REGULATORY PATHWAYS AND CLINICAL TRIAL DESIGN FOR LONG-ACTING PrEP

PERSPECTIVES FROM A THEMATIC ROUNDTABLE ORGANIZED BY THE IAS INDUSTRY LIAISON FORUM

BACKGROUND

Since the first Phase III trials eight years ago, tenofovir/emtricitabine (TDF/FTC [1]) as an oral pre-exposure prophylaxis (PrEP) has been approved for HIV prevention in 20 countries. To date, implementation has mainly been in high-income countries for men who have sex with men, with some smaller programmes for men who have sex with men and sex workers in low- and middle-income countries. Further scale up is underway in in sub-Saharan Africa for populations with high HIV incidence, including serodiscordant couples, adolescent girls and young women and pregnant and breastfeeding women, as well as in Brazil for men who have sex with men and transgender women. Challenges for the further rollout of oral PrEP include: the cost of the drugs and related health services (including regular HIV testing); the challenges of sustained adherence, especially among young people; and the need to further expand access for key populations, including people who inject drugs and transgender people. The increased availability of off-patent products, including generic TDF/lamivudine (3TC, which will become available in the US in 2018), may increase demand for oral PrEP.

Based on the experience with oral PrEP, long-acting (LA) formulations of antiretroviral drugs now in clinical development have the potential to increase adherence, convenience, uptake and efficacy of PrEP in the coming years and to reduce risk of drug resistance. The first LA product for potential use as PrEP is in late-stage clinical trials, with an estimated timeline for regulatory approval in 2022. As additional products enter clinical development in the era of effective antiretroviral treatment (ART) and PrEP, it will be increasingly challenging to design trials of sufficient power to demonstrate the efficacy (non-inferiority or superiority) of these new products for HIV prevention. It will also be necessary to ensure that LA PrEP trials collect adequate data on safety among target populations, including adolescents, young people and pregnant and breastfeeding women.

The perspectives expressed in the discussion that follows are based on a thematic roundtable organized by the IAS Industry Liaison Forum on 5 March 2018 at Fenway Health, Boston, USA.

CLINICAL TRIAL PIPELINE FOR LONG-ACTING PrEP

Data reported from the HPTN 077 trial in 2017 established the safety, tolerability, acceptability and pharmacokinetic profile of the LA injectable integrase inhibitor, cabotegravir (CAB-LA), injected every eight weeks [2]. By early 2018, enrolment was underway in two Phase III efficacy trials of CAB-LA as PrEP. HPTN 083 will test CAB-LA among at-risk cisgender men and transgender women who have sex with men in 43 sites in Argentina, Brazil, Peru, South Africa, Thailand, the US and Vietnam. The trial is a non-inferiority, double-blind, double-dummy design (see Figure 1 for an illustration of different clinical trial designs for PrEP).

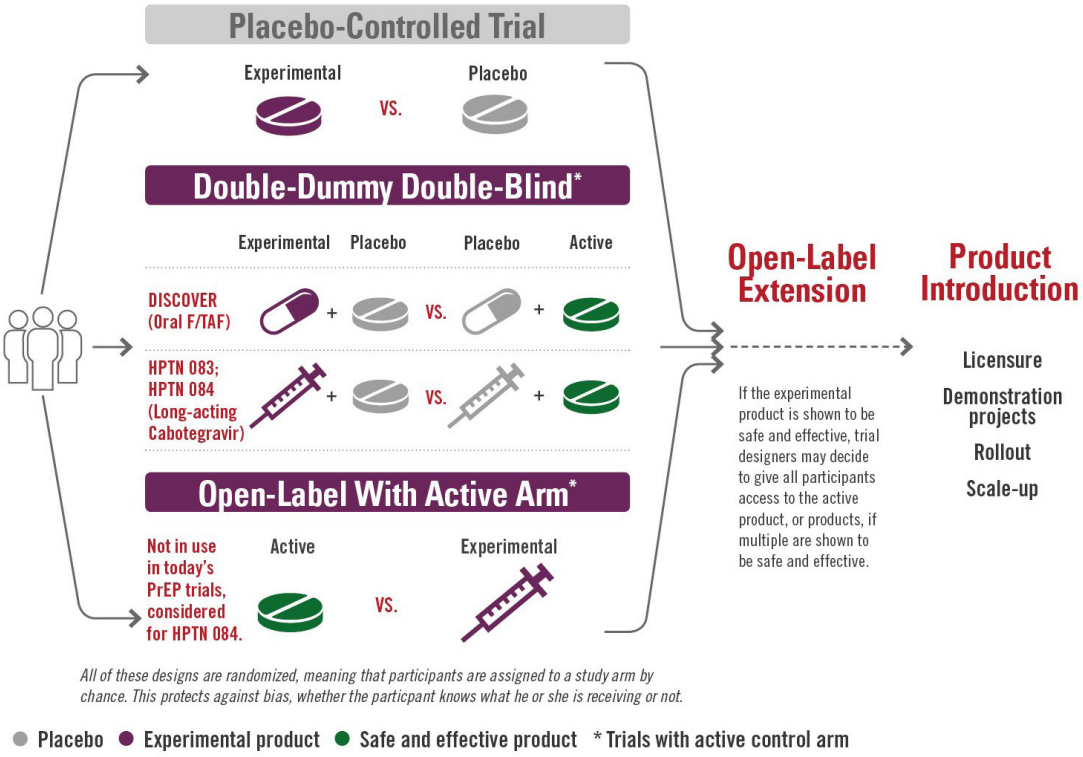

Figure 1. Illustration of different clinical trial designs for PrEP.
Used with permission from Px Wire: A Quarterly Update on HIV Prevention Research | Volume 10 | No. 2 | April-June 2017, see here.

Concurrently, HPTN 084 will test the efficacy of CAB-LA among at-risk women in 20 sites in sub-Saharan Africa. HPTN 084 is designed to show the superiority of CAB-LA over oral PrEP, which has shown variable effectiveness in women to date. Both HPTN 083 and HPTN 084 currently include a four-week oral cabotegravir induction phase to exclude adverse reactions before the long-acting injectable product is given. Results from both trials are anticipated in 2022 or earlier. The manufacturer, ViiV Healthcare, has also endorsed a bridging study to test the product in adolescents.

MK-8591 (previously called EFdA) is another LA product currently in pre-clinical development. This drug belongs to a new investigational class of antiretroviral drugs known as nucleoside reverse transcriptase translocation inhibitors or NRTIs. MK-8591 has been shown to be effective at a very low dose in non-human primates [3,4]. The developer, Merck, has highlighted that this drug has potential for both treatment and prevention, either as a long-acting oral pill or as a subcutaneous implant. Several other companies are also exploring the potential of long-acting implant technology.

Monoclonal antibodies are being studied for both treatment and prevention of HIV. Two Phase IIb HIV prevention trials of the product VRC01mAb (known as the Antibody-Mediated Prevention or AMP trials) are currently underway in 47 sites in 11 countries. The AMP trials focus on men who have sex with men and transgender women in North and South America and on women in southern Africa. VRC01mAb is given every eight weeks as an infusion. While monoclonal and broadly neutralizing antibodies pose significant challenges in terms of cost and complexity, including issues of potency, half-life, tissue penetration, manufacturing and supply chain, industry appears to be interested in testing several of these products.

New drug delivery methods are likely to be ready for clinical trials in the next few years. These include long-acting oral formulations, microneedle (also called microarray) patches, implants and antiretrovirals combined with long-acting hormonal contraception. Further information about long-acting products and delivery methods can be found on the website of the Long-Acting/Extended Release Antiretroviral Resource Program (LEAP), a US National Institutes of Health-funded initiative to support scientific collaboration, innovation, modelling and communications related to the development of long-acting and extended release antiretroviral drugs (www.leapresources.org).

TACKLING CHALLENGES IN CLINICAL TRIAL DESIGN FOR LONG-ACTING PrEP

Using STI data as a proxy for HIV incidence

In general, HIV prevention trials are becoming more difficult and expensive to perform. In the era of a highly efficacious standard of prevention (oral TDF/FTC) and highly effective ART, it is increasingly challenging to conduct studies that show statistically significant differences between HIV infection rates in trial arms without enrolling extremely large numbers of patients. Moreover, there is increasing competition for trial participants and real risks of study fatigue among the most vulnerable populations.

Using sexually transmitted infection (STI) data as a proxy for HIV incidence has been proposed as a potential solution to the challenge of using HIV infection as a study endpoint. Proponents argue that this approach should be considered to avoid running uninformative trials due to a low number of HIV exposures. On the other hand, not all STIs correlate with HIV in all parts of the world. Historical HIV prevalence data could also be used, similar to the use of historical pregnancy rates in contraceptive trials. It was also suggested that electronic medical records and databases could potentially be useful sources of data, for example, to create virtual cohorts or "cohorts within cohorts" to help address the challenge of cohort size.

It is noteworthy that investigators for the HPTN 084 trial of CAB-LA considered an open-label trial design that would have directly compared cabotegravir to TDF/FTC pills, but that the US Food and Drug Administration (FDA) favoured the double-blind, double-dummy design that was ultimately selected. In addition, although detection of STIs suggests potential exposure to HIV in some settings, the trial designers for HPTN 084 did not consider STIs (for example, rectal gonorrhoea) as a satisfactory de facto surrogate for HIV infection. They also felt that historical HIV incidence would be unreliable given the uptake of ART and its role in reducing transmission from people with HIV infection to their sexual partners.

In the US, the Food and Drug Administration Safety and Innovation Act 2012 and the Twenty-first Century Cures Act 2016 provide legal and policy frameworks that aim to help address current trial design challenges by promoting innovation and encouraging better use of data in research (including real-world data). The Forum for Collaborative Research is working with the FDA to establish a working group on HIV and STI incidence that will consider issues such as:

- **Whether rectal gonorrhoea could serve as a correlate of HIV incidence in prevention trials enrolling men who have sex with men**
- **Whether this approach could serve as proof of concept for a new PrEP trial modality**
- **What confirmatory trials would be needed to translate such an approach to other populations, such as heterosexual men and women, and adolescents.**

Accepting lower efficacy to expand prevention options

An emerging challenge is the potential conflict between new products that are "as good as Truvada" and new products that potentially have lower efficacy but increase the options available, for example, for people who are not able to take a daily pill. This raises questions such as:

- **How much efficacy could or should be given up for the sake of a trial?**
- **Would the FDA accept a lower level of efficacy or wider inferiority margins in trial design?**
- **What would be the largest clinically acceptable loss in efficacy between the experimental drug and the active control (in the language of trial design experts: the choice of "delta" for a study)?**

Engaging adolescents and youth early in HIV prevention trials

Because adherence to medication can be a major challenge for young people, long-acting PrEP formulations may offer a particular benefit to this population. While it can be challenging to include adolescents and youth (together, 10-25 years old) in trials, it can be done and should be prioritized. In many jurisdictions, adolescents and youth of 16 years and older may be able to give consent without parental approval, as they can for clinical interventions. However, many institutional review boards will not allow minors to consent to trials of a product with unknown efficacy. Enrolling adolescents and youth in large Phase III trials requires additional considerations. For example, assurances about confidentiality may be especially important for adolescents and youth concerned about exposure of their sexual identities or behaviours. Smaller sub-trials involving adolescents (or "bridging studies", which are smaller studies to collect specific types of data, for example, among populations not represented in the larger trial) may help address such concerns. Although the FDA prefers that adolescents be enrolled simultaneously with adults, it is not opposed to sub-trials for this population.

Adherence data in adolescents and youth will be especially important for the first long-acting product approved for PrEP as it is unlikely that generalizations can be made from the results of adult PrEP trials to these populations. However, data on adolescents and youth adherence in treatment studies could suggest a way forward for HIV prevention research. Extrapolation of safety and tolerability data from treatment studies in adolescents and youth to HIV prevention trials should also be considered.

Making long-acting PrEP beneficial to pregnant and breastfeeding women, infants and children

Pregnant women and breastfeeding mothers who are vulnerable to HIV infection may struggle with adherence to daily oral PrEP and therefore benefit from long-acting PrEP. Long-acting PrEP may also be beneficial for neonates and infants. Microarray patch technology offers potential to improve drug delivery to newborns and infants, both for HIV prevention and treatment. It is unlikely that pharmacokinetic data on long-acting products in infants will be enough for regulatory approval in this population. As a result, even though they are difficult to conduct, it is likely that efficacy trials in infants will be needed for these products.

A consultation conducted by the LEAP consortium in November 2017 recommended that clinical trials of long-acting antiretrovirals include children, adolescents and pregnant women from an early stage using a parallel rather than sequential approach to drug development and approval; this should happen as soon as adult safety and efficacy data become available. Furthermore, efforts should be made to include adolescents in adult clinical trials and to establish adolescent-specific trials only when necessary.

LOOKING AHEAD

To achieve an optimal mix of methods, in particular for the groups most vulnerable to HIV, such as women in sub-Saharan Africa, researchers and policy makers need not only consider where the greatest unmet needs for HIV prevention are located, but also:

- **What products people want and will use**
- **What trial designs can best answer questions quickly and ethically**
- **How next-generation PrEP will be delivered, considering the capacity of existing health services.**

Experience with HIV prevention trials to date shows that people routinely provide inaccurate information about their sexual behaviour and drug use, and that risk perception is very subjective. Accordingly, it is not always possible to generalize results from Phase III trials to real-life use.

Ongoing discussions between manufacturers, researchers, regulatory bodies, communities, potential end users and their partners, and providers will be needed to address the range of challenges currently faced by the HIV field in designing trials of new, long-acting products for HIV prevention, and also to understand and differentiate between need, demand, acceptability, access and real-life uptake. Novel approaches to data use may help expedite trials and ensure timely regulatory approval of new products. Encouragingly, the FDA has expressed openness to innovation to chart a path forward in the field of HIV prevention research.

Sustained efforts will also be needed to create demand for new products in diverse communities most vulnerable to HIV acquisition and to ensure that they are delivered in the most effective way to achieve impact. Above all, the HIV prevention field should avoid complacently stating that "we have all the tools we need to end AIDS" when new tools are still needed for both prevention and treatment.

[1] Also known as Truvada, a product developed by Gilead Sciences.

[2] Landovitz et al., Safety, tolerability and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected women and men: HPTN 077, IAS 2017, Abstract 5481.

[3] Markowitz et al., Low dose MK-8591 protects rhesus macaques against rectal SHIV infection, CROI 2018, Abstract 89LB.

[4] Matthews et al., Multiple daily doses of MK-8591 as low as 0.25 mg are expected to suppress HIV, CROI 2018, Abstract 26.

ABOUT THE ILF

The International AIDS Society's Industry Liaison Forum (ILF) works to promote and facilitate the full contribution of the biomedical industry to the global HIV response. By organizing bespoke meetings on key topic areas, the ILF brings to the foreground the contribution of an interdisciplinary group on current and emerging issues. The ILF also builds on its collaboration platform to address a range of issues in paediatric HIV and regulatory affairs. A multi-stakeholder ILF Advisory Group guides this work. More information can be found at http://www.iasociety.org/ilf

Produced by International AIDS Society
Avenue de France 23, CH-1202, Geneva, Switzerland
Tel: +41 22 710 08 00
Fax: +41 22 710 08 99
info@iasociety.org
www.iasociety.org