PxWire A Quarterly Update on HIV Prevention Research | Vol. 7 No. 2 | April–June 2014 | AVAC Global Advocacy for HIV Prevention

AVAC's Take

Women bear the burden of the global AIDS epidemic and also make daily contributions to great and practical solutions. We salute all of these women and take it as a sign of hope and promise that Debbi Birx and Glenda Gray, two scientists and activists, have taken new leadership roles. In April, Dr. Birx was confirmed as the new US Global AIDS Coordinator. She is the right person to take the helm of PEPFAR to ensure that the program makes good on its commitments to achieve an AIDS-free generation. She has stated that she intends to do so in the context of full human rights protections for gays and lesbians, who are endangered by homophobia and criminalizing laws, such as those recently passed in Nigeria and Uganda.

Also in April, Dr. Gray was appointed president of the South African Medical Research Council. Dr. Gray is the first woman to hold this position and will now help to coordinate an extensive public health research agenda, including vaccine trials to build on the Thai Prime-Boost study that found modest efficacy in 2009.

As new tools proliferate, we need to figure out how to use them—alone and in combination—and we need to develop next-generation products like a vaccine or the long-acting injectable ARVs described in this issue with attention to both science and acceptability. Dr. Birx and Dr. Gray will help lead the way. – *AVAC*

Data Dispatch

Who wants a long-acting injectable? We need to know.

Could an injectable ARV be used for long-acting PrEP? This possibility seized the HIV prevention spotlight in March after new animal data were presented at the annual Conference on Retroviruses and Opportunistic Infections (CROI). The data showed complete protection against vaginal challenge in female monkeys that received monthly injections of GSK744. Similar levels of protection were seen in a rectal challenge experiment presented last year. This evidence of protection provides a basis for moving ahead with evaluations in humans. Two phase II trials to explore safety and efficacy of GSK744—an integrase inhibitor—are being designed and implemented.

Rilpivirine, also called TMC278, is a non-nucleoside reverse transcriptase inhibitor that is widely used in oral form. A long-acting formulation is also being investigated for PrEP. A phase II trial of this compound is also being designed for implementation later this year.

Long-acting GSK744 and rilpivirine are also being evaluated as a two-drug "maintenance therapy" regimen that could be used by HIV-positive people who have achieved an undetectable viral load using oral triple combination therapy. See centerspread for more on this approach.

Selected Trials of Long-Acting Injectables for Prevention and/or Treatment of HIV (April 2014)

Active LA Drug	Other Name	Developer	Phase of Research	Trial Name	Population	Class of Drug
Long-acting TMC278	Rilpivirine (RPV), Edurant	Janssen	Phase II	HPTN 076 (planned)	HIV-negative at risk women	Nonnucleoside reverse transcriptase inhibitor
Long-acting GSK744	GSK1265744	GlaxoSmithKline (GSK)	Phase IIa	ÉCLAIR (ongoing); HPTN 077 (planned)	HIV-negative at-risk men, MSM; HIV-negative at risk women and men	Integrase strand transfer inhibitor
Ibalizumab	TMB-355, monoclonal antibodies	Aaron Diamond AIDS Research Center	Phase I	TMB-108 (completed)	HIV-negative women and men	Entry inhibitor
Oral TMC278 and **GSK744**	Rilpivirine (RPV), Edurant and Tivicay	Janssen and GlaxoSmithKline (GSK)	Phase II	LATTE (ongoing)	HIV-positive men (96%) and women	Nonnucleoside reverse transcriptase inhibitor plus integrase strand transfer inhibitor

For a complete list of long-acting injectable trials, visit *www.avac.org/long-acting-injectables*.
A full list of HIV prevention clinical trials is available at *www.avac.org/pxrd*.

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Global Advocacy for HIV Prevention

Introduction to Long-Acting Injectables

The term long-acting ARV injectable refers to an antiretroviral drug that is delivered via an injection and persists in the body for an extended period of time. These drugs are being developed as treatment for HIV-positive people and pre-exposure prophylaxis (PrEP) for HIV-negative people. The goal is to develop an injectable-only regimen that would minimize adherence requirements. For both treatment and prevention, daily dosing can be a challenge. Some HIV-positive and HIV-negative people might prefer a product that is discreet and requires less frequent dosing. The candidates that are furthest along are rilpivirine (also known as TMC278, brand-name Edurant) and GSK744, which is an analogue of the drug dolutegravir. Injectable antibodies are also being considered for PrEP.

The physical and chemical properties of ARVs like GSK744 and rilpivirine make them good candidates for long-acting injectables. Specifically, they are potent, poorly water-soluble and have relatively small oral doses, meaning that the volume of an injected dose will not be too high.

A drug only works if it is present in sufficient quantities in the body. Each medication is processed, or metabolized, by the body in a specific way. Some drugs are processed rapidly, others more slowly. Long-acting injectables have a long half-life, which means the drug remains in the system for a long time. This is good because it allows less frequent dosing. But it can be challenging if someone wants or needs to stop using the medication, since it takes some time for it to leave the body. For long-acting injectables, it is essential to understand how the drug is processed —the pharmacokinetics and pharmacodynamics of the drugs in the body—to be sure that a given dose leads to blood levels that are safe and effective.

What does it take to develop a long-acting injectable for HIV treatment and prevention?

TREATMENT

Could it CONTROL the virus?

The two leading long-acting injectables, GSK744 and rilpivirine, will be evaluated as a two-drug "maintenance" regimen that could be used after a person with HIV achieved an undetectable viral load with oral triple-combination ART. An ongoing trial is evaluating the oral form of the two-drug combo for this purpose. Rilpivirine injections have been tested as monotherapy in HIV-positive people.

What is the right DOSE?

The therapeutic doses for a maintenance regimen using injections will be determined using data from oral two-drug studies in HIV-positive people as well as data on the way different injectable doses are processed by HIV-positive and -negative people.

Does it WORK?

Current plans call for an efficacy trial of a two-drug combination (GSK744 and rilpivirine injections) to evaluate safety, tolerability and impact on virologic suppression compared to highly effective ART using oral formulations. Such a trial will incorporate a lead-in "induction" phase using oral formulations to be sure that the drugs are safe. It will also explore strategies for ensuring that individuals discontinue the drugs safely: since injectables persist in the body and there can be a "tail" of diminishing drug levels in the body after the last dose. These lower levels would be insufficient to control the virus but can lead to viral resistance if individuals don't have appropriate care during the transition.

IS IT SAFE?

Is an injection safe? How is the injectable form of the drug processed by the body?

The first step for evaluating long-acting injectables is to test the injection in healthy, HIV-negative people. These short studies (weeks or months) evaluate the tolerability and side effects of the drugs. They also provide pharmacokinetic (PK) and pharmacodynamic (PD) data: how the drug is processed by the body, and how levels of the drug change in the body over time. At this stage, dose-ranging studies gather information on the safety, tolerability, PK and PD of different dosages and regimens (e.g., one shot, two shots and so on).

TESTING THE CONCEPT

Is there evidence that an injectable could work?

To evaluate long-acting injectables for treatment, the next step is testing the oral formulations of drugs in HIV-positive people to be sure that they control viral load alone and/or in combination with other medications. Such evaluations "prove the concept" that injectable formulations could also achieve virologic control. For prevention, the concept can be tested in animal-challenge experiments, in which monkeys receive an injection and then are exposed to simian-human hybrid viruses that cause HIV-like illness.

ACCEPTABILITY

Do people want it?

A long-acting injectable for prevention and/or treatment may have potential benefits. For example, such a product might reduce adherence challenges, be used discreetly and ease some health systems challenges. But these benefits will only materialize if people want, like and use the product. Acceptability research shouldn't be an afterthought. Now is the time for product introduction planning to learn about interest in, concerns about and acceptability of the leading candidates as they are likely to be delivered.

FINDING THE RIGHT DOSE

What is the right dose and dosing schedule of an injectable?

Determining the right dose and dosing schedule for an injectable is a challenge whether the drug is going to be used for prevention or treatment. Issues related to side effects and safety are particularly pressing with a long-acting injectable since it can't be removed once it's in the body. This is one reason why people using long-acting injectables would probably start with an oral lead-in phase to establish that they could tolerate the drug.

TESTING FOR EFFICACY

EFFICACY

Does the drug work to control the virus in HIV-positive people or to reduce HIV risk in HIV-negative people?

Efficacy trials of long-acting injectables for both treatment and prevention are planned to start in the next 12–14 months. In both cases, there are unique design considerations related to use of drugs that persist in the body over time, including ensuring safety at an individual level, differences due to gender, age and other factors that might impact drug metabolism and developing strategies for safe discontinuation.

PREVENTION

Could it PREVENT infection?

GSK744 has been evaluated in a monkey model where a single monthly shot provided complete protection against repeated challenges with a simian-human virus similar to HIV. Rilpivirine hasn't been tested in monkey challenge experiments.

What is the right DOSE?

Different doses of GSK744 and rilpivirine injections are being evaluated in small trials with healthy HIV-negative men and women. These data, along with data on the drug levels associated with protection in animals, will guide selection of the dose used in efficacy trials.

Does it WORK?

Both GSK744 and rilpivirine are on track to enter efficacy trials in humans in the near future. Discussions are ongoing about trial design. It will be key to test participants regularly to detect HIV infections and minimize the risk of drug resistance. These trials will also need to explore how to provide effective treatment for people who become HIV-infected while using long-acting injectables.

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Long-acting injectables might be preferable to some people, in part because they reduce the adherence requirements of daily oral PrEP or ART. Even as the clinical trials move forward, this assumption should be tested via acceptability research that probes user preference, assumptions and concerns. Past experience makes it clear that acceptability trumps efficacy. If people don't like a product, they are unlikely to use it, whether it works or not.

Who wants daily oral PrEP? We are starting to find out.

In July, it will be two years since the US Food and Drug Administration approved daily oral TDF/FTC (Truvada) as PrEP. In that time, the strategy has been declared many things including *dangerous* (toxic and impossible to adhere to) or *dead in the water* (a strategy no one will want or use). But nearly 24 months out, the discussion is shifting to *doable*. With providers and prevention advocates in the US leading the way, there has been a steady drumbeat of blog posts, articles and editorials in which physicians and potential users—many of whom were originally PrEP skeptics—describe how they've come to view the strategy as an important niche intervention. These include an in-depth analysis on *gawker.com*[1] about the politics of using PrEP versus condoms and an April editorial by a doctor on *thebody.com*[2] whose encounter with a young man with acute HIV infection led her to change her mind about the utility of PrEP.

Such articles suggest that there is growing clarity about where and how daily oral PrEP can make a difference in the US.

Views are shifting in other parts of the world, too. In late March, the team behind the Partners PrEP trial of daily oral TDF or TDF/FTC in serodiscordant couples held a meeting in Nairobi to update Kenyan and Ugandan stakeholders on their ongoing demonstration project. The conversation was largely supportive of moving ahead with targeted PrEP use—including in gay men and other men who have sex with men, a key population made even more vulnerable by the surging homophobia in the region. Cost-effectiveness is critical, and one of the questions at the meeting was whether daily oral TDF could be used instead of TDF/FTC. (Partners PrEP found comparable efficacy for both drugs.) This is exactly the kind of question that can and should be answered by well-designed operational research and modeling.

Also of note: in the UK, the PROUD study evaluating daily oral TDF/FTC has completed enrollment of its pilot phase and generated the first information on participants' views and preferences.[3]

The initial pace of uptake of oral PrEP isn't a sign that people don't want it. If the world listens to users and providers, the new few years will bring real change. For the latest on PrEP, visit *www.prepwatch.org*.

Recently Released

Research & Reality – An ongoing webinar series about prevention research and advocacy; *www.avac.org/advocacy2014.*

Supplementary Tools for GPP – A new set of tools to help research teams and stakeholders implement *Good Participatory Practice (GPP) Guidelines for Biomedical HIV Prevention Trials; www.avac.org/gpp*

HIV RESEARCH FOR PREVENTION HIVR4P Shaping the Science of Prevention

The world's first and only scientific meeting dedicated exclusively to biomedical HIV prevention research takes place this October in Cape Town. *www.hivr4p.org*

About AVAC

AVAC Global Advocacy for HIV Prevention

Founded in 1995, AVAC is a non-profit organization that uses education, policy analysis, advocacy and a network of global collaborations to accelerate the ethical development and global delivery of HIV biomedical prevention options as part of a comprehensive response to the pandemic.

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[1] http://gawker.com/what-is-safe-sex-the-raw-and-uncomfortable-truth-about-1535583252

[2] http://www.thebody.com/content/74236/why-i-started-supporting-prep.html

[3] http://www.aidsmap.com/PROUD-UK-PrEP-study-completes-enrolment-first-data-gives-participants-background-and-risk-factors/page/2845218/