DOI: 10.1111/hiv.12187
HIV Medicine (2015), **16**, 73–75

EDITORIAL

Is HIV post-exposure prophylaxis required following occupational exposure to a source patient who is virologically suppressed on antiretroviral therapy?

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Following the recent publication of the US guidelines on the management of occupational exposure to HIV and post-exposure prophylaxis (PEP) [1], a review of UK guidelines has taken place by the Department of Health Expert Advisory Group on AIDS. In particular, the US guidance is at odds with that in the UK with regard to what to do following exposure to a source patient with an undetectable plasma HIV viral load. The US guidance states that this does not eliminate the possibility of HIV transmission nor the need for PEP and follow-up testing [1]. The guidelines acknowledge that the risk of transmission in this setting is thought to be very low but advocate that PEP should still be offered where it would not be in the UK. But what are the risks and are these quantifiable?

Our understanding of HIV transmission following occupational exposure comes from more than 20 longitudinal studies [2]. The average risk of transmission associated with percutaneous exposures is 0.32% and that associated with mucosal exposure is an order of magnitude less [3]. A number of factors have been associated with an increased risk of transmission and these include a deep penetrating injury, a blood-stained device and injury from a terminally ill source patient. It is assumed that these are all surrogate markers of the magnitude of the viral inoculum, more virus meaning more risk [3]. However, the use of zidovudine after exposure has been associated with a reduced risk of transmission. There is a wealth of literature from treatment guidelines which demonstrate that cART is more effective than monotherapy [4,5]. Furthermore, it would be impossible (because of the low numbers of endpoints) and unethical to perform a randomized controlled trial of any intervention following occupational exposure. We are therefore reliant on extrapolating from data from animal models and from other scenarios such as sexual or mother-to-child transmission (MTCT) of HIV.

The US guidelines base their conclusion on the knowledge that plasma viral load reflects only the level of cell-free virus in the peripheral blood and that the persistence of HIV in latently infected cells, despite cART, is well described [5,6]. Viral genetic material is found within these cells as integrated proviral DNA and as episomal circular DNA [7]. Although only a small proportion of proviral DNA is intact (much of it containing deletions and areas of hypermutation), it is clearly capable of productive replication as seen on cessation of cART associated with virological rebound [7]. In a monkey model of simian immunodeficiency virus (SIV) infection, cell-associated SIV was found to be an efficient means of HIV transmission by the intravenous route [8]. Indeed, as few as only two SIV-infected peripheral blood mononuclear cells were required to establish infection. In the same model, cell-associated virus was found to be less efficient in vaginal transmission [8].

The US guidelines also make reference to cases of HIV transmission that have been described from exposure to a source person who had an undetectable viral load in cases of sexual transmission [9] and MTCT [10]. The case cited of sexual transmission appears to be unique and controversial. There is an increasing wealth of data showing that antiretroviral therapy reduces sexual transmission: from the now famous 'Swiss Statement' claiming that an individual with completely suppressed viraemia is not sexually infectious [11], to the results of the HIV Prevention Trials Network 052 trial that demonstrated unequivocally that cART substantially lowers the probability of HIV transmission in serodiscordant couples, research earning *Science* journal's 2011 'breakthrough of the year' honour [12]. Data from the PARTNER study confirming similar findings in men who have sex with men (MSM) have also recently been presented [13]. The risk of HIV acquisition per coital act is largely influenced by the viral load of the HIV-infected partner, although the majority of these data are

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from African heterosexual couples [14]. However, the lower threshold at which risk disappears has not been established. A potential mechanism by which sexual transmission, in the absence of plasma viraemia, could occur is the compartmentalization of HIV. HIV RNA has been shown to be present in seminal fluid or vaginal secretions despite suppressive cART [15–17]. An alternative hypothesis is that cell-associated HIV DNA in genital fluid could be capable of transmission. Indeed, in an explanted colonic model of mucosal transmission, cell-associated virus has been demonstrated to be a more effective means of mucosal infection than free virus [18]. Whether this occurs *in vivo* is not clear. Perhaps for this reason, PEP remains recommended following the highest risk of sexual exposure (unprotected receptive anal sex) even when the sexual partner has an undetectable viral load [19].

MTCT has undoubtedly occurred in spite of virological suppression on cART at the time of birth [10]. In the French case–control study cited in the guidelines, all pregnant mothers had a viral load of < 500 HIV-1 RNA copies/mL at birth but the transmission cases were less likely to be on cART at the time of conception or virologically suppressed at earlier time-points during pregnancy than controls [10]. This study highlights the need for early and sustained virological suppression during pregnancy but provides no insight as to when or how MTCT happened in these cases. A possible explanation could lie in the presence of cell-associated HIV DNA in the genital tract. When antenatal cervicovaginal specimens are examined for the presence of HIV cell-associated DNA, levels of this have been shown to be independently associated with the rate of vertical transmission [20]. More recently, cell-associated virus has also been implicated in HIV transmission in breast milk and indeed is more important for early postpartum HIV-1 transmission (at 6 weeks) than cell-free virus [21].

The one important question not addressed in either UK or US guideline is that of the reliability of an 'undetectable' HIV viral load. Using sensitive assays, plasma HIV RNA can be detected in up to 80% of treated patients with HIV RNA < 50 copies/mL who are labelled as 'undetectable' [22]. The majority of studies show that this virus does not evolve but that full-length genomes can be cloned from plasma and shown to be replication-competent in culture [23]. Clearly, in cases of occupational exposure from a virologically suppressed individual with such low-level viraemia, the viral inoculum would be vanishingly small (if any) but the amount of virus required to establish infection is unknown. However, single-genome analysis of acute infections has revealed that the majority of HIV infections have evidence of productive clinical infection by only a single virus [24].

In summary, the data suggest that the risk of HIV transmission from virologically suppressed individuals on cART is extremely low (even assuming a significant injury) and this is likely to be outweighed by the potential risks associated with PEP. HIV cell-associated DNA might be a source of virus transmission in these individuals, but compelling data are lacking and require extrapolation from very different transmission scenarios. A panel of experts felt that a thorough review of the literature reveals no new data at this time to warrant a change in the UK guidance to bring it in line with that of the USA.

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