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Mini-review

Is HIV drug resistance a limiting factor in the development of anti-HIV NNRTI and NRTI-based vaginal microbicide strategies?

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Dedicated to Prof. Erik De Clercq on the occasion of reaching the status of Emeritus-Professor at the Katholieke Universiteit Leuven in September 2006.

Abstract

Antiviral drugs that act at specific sites within the HIV life cycle have important rationale for development as anti-HIV microbicides. However, to be effective, such drugs must act by directly interfering with viral enzymatic function and eliminate the ability of HIV to mediate infection. Compounds that are developed as microbicides must have high potency, and should ideally not be well absorbed from the vaginal cavity in order to minimize any potential problems of drug resistance. Such compounds should also be active over long periods of time and should be able to be combined with other active agents, in order to promote the concept of synergy, such as that which has been demonstrated in HIV therapeutic studies.

Keywords: HIV drug resistance; Microbicides; NNRTIs; NRTIs

Contents

1. Introduction

The worldwide HIV epidemic has become an enormous burden for women in the developing world (UNAIDS). Women are mainly infected by heterosexual transmission of HIV and often have no control over condom use by sexual partners. Estimates on the potential of vaginal microbicides for the prevention of HIV infection is promising (Foss et al., 2003; Smith et al., 2005), its use is thus clearly justified. Among the various compounds under investigation as potential microbicides specific anti-HIV drugs have a major role to play. Yet, an obvious concern is the potential of such compounds to select for drug resistance or the possible loss of activity of such substances against transmission of viruses from drug-resistant HIV carriers.

It is known that approximately ten percent of all new HIV infections in North America and Western Europe are now attributable to viruses that contain at least one drug resistance-associated mutation in either the reverse transcriptase (RT) or protease (PR) genes (Little et al., 2002; Salomon et al., 2000; Tamalet et al., 2003). In some cases, patients may be unlucky enough to become infected with viruses that contain multiple mutations that may remarkably confer resistance against all

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three families of antiviral drugs, i.e. protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside inhibitors (Brenner et al., 2002). The purpose of this review is to shed light on how and whether HIV drug resistance might affect the possible use of nucleoside/tide reverse transcriptase inhibitors (NRTIs) and NNRTIs as vaginal microbicides and to propose a framework for research on this topic.

Resistance may be an issue for several reasons. One is the potential for HIV transmission of resistant strains that may overcome a microbicide that is based on the use of specific antiviral drugs (ARVs). A second is the potential for selection of drug resistance by a woman who uses an ARV-based microbicide, without knowing that she is HIV-infected. The potential for relevant compounds to then be systemically absorbed and select for resistance will be key. It is also possible that the concentrations of drug that are ultimately present in the blood and lymphoid tissue will be inadequate to select for resistance in this circumstance.

A related subject is the use of a ARV-based microbicide by a woman who knows that she is HIV-positive but uses it to protect her sexual partner. Might she in any way be at risk of transmitting a resistant virus? Each of these topics is important, as is the subject of whether the vaginal microenvironment is one in which selection of resistant virus might take place. This might depend on the extent to which viral replication occurs in this environment as well as the propensity of an ARV to carry drug selection if formulated as a gel or foam. The answers to these important questions are not known.

2. Considerations of drug resistance

This problem assumes relevance in the context of developing country scenarios in which antiretroviral drugs have not generally been available, in view of the decision by the World Health Organization to scale up antiviral therapy through use of the co-formulation of stavudine/(d4T), lamivudine/(3TC), nevirapine (NVP). This combination of two nucleoside inhibitors plus a NNRTI has the potential to save millions of lives in the shortest possible period of time and hence should be supported. At the same time, however, the potential for development of drug resistance against any of the agents in this combination is very real and, accordingly, the World Health Organization (WHO) has instituted policies that will monitor the development of resistance in settings in which this combination is administered (Zewdie et al., 2004). This notwithstanding, it should be pointed out that two of the drugs in the combination, i.e. 3TC and NVP, possess a low genetic barrier for resistance. A fuller discussion of this problem can be found elsewhere (Wainberg, 2005).

Indeed, data from prevalence studies of HIV-1 drug resistance have revealed a wide range of results. In general, populations that have never been exposed to antiretroviral drugs (ARVs) may be expected to harbor low rates of resistance mutations (Gittens et al., 2003; Laurent et al., 2002; Petch et al., 2005; Vergne et al., 2003), since prevalence of drug resistance is closely coupled to access to therapy as shown in industrialized countries (Grant et al., 2002; Wensing et al., 2005). Under current circumstances in most developing countries, it may be impossible to discern individuals who have drug access from those that do not in regard to likelihood of harbouring susceptible viruses. A practical assumption may be to consider every patient as a potential carrier of drug-resistant viruses.

Consequently, a relevant issue that arises is whether microbicides might be equally able to protect against transmission of both wild-type and drug-resistant viruses in the developing countries. Several reports have revealed development of high rates of drug resistance when national HIV treatment programs were poorly implemented (Adje et al., 2001; Harries et al., 2001; Vergne et al., 2002). Drug resistance may become an issue in developing-country settings. To some extent, a danger exists for women who have received single dose nevirapine for prevention of mother to child transmission (MTCT), given that even limited exposure to this drug can result in selection of drug resistance (Abrams, 2004; Eshleman and Jackson, 2002; Eshleman et al., 2001; Jourdain et al., 2004; Martinson et al., 2004; Morris et al., 2004; Wainberg, 2005), since they may be compromised with regard to future therapeutic options. This subject also has relevance for NNRTI-based microbicide development, because women harbouring resistant viruses might conceivably transmit them to male sexual partners even if a microbicide were used. At the same time, vulnerable seronegative women could still potentially be protected by microbicides since their male sexual partners would in all likelihood not harbour resistant viruses if they had themselves never received treatment.

However, the WHO 3 × 5 initiative will likely transform the context of microbicide use so that we will ultimately need to be concerned about drug-resistant viruses harboured by the male sexual partners of women at risk and the nature of the mutations that are present in such population. A relevant question is whether or not all HIV drug-resistant viruses are likely to be transmitted with equal frequency or whether some viruses, that possess mutations associated with diminished replicative fitness, may be found less frequently in new infections than either wild-type viruses or viruses containing mutations that do not impact on fitness. Several studies, including one from our group, have reported that resistant viruses may be transmitted with a lower frequency than expected (de Mendoza et al., 2004; Leigh Brown et al., 2003; Yerly et al., 2004). In addition, estimates are that transmitted HIV-1 resistance will most likely remain low despite increased access to ARVs (Blower et al., 2001). For instance, viruses containing the M184V mutation in reverse transcriptase, associated with resistance to 3TC, are less likely to be found in new cases of HIV infection, i.e. primary HIV infection, than are either wild-type viruses or viruses containing mutations associated with resistance to other nucleosides and/or non-nucleoside reverse transcriptase inhibitors (de Mendoza et al., 2004; Quinn et al., 2000; Turner et al., 2004). This is interesting, but there are two important caveats in the interpretation of results. First, the 184V mutation may result in lower levels of viral load than those associated with wild-type viruses (Machouf et al., 2006). Therefore, the diminished frequency of transmission of M184V viruses may be attributable to the fact that individuals with low viral loads are less infectious in general than are people with higher viral loads (Turner et al., 2004; Wensing et al., 2005). Second, as pointed out in our paper, viruses carrying the M184V