



INTERNATIONAL **P**ARTNERSHIP *for* **M**ICROBICIDES

The Use of Antiretroviral Drugs (ARVs) in Microbicides and the Potential for the Development of Drug-resistant Strains of HIV

**A Consensus Statement by IPM and the Executive Committee of the
IPM Scientific Advisory Board**

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Introduction

Microbicides used as self-initiated vaginal products could offer women a new strategy to prevent sexually transmitted HIV.

Questions related to the issue of HIV drug resistance have been discussed since the first considerations of ARV-based vaginal microbicides. Specifically, questions regarding the risk for selection and transmission of HIV drug resistance through microbicide use have been raised. Since drug resistance has important implications for the therapeutic outcome of HIV-treatment, concerns regarding a microbicide's potential impact on HIV drug resistance or its spread merit study and discussion.

It is worth noting that other HIV-prevention interventions have moved forward notwithstanding similar issues and concerns. For example, in programmes designed to prevent mother-to-child transmission, the NNRTI nevirapine (NVP) has been found to select for resistance in some women, yet that has not precluded women from continuing to use it and benefiting from other regimens in the course of their treatment. In this case, it has become a matter of balancing potential risks to gain the known benefits of using an ARV to prevent HIV transmission to infants.

This document offers some background and structure on issues specific to vaginal microbicides:

- A comprehensive assessment of the balance of potential risks and benefits of using ARVs to prevent HIV transmission is a priority for those involved in HIV prevention research.
- The risk for the development of drug resistance is currently unknown.
- There is evidence indicating that effective HIV treatment outcomes using first-line therapy can be achieved even in those harbouring HIV drug-resistant virus.
- Resistance and transmission studies are essential to better understand the potential incidence of drug resistance and its outcome and management. Large scale phase III microbicide efficacy trials will need to incorporate relevant sub-studies on these issues.
- Once proof-of-concept is established, specific studies on resistance in HIV-infected women will be conducted.

Ultimately the possible selection for drug resistance by the use of ARV-containing microbicides and the clinical as well as epidemiological consequences can only be addressed in clinical trials.

ARVs as Candidates for HIV Prevention in Women:

Due to their proven efficacy as therapeutics, ARVs are obvious candidates for new HIV prevention tools (NPT) such as microbicides (Grant 2006, Subbarao 2006). Microbicides used as self-administered vaginal products could offer women the opportunity to prevent sexually transmitted HIV-infection.

Some questions that arise are:

- What is the risk for the transmission and selection of HIV drug resistance through use of microbicides? Specifically:
 - Could a vaginal microbicide select for HIV strains that are resistant to the drug (or drug class) in women who are already infected and are using the product? HIV-infected women may be either unaware of a pre-existing HIV infection (incorrect use of a preventative microbicide) or have become HIV infected while using the microbicide (microbicide failure or inconsistent use).
 - Could drug-resistant virus (from the male) override the barrier of an effective microbicide?

Background on HIV therapy and development of drug-resistant virus:

ARVs inhibit important steps in the replication of HIV leading to a dramatic decline in viral load and a sustainable improvement of the long-term clinical outcome, including preventing or delaying progression of HIV infection to AIDS.

The success of ARV therapy has, however, been accompanied by the risk of developing HIV drug resistance. “Drug resistance” refers to a reduced susceptibility of HIV to specific ARVs rather than a total invulnerability of the virus to all ARVs. During ARV therapy, the replication of wild-type HIV is largely suppressed. However, the virus’ rapid and error-prone replication often leads to the evolution of changes in the viral genome (mutations), which can enable the virus to replicate in the presence of usually effective concentrations of ARVs. With the continued presence of ARVs (“selective pressure”), the resistant virus continues to replicate and thus becomes the predominant virus in the infected person (Brown 2000, Martinez 2006, Johnson 2007, Weinstock 2004). However, the use of newer ARV combination therapies has proven to strongly diminish the residual replication of HIV and is therefore much more effective in preventing the development of HIV drug resistance.

Considerations about microbicide usage and HIV drug resistance:

The vast knowledge on the development of HIV drug resistance, which has been gathered in the therapeutic field, can now partly inform the development process of preventive microbicides.

In-vitro models are used to investigate which mutations of the viral genome confer resistance to a specific ARV and the extent to which changes affect the virus’ drug-susceptibility. However the real-life frequency of the emergence of these mutations and their true effect on the efficacy of an ARV-based microbicide can only be estimated through research during broader microbicide use.

There are important differences regarding the development of HIV resistance in treatment and prevention settings.

1. HIV prevention through ARV-based microbicides in non-HIV-infected women:

If a woman uses an effective ARV-based microbicide and does not become HIV-infected, there is no potential for the development of HIV drug resistance. Therefore, the best way to decrease the risk of a microbicide selecting for HIV drug resistance would be to seek the most effective preventive microbicide that would be used with good adherence.

(The potential use of microbicides to prevent HIV transmission from an infected woman to an uninfected man is not the subject of this document.)

2. Pre-existing drug resistant HIV (from the male) overcoming a microbicide:

Drug resistance is usually not an all-or-none effect, but rather it represents a reduced susceptibility of a mutant virus relative to the wild-type virus. The proportion of the viral population that is mutant could also impact the severity of drug resistance. A pre-existing resistant strain therefore could overcome a microbicide if it is not susceptible to the concentration of drug to which it is exposed in the vaginal lumen or target tissues. It is important to note that the vaginal drug concentrations that can be achieved through intravaginal dosing are likely to be much higher than the concentrations achieved through oral dosing. Therefore, use of the highest safe vaginal dose of an ARV could possibly reduce the chances of a resistant virus escaping the ARV's effect.

3. Selection of resistance in HIV-infected women using microbicides:

The use of an ARV-based preventive microbicide by a woman while unaware that she is already HIV-infected may result in the selection of resistant HIV strains. If this occurs, subsequent oral treatment with the same drug or drug class may be less effective in the woman.

- It is important to note that entry criteria for all current clinical trials with microbicides specify that only HIV-negative women can be enrolled, and frequent HIV-testing is part of the study protocols.
- It is expected that ARV-based microbicides, once approved and implemented into HIV prevention programmes, will only be used in HIV-negative women. Pre-screening and regular follow-up testing would reduce the risk of resistance development.

Parameters that influence whether HIV drug resistance develops are:

- The genetic barrier to drug resistance of the specific HIV target, i.e., the number of mutations needed to achieve drug resistance against the specific ARV
- The systemic and local tissue concentrations of the ARV and their relationship to the development of drug resistance. The relationship between drug concentrations and development of resistance varies for the different drug classes and drugs. Minimum thresholds of drug concentrations that are required to exercise "selective pressure" vary. It has been shown that vaginal delivery of ARVs provides relatively low systemic concentrations compared with the approved oral dosing.
- The duration of ARV exposure in the HIV-infected woman before the HIV infection is detected and microbicide use is discontinued.

It has been shown that in cases where resistance has developed during exposure to ARVs during treatment, patients who stopped their ARV regimen had rapid re-emergence of the wild-type virus because of its higher replication capacity (Deeks 2001), such that it became the predominant virus. Despite the presence of reduced drug susceptibility in these patients, ARV therapy still provided immunological and virological benefits by suppressing non-resistant virus (Di Giambenedetto 2007).

Much can also be learned from other HIV prevention programmes that have moved forward despite similar issues. In programmes designed to prevent mother-to-child transmission of HIV, a short exposure to NVP was found to select for resistance in some women (Chaix 2007). However a study has shown that these women could be successfully treated with a NVP-containing regimen despite previously acquired NVP resistance if sufficient time was allowed for the NVP-resistant virus titer to decline in the body. Further it was shown that the combination of single-dose NVP with a short course of AZT/3TC reduced the extent of NVP-resistance development.

From PrEP experiments with tenofovir in monkeys with a related virus (SIV), it is known that in those cases where PrEP failed, the initial breakthrough virus was not drug resistant.

These and other observations suggest that preventive microbicide use may not lead to a broad and rapid spread of HIV drug resistance.

Conclusions

- Strategies for microbicide use will involve balancing the potential risks with the benefits of using an ARV to prevent HIV transmission.
- The development of HIV drug resistance through ARV-based microbicides can occur only when HIV transmission is not prevented or HIV infection is preexistent. Prescreening for HIV-1 infection and increasing the preventive efficacy of a microbicide should strongly decrease the potential for HIV drug resistance.
- ARV-based microbicides might fail to prevent infection with some drug-resistant viruses. However, since drug resistance involves varying degrees of sensitivity to drug and not an all-or-none response, the high concentrations of ARVs that can be achieved through vaginal delivery of microbicides could still be effective.
- ARV-based microbicides could select for drug resistance.
 - The real risk for the development of drug resistance is currently unknown.
 - The impact of acquired HIV drug resistance on later HIV treatment is also unknown. There is some evidence that effective HIV treatment outcomes can be achieved in those harbouring drug-resistant HIV.
- The incidence of drug resistance with the use of ARV-containing microbicides as well as the clinical and epidemiological consequences can only be sufficiently addressed in clinical trials. Comprehensive resistance and transmission studies should include long-term follow-up of women who have become infected while using microbicides. Once proof of concept is established, IPM will conduct appropriate safety studies in HIV-positive women.

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Additional Information

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