



What does the future of ARV-based prevention look like?

SESSION REPORT

Public Satellite Session at the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011)

18 July 2011
Rome, Italy

Co-hosted by IAS & AVAC



Background

As part of an effort to promote HIV prevention research in resource-limited settings, the International AIDS Society's (IAS's) Industry Liaison Forum (ILF) and the AIDS Vaccine Advocacy Coalition (AVAC) jointly organised a satellite session at the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011), entitled "What Does the Future of ARV-based Prevention Look Like?" In recent years, the ILF and AVAC have co-hosted several meetings and conference sessions in order to address the ethical, scientific and operational issues related to pre-exposure prophylaxis (PrEP) and other ARV-based prevention modalities. At IAS 2009 in Cape Town, a satellite session – ["The Promise and Perils of ARV-Based Prevention: A Dialogue of Optimism & Informed Scepticism"](#) - highlighted the challenges for the HIV field in the context of clinical trials that were demonstrating efficacy. At the XVIII International AIDS Conference in Vienna, the ILF also organized two additional ARV-based prevention sessions: ["The Promise and Perils of ARV-based Prevention: Making it a Reality on the Ground"](#); and ["Using ARVs to Prevent HIV: Implications of the Outcome of the CAPRISA 004 Tenofovir-Gel Microbicide Trial"](#).

Over the past year, exciting and complex results from more recent HIV prevention research trials, namely iPrEx and FEM-PrEP, have raised more questions about how to advance this promising new biomedical intervention. The satellite session in Rome also followed presentations on the latest data from Partners PrEP/TDF2 studies and the HPTN 052 Treatment as Prevention (TasP) study (presented earlier on the same day at IAS 2011). This satellite sought to address the implications of these trials on the future pipeline of both oral and topical PrEP products. The topics that were covered included: (a) what the ideal PrEP/microbicide formulation and active agent could look like in the future; (b) from a research and development (R&D) perspective, how feasible it would be to develop such products in the near term; and (c) from an implementation/operational perspective, what the issues and challenges could be once such a product was brought to market. The IAS and AVAC recognize that both the immediate and future pipeline will have to account for the particularities of research, implementation and integration to existing services for at-risk individuals.

The ILF serves to help increase and improve clinical and operational research for the many populations who remain grossly under-served by the benefits of clinical progress. Established in 2001, the ILF emerged from a shared need identified by investigators, physicians and industry representatives that a number of confounding issues limit our potential for research success in resource-poor countries. At the same time, the role and responsibility of pharmaceutical and diagnostic companies in conducting research needed to be formally acknowledged. The ILF is committed to establishing opportunities for researchers from within and outside industry to coordinate with partner agencies to advance HIV research in resource-limited settings.

Introduction



In welcoming participants, session co-chair **Jim Rooney** (Gilead and current ILF Advisory Group Industry Co-chair) remarked on the significance of this meeting, particularly as the ILF has served to address important ethical issues pertinent to the conducting of HIV prevention research. Notably, in the early days of PrEP research, the ILF took a

leading role in convening the key stakeholders to move research trials forward. Co-chair **Quarraisha Abdool Karim** (Columbia University, University of KwaZulu-Natal and member of ILF Advisory Group) welcomed participants and thanked Gilead for its commitment to PrEP research, along with its most recent effort to expand access to treatment by entering a licensing agreement with the Medicines Patent Pool Foundation. Abdool Karim set the scene by explaining that “science should inform policy”; she outlined those randomized clinical trials testing ARV-based prevention interventions that have demonstrated efficacy (Figure 1).

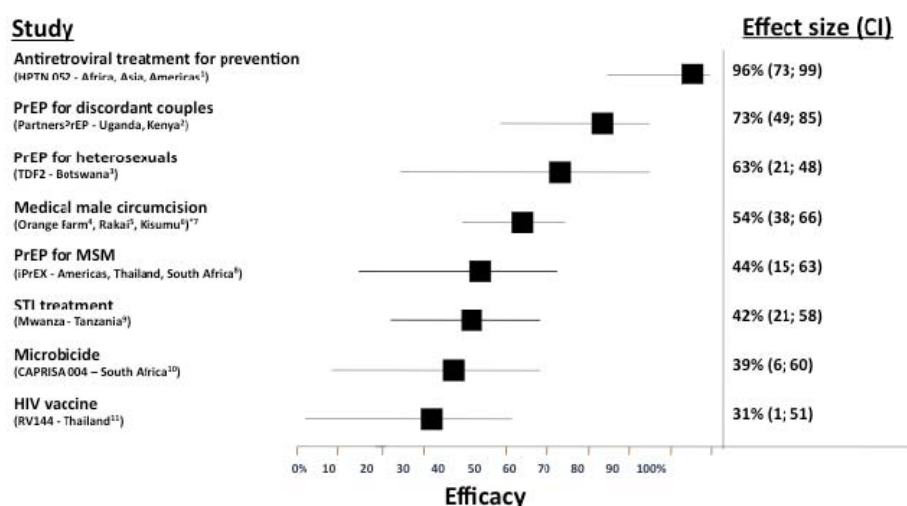


Figure 1. HIV prevention interventions shown to be effective in reducing HIV incidence in randomized controlled trials

Abdool Karim noted that there is a substantial difference between efficacy data and effectiveness data from use in real-world conditions. She further added that these new data contribute to a “prevention paradigm shift”. Abdool Karim described how the results from PrEP/microbicide research feed into a “cumulative body of knowledge” (Figure 2), and underscored how these approaches can be combined in order to provide more epidemic-responsive and population-specific interventions to individuals. She stressed that, despite the existing proof of principle, the field will have to think about how to transition to access and implementation. Lastly, Abdool Karim noted that the satellite session was about “future science” at two levels: “what more research do we need in terms of new drugs, drug combinations and formulations to enhance the efficacy of tenofovir and/Truvada”; and “how other companies can contribute through bringing more products and strategies to the table”.

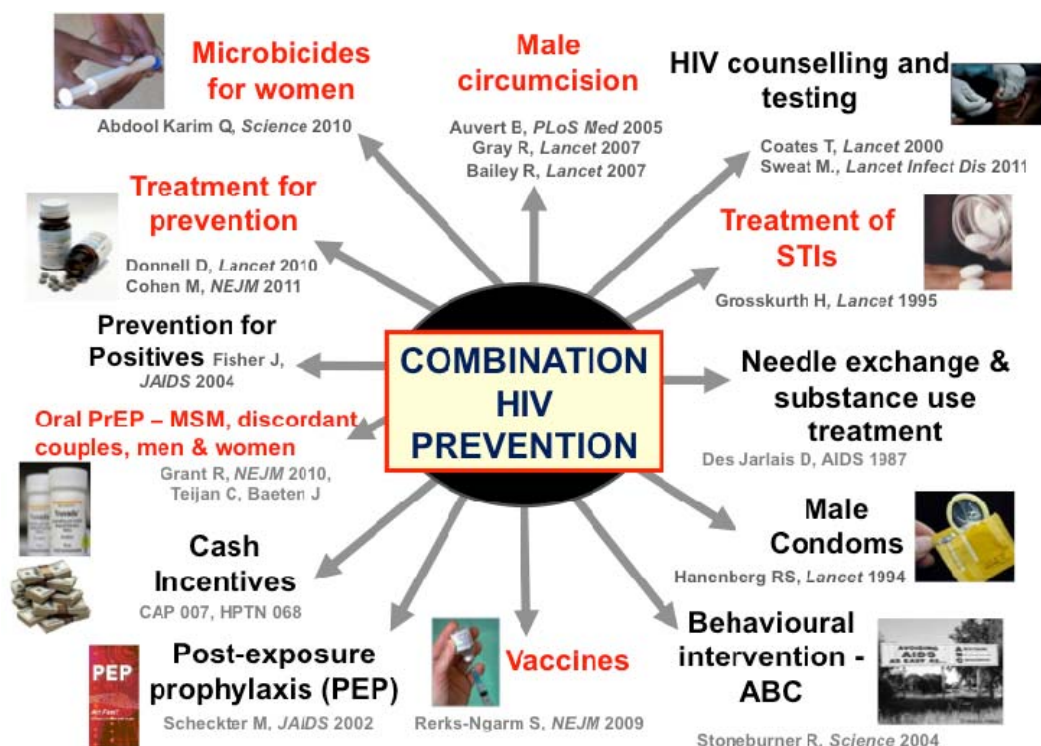


Figure 2. HIV prevention options

What is currently in the pipeline and what is ideal for an ARV-based prevention candidate?

Overview

By Carl W Dieffenbach, Director of DAIDS, NIAID/NIH



Carl Dieffenbach provided an overview of the ARV-based prevention modalities that are currently in the pipeline, and also described some key characteristics for an ideal product in the future. Setting the context of the current debate and enthusiasm around ARV-based prevention research, Dieffenbach first highlighted the historical significance of the 30 years since the Centres for Disease Control and Prevention (CDC) *Morbidity and Mortality Weekly* report on the first AIDS cases. In reference to IAS 2011, he underscored that the Rome conference would be remembered as an event where treatment as prevention (TasP) “really came to the fore in a sustained way”. Dieffenbach noted that he would address some of the challenges in conducting ARV-based prevention research, including questions over drug levels and behaviour (e.g., adherence).

Commenting on the HIV Prevention Trials Network (HPTN) 052 study’s potential role in curbing the HIV/AIDS epidemic, Dieffenbach echoed Abdool Karim’s earlier comment that multiple modalities, rather than one single tool, would be most effective in HIV prevention. On that point, he also emphasized that “we must know the epidemic which we are trying to

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tackle”, and indicated that no single prevention strategy would be 100% effective for everyone. Dieffenbach referred to the CAPRISA findings published last year in *Science* as “the signal” for an impact on reducing HIV transmission in the context of ARV-based prevention. Importantly, he noted that higher levels of adherence are predictive of greater efficacy in such preventative interventions. Dieffenbach also raised the issue of how studies measure adherence (referring to iPrex’s reported adherence of 73%), and cautioned that careful thought must be given towards improving this outcome in study participants. The transition from a study intervention to a licensed ARV-based prevention product to which people can adhere is a key challenge.

What happens when a trial shows no efficacy?

Recognizing that not all studies have yielded positive results, Dieffenbach touched on the findings of FEM-PrEP, a Phase II trial testing effectiveness of oral Truvada among HIV-uninfected women in Kenya, South Africa and Tanzania. In April 2011, the Independent Data Monitoring Committee advised that the study had reached futility. Dieffenbach remarked on the importance of understanding whether the lack of efficacy observed in FEM-PrEP was a function of particular biological factors, or whether participant adherence had influenced the efficacy of the intervention. In addition, he underscored that the field still needs to adequately answer the question of what drug levels are needed in the female genital tract to prevent HIV transmission. Dieffenbach argued that the impact of hormone levels on the efficacy of ARV-based prevention products needs to be evaluated, and noted that full data from this study (including drug levels) would become available later this year.

The new era

In reference to Partners PrEP and TDF2, Dieffenbach commented that the exciting results from these studies (presented earlier that morning at IAS 2011) would “launch us into a new era” of research. He touched upon the notion of enrolling and counselling a couple in a study, which in turn can promote a “mutually assured adherence”. Further to that point, Dieffenbach stressed that researchers need to define ways to better promote adherence, and again reiterated that it can be enhanced in a team setting. The linkage to adherence and behaviour, as he stated, will be critical to the success of such interventions in the future.

Dieffenbach provided an overview of VOICE (Vaginal & Oral Interventions to Control the Epidemic), a very important and ongoing transition study (Figure 3) that is examining the effectiveness and evaluating the extended safety of daily tenofovir 1% gel, oral TDF and oral TDF/FTC for HIV prevention in women. Furthermore, VOICE is evaluating adherence and acceptability to the daily vaginal and oral regimens, and assessing the selection of HIV-1 drug resistance in infected women during the study. Dieffenbach emphasized how important VOICE will be in providing critical data and insight into this population.

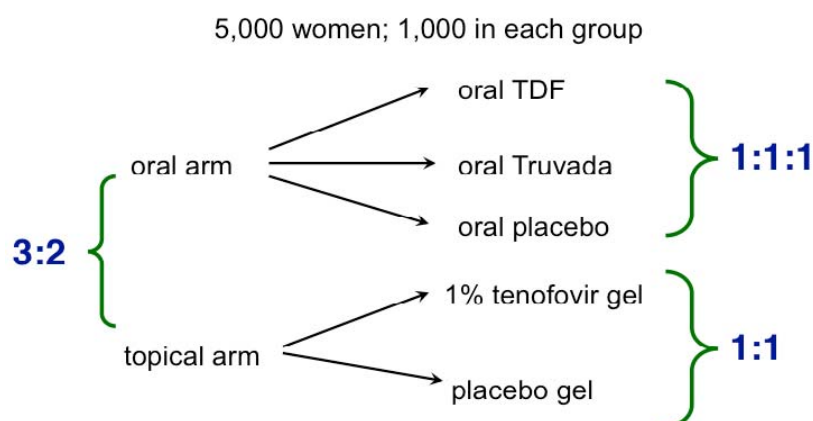


Figure 3. VOICE study design

In moving forward with PrEP research, iPREX OLE (Open Label Extension) “takes iPREX to the next level”. iPrEx OLE is a continuation of the iPrEx study designed to provide additional information about the safety of PrEP and behaviour of men who have sex with men (MSM) taking PrEP over a longer term. In the absence of a placebo, Dieffenbach raised the question of whether adherence can improve and risk-taking behaviour change among study participants. He also called for the conducting of demonstration projects by rolling out PrEP to community clinics in order to measure a host of parameters. Such demonstration projects could provide data that would inform the development of PrEP guidelines (e.g., CDC). Furthermore, the US could serve as a model for other parts of the world in understanding how to better optimize PrEP interventions.

For a TDF-based microbicide or oral formulation to be licensed, Dieffenbach commented on the need to complete safety studies in pregnant women and younger women. He also noted that there is still substantial research with existing products that needs to take place. In terms of microbicide trials, Dieffenbach highlighted some of the following:

- CHOICE, which is the open label of VOICE
- MTN 020, a dapivirine ring study (MTN stands for Microbicide Trials Network)
- MTN 01

What next?

Regarding future PrEP studies, HPTN 069 is a Phase II double-blind study which will test the safety and tolerability of a new range of combinations (maraviroc, maraviroc + emtricitabine, tenofovir, or tenofovir + emtricitabine) in at-risk MSM. Dieffenbach commented that it would be important to have a serious conversation over whether (and how) VOICE should be adjusted based on the recent data from Partners PrEP. Furthermore, he noted that the continuing support of rectal microbicide development for both MSM and heterosexual couples remains critical. Dieffenbach touched on the emerging “tension brewing” in the field (“do we optimize what we have or do we want to do better”) in reference to Truvada’s efficacy. With

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respect to the optimization of ARV-based products, on the one side, there will be the need to implement products already shown to reduce HIV transmission; on the other side, there will be the need for innovation (to develop second- and third-generation products). In closing, Dieffenbach challenged his colleagues from industry by presenting his “optimistic” long-range vision of a long-lasting formulation, which would be administered in four to 12 doses per year to an individual. He pointed to the need to determine “alternative strategies to reduce the behavioural component”, which serves as a key barrier in ensuring that ARV-based modalities prove effective and efficacious in a real-life setting.

Panel discussion: How can the spectrum of issues on development and implementation of future products be addressed?

Moderators: Mitchell Warren, AVAC
Quarraisha Abdool Karim, Columbia University, University of KwaZulu-Natal

Panel participants:

Carl W Dieffenbach	NIH
James Goodrich	ViiV Healthcare
Jim Rooney	Gilead Sciences
Peter Williams	Janssen
Roy “Trip” Gulick	Cornell University
Sandra Lehrman	Merck
Peter Anderson	University of Colorado, Denver

Opening remarks

Following Dieffenbach’s presentation, **Mitchell Warren** from AVAC and **Quarraisha Abdool Karim** moderated a panel discussion, consisting of both industry and non-industry experts on oral PrEP and microbicide research. **Sandra Lehrman** from Merck initiated the conversation by commenting on researchers being faced with making ARV-based prevention modalities more “friendly”, and arguing that discussions over the ideal product profile could have important implications for R&D. Referring to Dieffenbach’s vision of four to 12 doses per year as a serious challenge, Lehrman also stressed that researchers will have to think carefully about target populations for such modalities (in addition to the drugs themselves and routes of formulations). In the context of VOICE, Lehrman indicated that different individuals may prefer alternative prevention strategies, and encouraged the field to think about ways of optimizing such strategies.

Peter Anderson, a pharmacologist from UC Denver, voiced his enthusiasm over TDF/FTC, and underscored the need to improve methods for quantifying adherence levels in clinical trials. Furthermore, Anderson emphasized that researchers need to have a more accurate picture of the levels of adherence, and reiterated Dieffenbach’s earlier comment about the association between adherence and efficacy for these modalities. **James Goodrich** from ViiV Healthcare described the exciting development of his company’s next-generation HIV

integrase inhibitor (Dolutegravir; S/GSK-572), which has the potential of being administered by injection once a month. When comparing ARV-based prevention with ARV treatment, he also commented on the need to have a better understanding of the differences of drug levels in tissue. Goodrich emphasized the critical issue of determining why study participants receiving the intervention become subsequently infected with HIV.

Trip Gulick, an infectious disease specialist from Cornell University, interestingly noted that only the same drugs have been studied in oral ARV-based prophylactic prevention (tenofovir and/or emtricitabine). Gulick pointed to malaria prophylaxis where there are more drug options, and he argued that researchers in ARV-based prevention should be exploring more drug options in HIV prophylaxis. He also commented on study 069, which arose from such discussions, and mentioned that “NEXT PrEP” is looking at alternatives to Truvada. **Peter Williams** from Janssen commented on the exciting development of TMC278 (rilpivirine) injectable formulation, which is at an early stage of clinical development. Oral rilpivirine received approval as EDURANT from the US Food and Drug Administration in May 2011. Notably, he indicated the prospect of administering the injectable non-nucleoside reverse transcriptase inhibitor formulation every month (or potentially even less) to individuals.

Adherence: how critical is it?

In terms of ARV-based prevention modalities, Warren asked the panellists to share their thoughts on the impact of adherence. Anderson stressed that more pharmacology data (both intracellular and plasma) collected in the course of a clinical trial can more accurately inform the levels of adherence in study participants. In addition, Anderson added that his research team is collecting dried blood spots, and noted that red blood cells may be particularly informative as they have a longer half-life than peripheral blood mononuclear cells (PBMCs). Even with the best of adherence, Lehrman argued that one has to be cognizant that intra-subject drug levels can fluctuate, as is the case of women during menstruation. Further on that point, she underlined that it is especially important to understand how the pharmacokinetics (PK) can change in these women (even in cases of higher levels of adherence). Gulick also indicated how prevention science “can take note from the treatment world”, which itself has a rich body of evidence on ways of optimizing adherence in ARV-treated patients.

Future strategies: future partnerships

Abdool Karim raised the issue of whether R&D for ARVs should have two separate drug pipelines (one for treatment, and one for prevention). Gulick commented on how a drug developed specifically for prevention may be ultimately necessary, given emergence of resistance. Williams also suggested that a drug with a different mechanism of action than those of the existing ARVs used for treatment could provide added benefits.

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In promoting ARV-based prevention research (and the eventual implementation of evidence-based interventions), the panel discussion touched on the ways in which partnerships between various global, national and local stakeholders can be fostered. Goodrich reiterated the commonly shared stance that active researchers need to seek out new partners, especially in light of “the flood of data on proof of concept”. Goodrich also proposed that public-private partnerships could serve as a vehicle for spreading research costs. Lastly, Lehrman commented on how experts could improve on the “wonderful proof of concept” by collaborative work.

Addressing the complexities of research and regulation

Given a continuous population-level increase in drug resistance, Goodrich posed the question of how one responds to a scenario where a drug with a novel mechanism of action is discovered. In this context, he argued for the prioritization of treatment first, followed by PrEP. Goodrich also made reference to an advisory board on microbicides from 2003 that examined the complexities in bringing a microbicide to market. Rooney suggested that a new regulatory body could be created to focus specifically on ARV-based prevention products, and shared Goodrich’s viewpoint on the research particularities, both from a statistical and a clinical perspective.

In the near future, Abdool Karim commented on the prospect that surrogate markers/correlates for protection could be identified, which consequently would transform endpoint ascertainment in a manner similar to the way CD4 counts and viral load (VL) transformed ARV treatment trials. Furthermore, she argued that the use of placebo, despite its “attractiveness”, would become increasingly unjustifiable scientifically and ethically. Regarding study design, Gulick also cautioned that proper assessment of safety should be based on the requirement of blinding.

In recognition of non-adherence in trials, Bob Grant (from the floor), principal investigator of iPrex, commented on “dynamic couples” and “creative participation in trials”, and voiced his optimism over the establishment of surrogate markers in the PrEP field. Ian McGowan, co-principal investigator of the University of Pittsburgh-based Microbicide Trials Network (MTN), proposed the strategy of challenging animal and human biopsies, in combination with an open safety study. McGowan noted that ARV drugs must protect tissue at the site of exposure, and referred to the challenge of performing vaginal biopsies. Recognizing the need for more science and a better understanding of appropriate surrogate markers, Goodrich stated that the rhesus macaque model could be incredibly informative. McGowan supported Goodrich’s stance on the need for more research, and indicated that research agencies also need to invest in gut tissue studies. Lastly, Sheena McCormack, lead investigator from the Microbicides Development Programme, commented on the drafting of the CDC guidelines for MSM and Truvada, and stressed the need for programmatic and/or demonstration projects.

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Ian McGowan asked panellists to comment on the structural challenges in forging public-private-academic partnerships, and to offer their thoughts on licensing of ARV-based prevention products. Rooney commented on Gilead's out-licensing of TDF gel, while Williams cited the royalty-free licensing for IPM (International Partnership for Microbicides). Goodrich referred to intellectual property being a "major stopping point for some of these partnerships", particularly at the onset of drafting a contract with other partners.

Abdool Karim briefly touched on the gap in the public sector on regulatory expertise in relation to submissions for licensure and flagged a role that industry partners could play through technical assistance. Goodrich commented on industry's expertise in conducting efficient randomized controlled trials, and the opportunity to share this with research partners.

Closing remarks

With respect to regulatory issues, Mitchell Warren referred to a bridging session at IAS 2011 on regulation of oral PrEP. He also noted that regulatory processes in developing countries differ from those in resource-rich countries. Warren cited UNAIDS' theme of "knowing your epidemic", and commented on the importance of "knowing your country and your regulatory system". In thanking all participants, Warren stressed that careful thought has to be given to the exciting developments in TasP, PrEP and other ARV-based prevention strategies. Jim Rooney referred to the insightful presentation and vision laid out by Carl Dieffenbach, and commented on the interesting perspectives shared by the panel participants. In light of the exciting data, Rooney also emphasized the need for more PK/PD studies and work on animal models. Quarraisha Abdool Karim brought the session to a close by expressing her optimism on the movement to improve formulations and adherence and to promote drug development and implementation of what works. She stressed that, in addition to the need for more science, partnerships would be critical if "we are to realize the public health impact of these proposed interventions". Abdool Karim emphasized how partnerships, including the one with industry, will ultimately help bring an end to the epidemic.

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About the ILF

The Industry Liaison Forum (ILF) is an initiative of the International AIDS Society (IAS) that brings together industry, independent investigators, non-governmental organizations, foundations and other stakeholders to enhance HIV treatment access and outcomes in resource-limited settings, with a particular focus on the role and responsibilities of industry. The ILF provides the unique platform that allows industry to engage, communicate and collaborate with other stakeholders to enhance HIV research, and thereby promote evidence-based health policy and health delivery in resource-limited settings.

The ILF fulfils its mission by: identifying research gaps; promoting targeted research; identifying challenges and best practices; analyzing available data and evidence; disseminating information; consulting and convening stakeholders; providing industry expertise; and supporting capacity building for research and health delivery.

As part of its new Strategic Plan (2012-2014), the ILF is committed to focusing on scientific, ethical and policy issues related to HIV research for women and children by identifying research gaps in this area.

For more information regarding ILF activities, please visit our website at <http://www.iasociety.org/ilf.aspx>, or follow us on Facebook & Twitter:



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