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Future Prospects and Perspectives on Microbicides

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Abstract

As ‘proof of concept’ has now been well validated for topical microbicides, the progress has, appropriately, refined the questions of who, how, when and at what risk and cost. These are welcome challenges requiring intensified, cross-disciplinary responses. This is especially true in the areas of adherence and pharmacokinetic/pharmacodynamics (PK/PD) sampling and modeling to optimize preventive trials measuring “efficacy”, which is well known to reduce when measured as “effectiveness” in real-world use. Intensified exploratory and Phase I safety trials to investigate acceptability, adherence, PK and *ex vivo* efficacy with drug-exposed tissue biopsies/compartments fluids even though they are complex in design, management, assays and monitoring are moving forward. As well, great strides in recent efforts in a variety of delivery formulations are promising. These current and future efforts will provide potential insights earlier than at Phase IIb or III in the development pipeline.

Keywords

Microbicides; topical PrEP; HIV preventive; mucosa; pipeline; development; intensive Phase I trial; translational

This special issue of *Current HIV Research* emphasizes two uncontestable facts: (i) HIV prevention is an essential public health and moral imperative and (ii) microbicides (AKA: “topical PrEP”), as one mode to address this need, have arrived as contenders in the fight. While the chapters here detail the increasing numbers of agents which may potentially contribute to a combination prevention approach (essential), they also highlight critical advances in the fields of understanding HIV transmission [1], selection of optimal combinations of drugs for pre-exposure prophylaxis and formulation science. The articles also serve to remind us all how far and how fast this field of HIV prevention has grown. The successes in recent, large-scale, complex prevention trials with geopolitical, cultural, gender and behavior diversity have demonstrated significant reductions of new HIV infections, a dramatic achievement by dedicated teams, institutions and participating study populations [2,3]. And, as with any successful venture, the same successes have opened new controversies and challenges. The future plans, development and application are as strategically important now as before, with no appreciable decrease in the ~7000 new infections daily around the world. This is where “efficacy” will be translated into “effectiveness”. This field’s charge is to provide more options to analyze and address these

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CONFLICT OF INTEREST

Declared none.

needs as the first preventives are rolled-out into more public use, which will include HIV-positive and HIV-unknown populations as well as multiple-infected individuals.

The charges for future innovation and improvement are becoming clearer. The degree of success in recent trials would have benefitted from more accurate, behaviorally-transparent metrics of adherence, if they existed, enabling more confident subset analyses and, perhaps, earlier, focused roll-out of approved agents. This single feature would have assisted more in larger public health goals of determining how generalizable trial results might be and for which more-at-risk populations. Having improved confidence on which study sub-groups actually took the drug in prescribed fashion would help distinguish a ~40% versus ~90% protection trial result and is critical.

But having to wrestle with these issues is, in itself, a huge advance in HIV prevention. Proof of concept has now been achieved. That a topically-applied or an orally-delivered anti-HIV medication can significantly reduce acquisition of new HIV infection in real-world populations is no longer debated. How to do it better, safer, cheaper, provide options for application independent of coitus (surreptitious, if needed), user-driven, stable, acceptable and accessible are now more tangible and real challenges. From this point, the call to safely implement effective preventives in HIV-positive/HIV-status unknown, younger adolescent, pregnant and other subpopulations and to bridge HIV prevention with contraception and other STI preventions will emerge as key factors as prevention science advances.

The following topics identify some important, focused areas for future development of HIV preventives. The topical PrEP (microbicide) field has, for the past 2–3 decades been exemplary in cross-disciplinary, complementary, collaborative research efforts. Many, including the very proactive advocacy groups, have been at the table on all levels helping focus on acceptability, actual-use preferences, potential product roll-out, political and financial feasibility, community educational and marketing aspects that bring these research/science-based advances into daily, health-promoting practice.

UNIFY PROGRAMMATIC, DEVELOPMENT EFFORTS TO FOCUS ON SEXUALLY-EXPOSED COMPARTMENTS

Having an adequate concentration of active drug present in the sexually-exposed tissue is the most important feature of any non-vaccine preventive. As the various research fields of prevention align efforts, the primary goal will be to demonstrate that, regardless of route of delivery (*topical, oral, intramuscular etc*), timing and product formulation (*including films, rings, tablets, nanoparticle etc*), the goal will be documentation of sufficient concentrations of biologically active HIV-inhibiting drug(s) delivered safely to the sexually-exposed mucosal compartment with clinically-relevant time of coverage peri-coitus. From this aspect, ‘topically-applied microbicides’ and ‘pre-exposure prophylaxis’ require the same end result. This will require optimized pharmacokinetics and models to test efficacy (pharmacodynamics).

SAMPLING SEXUALLY-EXPOSED MUCOSAL COMPARTMENTS GIVEN DIFFERENTIAL RISKS OF INFECTION

Of the main sexually-exposed mucosae (*oral, vaginal, rectal, urethral, foreskin*), the possibility of oral transmission *via* unprotected oral exposure to HIV-infected fluids is of negligible risk. Conversely, current reports put unprotected receptive anal exposure 20–2000 times more vulnerable per sex act than unprotected receptive vaginal exposure; unprotected penile risk (whether urethral and/or foreskin) is also significant. Identifying the factors that contribute to the differential risk of HIV infection is critical and research efforts are

underway. However, the challenge for the microbicide/prevention field is to continue to press forward in developing safe, effective therapies without waiting for clarification of the pathogenesis questions. This is uncomfortable but we have been doing it thus far and must continue.

How to streamline efforts? Perhaps moving investigative and safety trials of the most vulnerable compartment (rectal) more front-line in safety and early intensive PK/PD studies, where clinically-relevant, would be beneficial. This is based on the reported increased infectibility, the increasingly acknowledged higher prevalence of receptive anal intercourse in women in many cultures and the ease/rapid repair of multiple samplings in the colorectal compartment. Multiple tissue sampling is more difficult in the anatomically smaller areas of the cervicovaginal, urethra and foreskin. It is assumed that a microbicide with vaginal efficacy but significant rectal toxicity would require FDA labeling that would limit its use in this compartment. Because of the advantages of tissue sampling in the gastrointestinal tract (colorectal area), inclusion of rectal safety as an initial screening site for proposed microbicides might not only increase the confidence of safety here for a licensed product, but also facilitate microbicide research by giving access to *ex vivo* HIV biopsy challenges (see below) and other assays that are limited or not possible in the vagina.

As the field develops confidence in less-invasive, surrogate markers of biopsied tissue, prioritizing rectal trials with tissue samples first becomes less important. An important limitation of this strategy is the inability to evaluate intravaginal rings, which are being prioritized because of wide acceptability of contraceptive rings and the likelihood that sustained ring delivery will overcome some of the problems of adherence.

COMBINATION THERAPY: TARGETS, DELIVERY, ROUTE AND TIMING

One of our greatest challenges, over 30 years into this epidemic, is that we remains unclear of which mucosal cells are the primary target(s) for HIV and the duration of their infectible potential post-exposure to HIV. This is extremely clinically-relevant as is knowing how long (and where) some of these target cells (e.g.: DC-SIGN-expressing and/or dendritic cells) can harbor still-infectious HIV. These research efforts are now among the most critical.

The need for combination therapy, with drugs that ideally target more than one step in the HIV life cycle, is well-accepted. Combination therapy in terms of complementary timing and multi-route delivery (e.g. *oral plus topical or vaginal plus rectal or mucosal vaccine plus topical*) has only recently been recognized as an important consideration. The challenges in testing and eventual use will require expert input from our formulation and pharmacology colleagues (to evaluate drug-drug interactions in the same formulations as well as delivery requirements to ensure that active drug reaches target cells in adequate concentrations) and behavioral colleagues (to provide guidelines on use, acceptability, multi-compartment intercourse sequencing, lubricant use (or not) and peri-coital activity and hygiene). These issues further underscore the importance for programs in non-vaccine preventives to unify efforts so that information from topical (*gel, film, suppository*), oral (*pill or food*), injection, ring or others are integrated to provide a variety of approaches aimed at getting needed drugs to needed targets.

Much of this challenge requires improved communication and aligning of financial and other resources. Regulatory aspects impact significantly here as well. INDs for already approved drugs now used in combination for a new indication require a certain level of investment to prepare, especially benefitted by the helpful “pre-IND” meetings offered by the FDA. Strategies for more rapid testing in humans of not-yet-approved medications need further innovative efforts to speed development while ensuring safety in healthy HIV-

negative populations. The “first A then B then A+B” approach may have to remain, if creative approaches while optimizing safety cannot be developed.

MUCOSAL COMPARTMENTS & PK MEASUREMENTS

It becomes apparent that PK quantification of active drug concentrations in sexually-exposed mucosal compartments is a critical endpoint in early human trials. These *tissue* (cervicovaginal and/or rectal and/or foreskin biopsies) and *fluid* (cervicovaginal lavage (CVL), vaginal and/or rectal sponges, ejaculate) PK assays are difficult and still early in development with significant inter-subject variability. Nevertheless, in the first sets of human data, there appear to be dramatic differences (up to 100-fold) in the same tissues (*rectal or vaginal*) when comparing drug levels following an topical versus oral dose. Intriguing, and currently without an understood mechanism, is the observation that a vaginally-delivered drug can be found in significant concentrations in concurrently obtained rectal compartment samples, and vice-versa [4]. These findings merit further investigation now and raise the welcome possibility for dual-compartment protection, which behavioral studies support.

HIV-INFECTION ASSAYS, ESPECIALLY IN EARLY HUMAN TRIALS

Determining whether a prevention strategy is efficacious, defined by reduced numbers of new infection, is conventionally the bailiwick of Phase IIb-III clinical trials. With the anticipated advancement of partially protective products (oral TDF, tenofovir gel) into the clinic, placebo-controlled trials will no longer be tenable. Thus, the conduct of future clinical trials will become more difficult and more costly. The development and validation and acceptance of “biomarkers of efficacy” in the form of *ex vivo* HIV challenges of *in vivo* exposed tissue (biopsies) will become crucial. *Ex vivo* challenge has been best studied in non-human primate models and human pilot studies with recent evidence (successful) that this approach can be incorporated even into Phase I trials [5,6]. This strategy holds potential by providing a new and clinically-relevant metric to help guide selection of which product(s) to advance to Phase II testing from a larger group of Phase I agents that have *all* demonstrated safety. Whether in human exploratory/Phase I and/or animal models, the ability to have *reduction of tissue/organism infection as an endpoint* will continue to be progressively critical, and lead to conservation in human, infrastructural and dollar resources.

PK-PD CORRELATIONS

Believable results from compartment PK (pharmacokinetics) and compartment infectibility assays (pharmacodynamics: PD) would enable statistical modeling, even in trials of small subject numbers. The ability to characterize the relationship between compartment-specific measured drug(s) (both peak/decaying levels) and compartment-specific efficacy in suppressing *ex vivo* infection in acquired tissue is potentially powerful and progressive. Only recently have the first PK-PD results from small Phase I trials been reported, demonstrating that tissue EC₅₀ (and, likely, EC₉₀, EC₉₅) can be derived. Admittedly, these are first-pass efforts and improvements in accuracy and sensitivity of each of the contributing assays will enhance the modeling efforts. These data potentially provide earlier functional and comparative insights into dosage and route, timing of delivery and potential duration of effect. While already the case in animal models, these aims further support the NIAID stated backing of much more intensive-sampling during early human clinical trials.

DEVELOPMENT PIPELINES

The microbicide field, perhaps more than any other I have been associated with, has benefited from innovative approaches and deep-rooted, cross-disciplinary, intertwined development efforts. That these collaborations have been so productive in HIV-uninfected populations is even more impressive as the incentives for these populations to participate in research are usually thought to be low. This field's iterative, tight-feedback loops have enabled active discussion with diverse researchers in readdressing the conventional linear approach to drug development (*cell lines to primary cells to animal models to non-human primates (NHP) to human safety and then human efficacy trials*). There is now enough evidence accumulating that individuals, even if not in routinely defined higher-risk groups, are willing to participate in early, repeatedly invasive studies and trials, enabling the field to test questions early, in the most clinically-relevant populations, tissues and fluids. Early human-derived data can then feed back to enable optimized and more focused dose/effect trials in NHP etc. The approach seems likely to save significant time, funding, animal and human resources with an improved feedback translational loop.

The microbicide field should continue to optimize this by now moving more aggressively to include behaviorally and biologically relevant features during the very act of sex. These factors may be critical and better assessed early rather than later. More routine and early evaluation of other potential but real confounders of a topical preventive's activity are now essential. These include the impact of vaginal and rectal fluid, ejaculate, cyclic (and other) hormones, resident microbial populations and mucosal immune-cross-talk, the physical trauma of sex and possible epithelial injury and/or inflammatory consequences as well as the most important factors of enhancement of HIV infection or inactivation of compartment drug activity when studied in "real-life" conditions. Increasing intensification of early observation and Phase 1 study design with human tissue sampling with direct feedback to earlier pipeline development efforts, including NHP and other animal models, will provide significant, bundled benefits for the field and the legions of not-yet-infected.

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