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Beyond HIV microbicides: multipurpose prevention technology (MPT) products

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Shortened running title: Beyond HIV microbicides: MPT products
Summary

Multi-purpose prevention technologies (MPTs) that aim to simultaneously prevent unintended pregnancy, human immunodeficiency virus type 1 (HIV-1) infection and other sexually transmitted infections (STIs) are among the most innovative and complex products currently in development within women’s sexual and reproductive healthcare. In this review article, MPTs are placed within the wider context of combination products, combination drug products and multi-indication products. The current MPT product landscape is mapped and assessed with reference to existing products for the corresponding single indications, before identifying the gaps in the current MPT product pipeline and highlighting priority products and challenges moving forward.
Introduction

Since 2010, following the first encouraging data to emerge from clinical testing of an antiretroviral-based HIV microbicide candidate, there has been extensive talk, consideration and early stage development around next generation products, termed ‘multipurpose prevention technologies’ (MPTs), that aim to combine HIV prevention with prevention of unintended pregnancy and/or prevention/treatment of other sexually transmitted infections (STIs) and reproductive tract infections (RTIs). In addition to the significant number of agenda-setting and commentary/review articles published on MPTs, there has also been a limited number of original research articles describing new MPT concepts. MPTs are not a new product class, despite the new (and somewhat confusing) name. Male condoms, which offer effective barrier protection against pregnancy, HIV and other STIs, have been used for more than 400 years, and their female counterparts have been available since the 1980s. However, despite their effectiveness, condoms are often not used consistently and correctly and have clear limitations for women. Therefore, there is an urgent need for new and innovative MPT products that offer women in particular greater choice and improved acceptability in controlling their sexual and reproductive health.

With recent interest focused almost exclusively on microbicidal-based (and, more specifically, antiretroviral-based) strategies for prevention of sexual transmission of HIV, newer MPT approaches have inevitably included at least one active pharmaceutical ingredient (API), resulting in either a ‘combination product’ (CP) or a ‘combination drug product’ (CDP), to use more conventional pharmaceutical regulatory terminology (Table
1. Figure 1). For example, the microbicide-releasing diaphragm device recently reported is considered a ‘combination product’ (Table 1, Figure 2), comprising a medical device (a cervical barrier diaphragm) coupled with an additional drug delivery function (controlled release of an antiretroviral microbicide). A vaginal ring device that provided simultaneous sustained/controlled release of an antiretroviral, a contraceptive progestogen and/or an anti-HSV drug would formally be classified as ‘combination drug products’ (Table 1, Figure 1, Figure 2). Regulatory definitions of a ‘medical device’ and a ‘drug delivery device’, for which there is often considerable confusion, are also provided in Table 1.

Combination drug products: the wider context for MPTs

Many of the MPT strategies currently being pursued rely solely on simultaneous delivery of multiple APIs, and are therefore formally classified as CDPs. For this reason, it is worth considering CDPs in more detail to help contextualise MPTs. CDPs (also known as ‘fixed-dose combinations’; Table 1, Figure 1, Figure 2) have become increasingly important in the public health arena. CDPs comprise a particular combination of actives, in a fixed ratio of doses, that is both safe and effective and where each API contributes to the overall therapeutic effect. For patients, these combination products often lead to simplified therapy, improved clinical effectiveness, reduced incidence of adverse side effect and increased adherence. For pharmaceutical companies, CDPs also offer excellent opportunities for life cycle management of marketed drug products. Currently marketed CDPs are mapped in Figure 1 according to the number of APIs in the product and the number of clinical conditions that the product is intended to treat. Unlike the vast
majority of drug products that contain a single active and treat a single disease, marketed
CDPs comprise two, three and even four actives for treatment of a single disease, most
commonly HIV/AIDS, asthma, malaria, contraception, high blood pressure and
tuberculosis (Figure 1). Examples of CDPs that are used in the treatment of two distinct
(but clinically related) diseases include Caduet®/Envacar® (containing atorvastatin and
amlodipine; used in the treatment of high cholesterol and high blood pressure,
respectively) and Juvisync™ (containing sitagliptin and simvastatin; used in the
treatment of diabetes and high cholesterol, respectively) (Figure 1). Not surprisingly, the
complexities associated with preclinical and clinical development of multi-indication
products, including CDPs and MPTs, are significantly greater than those for single API
products.

Multipurpose prevention technologies (MPTs)
MPTs are effectively a sub-category of CPs and CDPs, specifically focused on prevention
of a triad of specific (and inter-related) clinical conditions within women’s sexual and
reproductive health, namely pregnancy, HIV infection and/or other STIs. As such, MPTs
are multi-indication products (Figure 1), either comprising (i) multiple active agents,
individually effective for a different indication, (ii) a single active agent effective for
multiple indications (e.g. a single active drug with both microbicidal and contraceptive
properties), or (iii) one or more active agents incorporated into a medical device (e.g. a
microbicide-releasing condom or diaphragm). Figure 3 provides an overview of the
formulation/dosage form options being used or actively developed for
prevention/treatment of the individual clinical indications and the various combinations of indications that define MPTs.

It is worth making several comments based on Figure 3. First, the mature contraceptive market offers the greatest choice of formulation options, with thirteen distinct product types administered across a very diverse range of delivery routes (i.e. oral, vaginal, subdermal, subcutaneous, cervical and transdermal). This diversity is rather unique, particularly given the rather limited choice of APIs currently available for contraception.

The main factors contributing to the diversity of dosage forms and delivery routes used for hormonal contraceptives include: (i) contraceptive drugs may be delivered locally or systemically, although most are administered systemically, (ii) the relatively high therapeutic potency of hormonal contraceptive agents, at least compared with currently available antiretrovirals and anti-STI agents, and (iii) consequently, the need for only very low doses for clinical efficacy. It is likely that the next generation of MPT products will be based around these existing contraceptive technologies rather than a completely new product concept.

Second, seven MPT strategies have been identified within the intersection areas of the Venn diagram in Figure 3 (products identified by the following codes: 1DJ, 6G, 6+9D, 9D, 11A, 11G and 11AG). Most of these MPT products are in pre-clinical development (condoms being the exception) and all are based upon existing contraceptive technologies, most notably vaginal gels, vaginal ring and cervical diaphragms. Interestingly, this observation largely reflects current HIV microbicide development priorities and MPT product preference research, in which women rate favourably products that are easy to use and/or increase adherence.\textsuperscript{21} Since product adherence will be
critical for the clinical effectiveness of MPTs (as it is for HIV microbicides), sustained release products, such as vaginal rings, subcutaneous injectables and subdermal implants, have been identified using target product profile (TPP) methodology as a development priority.

Third, current MPT development work is focused primarily on HIV+contraception and HIV+HSV strategies (Figure 2), the former reflecting women’s health priorities in Africa where HIV is most prevalent, and the latter the fact that vaginally-administered tenofovir is inherently active against both HIV and HSV.

Where are the gaps in the MPT product pipeline?

It is not surprising that HIV prevention is a major component of most current MPT strategies, since MPT research has stemmed primarily from within the HIV microbicide field. Based on consideration of Figure 3 and the associated scientific literature, certain gaps and deficiencies in the MPT product landscape can be readily identified.

(i) There is an over-reliance on reverse transcriptase inhibitors (RTIs) for topical (vaginal and rectal) HIV prevention. This is particularly true of tenofovir and to a lesser extent dapivirine, both of which are lead candidate microbicides currently in late stage clinical testing. Anti-HIV compounds other than RTIs are slowly beginning to emerge as potential microbicides. These include small-molecule CCR5 entry inhibitors such as maraviroc and CMPD167, integrase inhibitors, protease inhibitors and various peptides/proteins. However, very few of these HIV inhibitor molecules have progressed to early stage clinical testing as microbicides, despite the fact that many are already marketed for HIV treatment.
(ii) There is presently a distinct lack of interest/commitment in the development of non-antiretroviral HIV prevention methods, although this has not always been the case. Previously, several non-antiretroviral microbicide candidates, including nonoxynol-9, cellulose sulphate, BufferGel, Carraguard and PRO 2000, were evaluated in late stage effectiveness trials, although none demonstrated protection. Vivagel, a second generation non-antiretroviral microbicide comprising a dendrimer-based gel product, has shown a broad spectrum of activity against HIV and HSV-2, although it is mostly being evaluated in ongoing clinical studies for the treatment of bacterial vaginosis. The general lack of specificity and potency of these non-antiretroviral microbicides is mostly attributed to the fact that their mechanisms of antiviral activity are confined to disrupting the virus or preventing its attachment to cells in the vaginal lumen rather than the intracellular activity afforded by antiretrovirals. Also, many of these non-antiretroviral microbicides were developed as coitally dependent, on-demand vaginal gel formulations, which, although being considered for MPTs, are probably not as high a priority as sustained release products.

(iii) Given ongoing concerns over the short and long term side effects associated with hormonal contraceptives (such as irregular bleeding, weight gain, nausea or lower libido, and slightly increased risk for certain cancers), the lack of innovation around non-hormonal contraceptive methods that might be leveraged by new MPT products is rather surprising. Barrier methods (exemplified by condoms, diaphragms and cervical caps) and the Paragard® intrauterine device, are the most common non-hormonal devices used for contraception. Of these products, only the diaphragm is presently being considered as a potential MPT, either used in combination with an antiretroviral gel or through direct
incorporation (and subsequent slow release) of an antiretroviral drug into the polymeric spring core component of diaphragm device itself.\textsuperscript{13} Investment in new contraceptive technologies, and particularly non-hormonal methods, is needed to achieve consistent and correct contraceptive use, to lower unintended pregnancy rates, and to widen contraceptive choice for women.

(iv) There appears to be no current activity in the development of non-HIV MPT methods (Figure 3), despite the fact that strategies that focus on preventing pregnancy and other STIs are deemed priority indications in a number of countries, including India, China and potentially Europe and the USA.\textsuperscript{21} Potent new drugs that specifically target other STIs are generally lacking, and identifying pathogen-specific actives for both bacterial and viral STIs is certainly a key priority in future MPT development.

(v) MPT product concepts comprising a vaccine component to target any of the three clinical indications that define MPTs are much further down the developmental pipeline compared with non-biologic strategies.\textsuperscript{10} Although HIV and contraceptive vaccines are in development, only an HPV vaccine is currently available (Figure 3). In general, biologic-based MPT product concepts remain largely unexplored. A vaccine and microbicide combination for preventing HIV-1 sexual transmission has been reported recently, albeit the components are administered separately via the intramuscular and intravaginal routes, respectively.\textsuperscript{35} Potential MPT product concepts offering a vaccine component include a single-dose depot injection comprising a contraceptive hormone (like Depo Provera\textsuperscript{\textregistered}) combined with an HIV or STI antigen, or a vaginal ring device delivering a vaccine candidate (either HIV or STI) and one or more ARV-based HIV microbicides. Vaginal
ring devices suitable for formulation and sustained release of biologics have been reported.\textsuperscript{15,36}

(vi) Sustained/controlled release progestogen-only products in the form of subcutaneous injectables (e.g. Depo Provera) and subdermal implants (e.g. Nexplanon/Implanon) are already marketed for long-term contraception. In fact, Depo Provera is the most common form of contraception in Africa. It is conceivable that MPT products could be developed based around existing injectable and implantable progestogen formulations. However, a major challenge would be achieving sufficient loading and release of the antiretroviral and/or anti-STI drug(s) to prevent sexual transmission of the associated microorganism(s). To date, this product concept has not been widely considered.

What are the MPT product priorities moving forward?

A key consideration for future MPT products will be user adherence to the prescribed regimen, a particularly pertinent issue for on-demand products. The importance of user adherence is well understood and documented within the contraceptive field, where the differences between actual-use and perfect-use failure rates are highly dependent on whether the products are user-dependent (e.g. oral pill, diaphragm, vaginal ring) or non-user dependent (e.g. intrauterine device, injectable, implant, and sterilisation).\textsuperscript{37,38} Growing concern over (lack of) adherence to experimental microbicide products and placebos in clinical studies, particularly with vaginally administered gel products,\textsuperscript{1,39,40} has led to prioritisation of sustained release over on-demand methods for MPTs. Sustained drug release vaginal rings are already marketed for contraception (Nuvaring\textsuperscript{®})
and Progering®), estrogen replacement therapy (Estring® and Femring®) and hormone supplementation during in vitro fertilisation (Fertiring®). Rings releasing small molecule antiretrovirals are also at the forefront of current HIV microbicide efforts. A vaginal ring comprising 25 mg of the non-nucleoside reverse transcriptase inhibitor dapivirine (also known as TMC120) dispersed within a silicone elastomer matrix is presently being tested in two Phase III studies (MTN-020 and IPM027) in Africa. Although high levels of acceptability and user adherence have been reported for non-microbicide vaginal rings, it is not yet clear if microbicide-releasing rings will offer improved adherence. The ability to combine and/or compartmentalise multiple drugs within a single ring device bodes well for developing a practical ring-based MPT strategy.

The challenges moving forward

Despite the obvious urgency for development of new MPT products for use in both developed and developing countries, the only options currently available for simultaneous protection against unintended pregnancy, HIV and/or other STIs remain male and female condoms. None of the MPTs currently in development have yet progressed beyond preclinical testing, although an investigational new drug (IND) application has recently been submitted for the tenofovir/levonorgestrel vaginal ring. When they do eventually make it to clinic, many complex hurdles and challenges will likely prevent a quick route to market. For example, the same issues that may challenge antiretroviral-based HIV prevention around the potential for development of resistant virus will also apply to MPT products containing antiretrovirals. This is likely to fuel demand for sustained release products that promote user adherence. Also, given the complexity of multi-indication
combination products having constituent parts corresponding to drug products, medical
devices and biologics, MPTs will invariably involve unique and challenging regulatory
considerations. Regulatory challenges, considerations, and decisions will be product-
specific as well as indication-specific. In both the EU and the US, a single regulatory
center will have primary jurisdiction for the MPT product, and assignment is based on the
product’s primary mode of action (although quite how the primary mode of action will be
defined is still unclear for many product concepts). Other major challenges for MPTs
include the design and assessment of results from clinical studies and appropriately
scaled manufacturing solutions for what are likely to be relatively complex and possibly
expensive devices.

Conclusions

Increased awareness and interest in new MPTs have largely been stimulated by recent
progress in the HIV microbicide field with the continued clinical development of the
tenofovir vaginal gel and the dapivirine vaginal ring. Based on the current clinical
schedules, and depending upon study outcomes, successful approval of these products is
unlikely before 2015. Meantime, in preparation for success and in order to ensure rapid
follow-through, it is imperative that new MPT concepts are considered, funded,
developed and evaluated now. Perhaps more than any other drug/combination product
type to date, MPTs will require diverse and extensive collaborative efforts across multiple
disciplines in order to achieve the laudable goal of creating innovative and converged
technologies that simultaneously address the most important issues in women’s sexual
and reproductive health today.
Disclosure of interest

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Figure 1. Mapping of number of active pharmaceutical ingredients per product versus number of clinical indications per product for ‘combination products’ and ‘combination drug products’ (including MPTs) (see Table 1 for definitions). MPTs fall within the product categories targeting two or more clinical indications, irrespective of the number of pharmaceutical ingredients in the product. Italicised text indicates representative marketed products or product classes. Non-italicised text indicates products in development. Underlined text represents MPT products.
**Figure 2.** Classification and regulatory framework for drug products, biologic products, medical devices and their combination products (depicted in grey). MPTs may be placed within several of these sub-categories, including medical devices, combination products, and combination drug products (CDP). A combination biological product (not shown) targeted at two or more clinical indications (pregnancy, HIV and/or other STIs) would also classify as a MPT product. The product types indicated in the diagram are examples representative of the classification.
Figure 3. Marketed and development product landscape for prevention/treatment of HIV, pregnancy, and other sexually transmitted diseases. All of the products captured within the HIV circle contain one or more antiretroviral compounds that act against HIV. Intersection areas (depicted in grey) represent MPT products. * HPV can infect areas that are not covered by a condom, and therefore condoms may not fully protect against HPV (http://www.cdc.gov/std/hpv/stdfact-hpv.htm)
<table>
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<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>combination drug, combination drug product or fixed dose combination</td>
<td>a single dosage form comprising two or more active pharmaceutical ingredients (APIs); may target single or multiple (often related) disease states; in tablet or capsule form, combination drugs are referred to as ‘polypill’ or ‘combopill’</td>
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<tr>
<td>combination product</td>
<td>a product comprised of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product</td>
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<tr>
<td>combination therapy, polytherapy or polypharmacy</td>
<td>use of more than one medication or therapy; most commonly used to treat a single disease; may involve administration of separate drug products or combination drug products; conditions treated with combination therapy include tuberculosis, leprosy, cancer, malaria, and HIV/AIDS; ‘polypharmacy’ is often defined as the use of five or more regular medications (more common in older patients).</td>
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<tr>
<td>drug delivery device</td>
<td>any device that provides delivery of one or more drug substances</td>
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<tr>
<td>medical device</td>
<td>“any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease; diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; investigation, replacement or modification of the anatomy or of a physiological process; control of conception; and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;” (Medical Devices Directive 93/42/EEC (MDD))</td>
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<tr>
<td>medicinal product</td>
<td>“any substance or combination of substances presented as having properties for treating or preventing disease in human beings; [or] any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.” (European Union Directive 2004/27/EC)</td>
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<tr>
<td>monotherapy</td>
<td>use of a single medication for treatment of a single disease</td>
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<tr>
<td>multi-purpose prevention technology</td>
<td>the term is exclusively used to describe technologies, preferably single-product technologies, that simultaneously address at least two of the following clinical needs: (i) prevention of unintended pregnancy, (ii) prevention of HIV, (iii) prevention or treatment of other sexually transmitted or reproductive tract infections</td>
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