells that have undergone reverse transcription will continue to produce virus, whereas with raltegravir only cells that have undergone viral integration will produce virus. This is likely the basis of the more rapid decay in plasma HIV-1 RNA levels in patients starting raltegravir [3]. However, with respect to occupational exposure, the critical issue is not the absolute level of plasma virus, but rather the level of infectious virus.

In theory, virions produced by previously infected cells in a patient starting an integrase inhibitor will be fully infectious if transferred to another host, because integrase inhibitors

act only on the integrase-viral DNA complex in newly infected cells and not on the free enzyme in the virion [4]. The situation is different in patients starting protease inhibitors. These drugs inhibit the enzyme responsible for the cleavage of immature viral proteins within the virion during and after budding from the host cell. Previously infected cells at all stages of replication will continue to produce virions when a protease inhibitor is initiated [3]. For this reason, the viral load decay on protease inhibitor regimens is not as rapid as that observed with raltegravir. However, all virions produced in the presence of therapeutic concentrations of a protease inhibitor are immature and incapable of infecting a new target. Thus, within hours of initiating a protease inhibitor-based regimen, patients will have a falling viral load composed of immature, non-infectious virions that likely represent a minimal risk for blood borne viral transmission.

In the case of protease inhibitors with a slow off rate such as darunavir [5], enzyme inhibition may persist following occupational transmission of virus particles to a recipient for longer than the virion lifetime, affording complete protection. If the drug does dissociate, the virion would still need to complete the maturation process to become infectious. The non-nucleoside reverse transcriptase inhibitors potentially represent an intermediate case. In principle, they can bind to the reverse transcriptase molecules in virions, rendering them non-infectious. However, as soon as the inhibitor dissociates, reverse transcription could continue. Thus in order to minimize the probability of occupational transmission, slowly dissociating protease inhibitors offer the most rapid way to reduce infectious virus in the plasma.

A potential concern of the drug regimen described by Papendorp and van den Berk is the relatively low barrier to resistance of both efavirenz and raltegravir [6], which may present a risk to the patient long after surgery. This risk is compounded by initiating HAART on an urgent basis in a setting radically different from the outpatient HIV clinic, where a support structure is ideally in place to maximize long-term positive patient outcomes. Protease inhibitor-based regimens have a significantly higher barrier to resistance than efavirenz or raltegravir, and for this reason can often be given with confidence in settings when the presence of drug-resistance mutations cannot be fully assessed. In summary, both the mechanism of action and the superior resistance profile of protease inhibitor-based HAART argue for its use in this specific setting. In regard to blood borne transmission risk, the quality as well of the quantity of virus should be considered.

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