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OPINION ON THE POTENTIAL BENEFITS OF THE CONCEPT OF HIV/AIDS PRE-EXPOSURE PROPHYLAXIS (PREP)

ADOPTED BY THE FRENCH NATIONAL AIDS COUNCIL ON 12 JANUARY 2012

This *Opinion* was adopted by the National AIDS Council at a plenary session on 12 January 2012, by the majority of members present with one abstention.

The document can be downloaded at http://www.cns.sante.fr/IMG/pdf/cns_opinion_prep_20120112.pdf

The French National AIDS Council (Conseil national du sida - CNS) is an independent, consultative French agency that was set up in 1989.

It comprises 24 members: specialists working in the field of HIV/AIDS, representatives of civil society, and members of associations.

The CNS delivers opinions and recommendations on the full spectrum of issues that society faces as a result of HIV/AIDS. These papers are addressed to the French authorities and to all those involved in or concerned by the epidemic.

It is the intention of the CNS to participate in this manner in the development of public policy, within a framework that promotes respect for fundamental ethical principles and human rights.

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Paris, le - 4 MARS 2011

Monsieur le Professeur Willy ROZENBAUM
Président du Conseil National du Sida (CNS)

Copie à Monsieur le Professeur Patrick YENI
Président du groupe d'experts

Objet : Saisine du Conseil National du Sida sur les questions d'éthique et de société soulevées par la promotion du concept de Prévention Pré-Exposition (PreP) du VIH

Monsieur, cher Collègue

Vous connaissez le contexte scientifique actuel sur le thème de la prévention pré-exposition du VIH : publication de l'étude iPreX fin 2010 et plus récemment avis des CDC américains (Centers for disease control and prevention) sous forme de recommandations transitoires (« interim guidance ») pour les médecins qui décident de recourir à cette prévention chez les hommes ayant des rapports sexuels avec des hommes (HSH) et qui sont à haut risque de contamination pour le VIH.

En France, un essai de l'agence nationale de recherches sur le sida et les hépatites virales (ANRS) en cours de mise en place, va poursuivre la recherche clinique sur cette voie en explorant un schéma de PreP intermittente.

Au niveau européen, une réflexion est en cours à l'EMEA (European medicines agency) pour définir les exigences règlementaires qui seraient adressées aux firmes qui souhaiteraient déposer une demande d'enregistrement d'antirétroviraux pour cette indication.

Pour la Direction Générale de la Santé, l'approche PreP pose d'importantes questions en termes de santé publique, d'éthique et de société (cf. annexe).

Aussi, même si les données actuellement disponibles sont insuffisantes pour envisager prochainement des recommandations d'usage dans la pratique hors recherche clinique, **j'ai souhaité vous interroger sur les implications éthiques et sociétales de ce concept**.

J'interroge également le groupe d'experts dirigé par le Professeur Patrick Yeni sur les questions plus directement techniques qui touchent à l'efficacité potentielle au-delà des essais, la tolérance à long terme, le risque de résistance, les hypothèses de rapport coût-efficacité, la nécessité d'émettre dès cette année des mises en garde et des recommandations en cas de volonté de recours à la PreP, comme l'ont fait les CDC.

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Je souhaite que vos deux instances, CNS et Groupe d'experts, travaillent de façon indépendante, chacune prioritairement sur son champ d'expertise traditionnel et avec ses méthodes habituelles et rendent leurs conclusions, même provisoires, à l'automne prochain, à l'occasion d'une réunion commune avec mes services.

Vous serez particulièrement attentif au respect des règles de déclaration publique d'intérêts des membres de votre conseil et des personnes que vous auditionnerez.

Je suis à votre disposition pour apporter toute précision utile dans cette démarche et vous prie d'agréer, Monsieur, l'expression de ma considération distinguée

Professeur Didier HOUSSIN

ANNEXE : Questions posées par la prophylaxie pré-exposition VIH

- Le risque de favoriser une diffusion de la **résistance** du VIH aux antirétroviraux (ARV) disponibles ne peut être écarté. En effet pour tous les anti-infectieux, la progression de la résistance est directement corrélée à la taille des populations les utilisant : l'utilisation préventive des ARV entrainerait une multiplication très importante du nombre d'utilisateurs. Les essais thérapeutiques ne pourront pas évaluer l'effet de cet usage sur l'incidence de la résistance sur une durée assez longue pour être informatifs. Les antirétroviraux, comme les antibiotiques, pourraient être considérés comme un bien commun à protéger ; ainsi, prendre le risque de réduire la palette des antirétroviraux disponibles pour faire bénéficier d'une chimioprophylaxie certaines personnes qui n'adoptent pas un comportement préventif pose une question d'éthique et de société.

- Le coût de cette approche de prévention serait élevé, supportable par peu d'usagers, et la question de son éventuelle **prise en charge par l'assurance maladie** se posera. Cette question pourra entraîner des comparaisons avec d'autres méthodes de prévention moins coûteuses (par exemple les préservatifs dans le champ du VIH ou la prophylaxie antipaludéenne dans d'autres domaines), qui ne sont pas prises en charge. Les sommes à engager seraient alors très importantes dans un contexte de budgets très contraints alors que le rapport coût-efficacité d'une telle méthode de prévention a encore été insuffisamment évalué: il s'agit ici d'une autre question d'éthique et de société à explorer.

- Tant que les études d'efficacité comportent un groupe témoin contenant un placebo, l'effort est mis sur les autres mesures de prévention, et les personnes, ignorant si elles reçoivent le placebo ou le produit actif, sont motivées à suivre, au moins en partie, ces mesures. Quand il s'agira d'utiliser la PreP de façon ouverte, **une modification des attitudes de prévention** allant dans le sens d'une moindre utilisation des préservatifs pourrait favoriser la transmission d'autres IST et augmenter potentiellement paradoxalement le risque d'acquisition du VIH, y compris avec la sélection de formes résistantes. Cette question de la modification potentielle des comportements de prévention est complexe et doit être explorée par une approche interdisciplinaire.

- La question de la toxicité du traitement pour des personnes saines, chez lesquelles l'exigence de tolérance est plus élevée que chez des personnes malades, ne peut pas non plus être suffisamment explorée par les essais en raison de leur durée trop courte.

- Le risque d'un effet inverse, à moyen terme et en population, à celui observé à court terme et au niveau individuel dans le cadre d'essais thérapeutiques ne peut être écarté. Ce risque, théorique, n'empêchera pas la demande de l'accès au produit si son efficacité était confirmée dans les essais en cours ou à venir. L'intérêt individuel et l'intérêt collectif pourraient se trouver alors en opposition. Le produit utilisé dans les essais comme prévention pré-exposition par voie orale, le Truvada, est disponible sur le marché, comme médicament entrant dans les combinaisons thérapeutiques pour les personnes infectées par le VIH en primo-prescription hospitalière et il pourrait voir son usage en prévention se développer avant même que l'indication ne soit autorisée par les agences d'enregistrement.

PREAMBLE

There is a widespread consensus, thirty years after the detection of the first cases of AIDS, on the need to drastically reduce the number of new infections in order to stabilize, and subsequently reverse the spread of a pandemic which current prevention measures have failed to contain. Significantly improving the effectiveness of prevention is therefore essential in terms of both the individual and collective benefits it offers. This means that no new avenue for exploring this issue should be excluded.

Pre-Exposure Prophylaxis (PrEP) using antiretroviral (ARV) drugs, which involves proposing antiretroviral therapies to uninfected populations in order to prevent them contracting HIV, is currently the focus of numerous scientific studies, and has generated intense debate.1 Although there is currently no approved, definitive guidance on this new use of ARV for prevention purposes, interim guidance was issued in January 2011 in the United States of America2. More recently, on 15th December 2011, a supplemental New Drug Application (sNDA) for the use of a combination antiretroviral therapy as PrEP was submitted to the U.S. Food and Drug Administration (FDA). Despite the numerous uncertainties which subsist at this preliminary stage, it is important to carefully analyze PrEP, in order to determine whether this strategy could, in the near future, enhance the existing range of means of protection.

This opinion has been produced in response to the letter of mission from the Director General of Health dated 4th March 2011. It works off the hypothesis that the results of scientific studies underway will confirm the benefit of developing a PrEP offering in certain circumstances, and is intended to examine the potential benefits and limitations of this approach in order to anticipate the consequences for prevention as a whole. In accordance with its remit to inform public decision-making, the Council has set itself the triple objective of producing a precise inventory of current knowledge and debate, proposing an interpretation of these that encompasses the multitude of issues involved, and formulating preliminary guidelines on the use of PrEP in France.

Over the last ten years, the use of biomedical tools to prevent HIV transmission has increased dramatically, this is the context in which the new PrEP tool, using antiretroviral drugs, has been introduced. The possibilities opened up by these new approaches have shaken up the prevention paradigm that has been in place since the emergence of the epidemic, resulting in the emergence of the "combination prevention" concept. These new possibilities are intended to develop the necessary synergies between what are known as behavioral, structural and biomedical prevention strategies, the latter incorporating both screening and the different uses of therapies for preventive purposes.

The need to implement this new conception of prevention is all the more urgent given the possible and probable development of PrEP. This new tool, given its own specificities, should be reserved for targeted use in situations where exposure to the risk of HIV infection is highest, rather than for widespread use in the general, uninfected population. Consequently, developing PrEP requires a "personalized" approach, adapted to the specific prevention needs of the individuals concerned, which requires a profound shift in the prevention discourse and offering.

The thinking developed in this opinion follows on from the Council's work as presented in the opinion dated 9th April 2009, on the use of treatments for preventive purposes for infected persons. It places considerable emphasis on the challenge of reinforcing individuals' autonomy, helping them to use new prevention methods in conjunction with the range of means already available so they can make informed and reasonable use of these. This should also allow them to build personal prevention strategies adapted to their situation, constraints, desires and practices.

[1] World Health Organization, Report of a consultation: preparing for pre-exposure prophylaxis (PrEP) results: from research to implementation, WHO, October 2009.

[2] Centers for Disease Control and Prevention. "Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men". *Morbidity and Mortality Weekly Report*, January 28, 2011.

I. EXAMINING PREP IN THE CONTEXT OF THE REDEFINITION OF PREVENTION STRATEGIES AND OBJECTIVES

Interest in PrEP research is currently very high, something some would consider a "fashion", not only within the scientific community and HIV non-profit organizations, but also the international bodies responsible for AIDS control policies, and the pharmaceutical industry which has devoted considerable resources to this area.

As well as the obvious economic interest for the pharmaceutical sector (this area of research is likely to result in an unprecedented expansion of the ARV market) the development of PrEP is the result of a fundamental re-assessment of prevention challenges made by all stakeholders in the second half of the 2000s. This consequently resulted in a general increase in investment in research into new methods and strategies likely to improve the effectiveness of prevention measures.[3]

Research and debate on the use of PrEP therefore form part of a dual movement: on the one hand the broadening and diversification of the prevention methods available; and on the other reflection on how different approaches and methods can be combined to implement more effective prevention strategies, better adapted to the diversity of epidemiological situations and the difficulties individual people encounter when trying to protect themselves.[4]

I.1. REMOBILIZATION VITAL TO IMPROVE PREVENTION

Despite the successful efforts of the last few decades to prevent HIV transmission, which have contributed to slowing down the spread of the epidemic, these measures have not succeeded in its reversal.

In the terms of global epidemiology, it has been established that the incidence of infection, which peaked in the early 2000s, is now decreasing. The role prevention efforts have played in this reduction remains difficult to assess, as this decrease can be partly attributed to the mortality rates in the Southern countries worst affected by the epidemic, where access to treatment has long been non-existent or insufficient and remains seriously unsatisfactory.[5]

Whilst the reduction in incidence is in itself encouraging and helps to slow down the spread of the epidemic, it is not sufficient to even stabilize let alone reverse the epidemic. It also masks very deep-rooted disparities as, despite the overall decrease, incidence has not diminished and indeed has even increased in some specific countries or regions and/or within certain population groups, both in areas of generalized and concentrated epidemics.

In this context, the efforts made over the last decade to increase access to effective treatment have been both substantial and yet insufficient, as the ultimate objective of universal access has not yet been attained. The level of HIV transmission is still high and threatens the sustainability of these efforts which today seem to constitute a losing battle. The annual number of new infections is still two times higher than the number of new persons accessing to treatment.[6] Achieving a significant reduction in the number of new infections is crucial to breaking the dynamic of the epidemic, reversing its spread and ultimately eradicating it entirely.[7]

I.2. THE EMERGENCE OF THE CONCEPT OF COMBINATION PREVENTION: THE CRUCIAL ISSUE OF HOW PREVENTION, SCREENING AND TREATMENT CAN BE USED TOGETHER

NEW PERSPECTIVES FOR PREVENTION

Historically, with no vaccine or curative treatment available, HIV/AIDS protection has been based on a model combining two types of strategies: behavioral strategies, i.e. strategies intended to change from high risk individual and collective behaviors as regards virus transmission, to safer behaviors; and structural strategies, which act over

[3] Merson, M. H., *et al.*, «The history and challenge of HIV prevention », *The Lancet*, Vol. 372, n° 9637, August 2008, pp. 475-488; Piot, P., *et al.*, « Coming to terms with complexity: a call to action for HIV prevention », *The Lancet*, Vol. 372, n° 9641, September 2008, pp. 845-859.

[4] Padian, N. S., *et al.*, « HIV prevention transformed: the new prevention research agenda », *The Lancet*, Vol. 378, n° 9787, July 2011, pp. 269-278.

[5] The number of people in the world living with HIV who have access to ARV was multiplied by 13 between 2004 and 2009, but 10 million people eligible still do not have access to treatment today. (World Health Organisation (WHO), UNAIDS and United Nations Children Fund (UNICEF), *Toward universal access : scaling up priority HIV/AIDS interventions in the health sector : progress report 2010*, World Health Organisation, 2010. http://www.who.int/hiv/pub/2010progressreport/summary_en.pdf)

[6] In 2010, according to data from UNAIDs, it is estimated that whilst 1.35 million additional persons have obtained access to treatment, 2.7 million persons are newly infected. UNAIDS, *Worlds AIDS Day, Report 2011*, November 2001, http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2216_WorldAIDSday_report_2011_en.pdf

[7] Padian, N. S., *et al.*, "HIV prevention transformed: the new prevention research agenda", 2011, *op. cit.*

a broader scope on the social, economic, legal, cultural and educational factors likely to increase the vulnerability of the most at-risk persons and groups, which constitute a barrier to behavioral change. [8]

The dual behavioral and structural approach to prevention, a legacy of the history of the epidemic, has long been the mainstay of prevention policies at national and international level. However, different preventive uses of ARV treatments have emerged which make it possible to reduce the risk of contracting the virus or passing it on to others.

Today, three different uses of ARV treatments for preventive purposes have been approved and implemented:

- since 1994 for the **prevention of mother-to-child transmission (PMTCT)**. Pregnant women with HIV can pass the virus on to their child during pregnancy, at birth or whilst breastfeeding. Without treatment, the rate of transmission varies between 15 - 30% if the mother is not breastfeeding and up to 30 – 45% if the mother is breastfeeding. In 1994, a study demonstrated the feasibility of preventing mother-to-child transmission by treating the mother with zidovudine during pregnancy. In developed countries, prophylactic treatments currently use the same drug combinations as for therapeutic protocols. The rate of transmission is less than 1%. It has also been proven that treating the child preventively and simultaneously continuing with the mother's treatment can prevent transmission during breastfeeding.9
- since 1998, as **post-exposure prophylaxis (PEP)**. Health professionals exposed to HIV through accidental exposure to blood can receive prophylactic treatment in the 48 hours following exposure, for a duration of four weeks. Persons who have had unprotected intercourse, an accident when using condoms, or who have been in contact with potentially infected needles or syringes can also access this type of treatment.10
- Since the 2000s, it has been demonstrated that ARV treatments administered for therapeutic purposes to persons with HIV, significantly reduce the risk of sexual transmission of the virus by bringing the blood viral load down to a very low level. This preventive effect has lead to the implementation of numerous studies to assess the benefit of the screening and early treatment of those infected, both as a new means for individual prevention and collective HIV control.11 The use of treatments for preventive purposes in infected persons, known as **TasP (Treatment as Prevention)**, is today considered as a major lever for reducing the number of new infections and curbing the epidemic on a global scale.12 As an individual prevention tool, a study recently carried out amongst heterosexual serodiscordant couples showed that the early treatment of the infected partner reduces the risk of HIV transmission to the uninfected partner by 96%.13

Research into PrEP follows on from the development of prevention methods based on the ability of ARV to block the HIV infection mechanisms. Whilst the use of ARV for TasP concerns persons already infected with HIV and aims to prevent the secondary transmission of the virus, PrEP, if approved, will target uninfected persons, with the aim of ensuring they do not contract the virus.

The emergence of these new treatment-based methods is indissociable from reinforced **screening**, a prevention tool in its own right which now constitutes one of the cornerstones of all prevention strategies. Its preventive impact is two-fold:

- In terms of *behavior*: It has been shown that detection of the infection and its care management are key factors for ensuring people adopt prevention practices, and that at-risk behaviors are most prevalent in people who are not infected or are unaware of their HIV status. [14]

[8] Coates, T. J., *et al.*, « Behavioural strategies to reduce HIV transmission: how to make them work better », *The Lancet*, Vol. 372, n° 9639, August 2008, pp. 669-684, as well as Gupta, G. R., *et al.*, « Structural approaches to HIV prevention », *The Lancet*, vol. 372, n° 9640, August-September 2008, pp.764-775, provide a summary of the history and current challenges in behavioural strategies and comportmental approaches in HIV prevention, respectively.

[9] Yeni, P. (dir.), 2010 report from a group of experts in the care management of persons with HIV, La documentation française, 2010, pp. 160 sqq.

[10] Yeni, P. (dir.), 2010 report from a group of experts in the care management of persons with HIV, La documentation française, 2010, pp. 350 sqq.

[11] National AIDS Council, *Opinion and recommendations regarding the potential for treatment as an innovative tool for fighting the HIV epidemic*, 9 April 2009.

[12] Lima, V.D., *et al.*, "Expanded Access to Highly Active Antiretroviral Therapy: A Potentially Powerful Strategy to Curb the Growth of the HIV Epidemic", *Journal of Infectious Diseases*, vol. 198(1), July 2008, pp. 59-67 ; Granich, R.M, *et al.*, "Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model Original", *The Lancet*, vol. 373, n° 9657, January 2009, pp. 48-57 ; Montaner, J. S. G., *et al.*, "Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study", *The Lancet*, vol. 376, n° 9740, August 2010, pp. 532-539 ; The Lancet (Editorial), "HIV treatment as prevention–it works", *The Lancet*, vol. 377, n° 9779, May 2011, p. 1719.

[13] Cohen, M.S., *et al.*, "Prevention of HIV-1 Infection with Early Antiretroviral Therapy", *New England Jounal of Medecine*, vol. 365, August 2011, pp. 493-505.

[14] Marks, G., "Meta-Analysis of High-Risk Sexual Behavior in Persons Aware and Unaware They are Infected With HIV in the United States - Implications for HIV Prevention Programs", *Journal of Acquired Immune Deficiency Syndromes*, vol. 39 (4), August 2005, pp. 446–453 ; MacKellar,

- In terms of *strategy*: Up-to-date awareness of one's HIV status is the requisite starting point for accessing treatment for preventive and/or therapeutic purposes. Notably, in the context of a TasP strategy, early screening is a pre-requisite for optimal access to treatment, both in terms of its therapeutic and its preventive benefit.[15,16] If the development of PrEP continues, it will lead to a *de facto* reinforcement of close HIV status monitoring, as initial screening and regular testing are indispensable for ensuring the person is, and remains, HIV negative. This also makes it possible, should they be found to be HIV positive at the initial screening or during PrEP follow-up, to diagnose an infection as early as possible, and to provide conventional care management.

EFFECTIVELY COMBINING METHODS AND APPROACHES

Given the collective and individual challenges of improving the prevention offering and its effectiveness, and the diversity of methods and strategies capable of meeting these, a widespread consensus has emerged in recent years on the need to effectively combine behavioral, structural and biomedical approaches.[17] This strategy known as combination prevention aims to comprehensively address the indissociable issues related to prevention, behavior change, screening and treatment, and requires the promotion of the combined, complementary use of the different methods available.[18] This constitutes a vital conceptual framework for examining the different uses of treatment for prevention purposes and consequently envisaging the potential uses of PrEP.[19]

D.A., *et al.*, "Unrecognized HIV infection, risk behaviors, and perceptions of risk among young men who have sex with men", *Journal of Acquired Immune Deficiency Syndromes*, vol. 38(5), April 2005, pp. 603-614.

[15] National AIDS Council, *Opinion and recommendations regarding the potential for treatment as an innovative tool for fighting the HIV epidemic*, *op. cit.*

[16] Gardner, E.M., *et al.*, "The Spectrum of Engagement in HIV Care and its Relevance to Test-and-Treat Strategies for Prevention of HIV Infection", *Clinical Infectious Diseases*, vol. 52 (6), March 2011, pp. 793-800.

[17] Piot, P., *et al.*, "Coming to terms with complexity: a call to action for HIV prevention", *The Lancet*, 2008, *op. cit* ; Joint United Nations Programme on HIV/AIDS (UNAIDS), *Combination HIV Prevention: Tailoring and Coordinating Biomedical, Behavioural and Structural Strategies to Reduce New HIV Infections – A UNAIDS Discussion Paper*, UNAIDS, September 2010 ; Padian, N. S., *et al.*, "HIV prevention transformed: the new prevention research agenda", *The Lancet*, 2011, *op. cit.*

[18] Padian, N.S., *et al.*, "Evaluation of Large-Scale Combination HIV Prevention Programs: Essential Issues", *Journal of Acquired Immune Deficiency Syndromes*, vol. 58(2), October 2011, pp. e23-e28.

[19] Underhill, K., *et al.*, "Packaging PrEP to Prevent HIV: An Integrated Framework to Plan for Pre-Exposure Prophylaxis Implementation in Clinical Practice", *Journal of Acquired Immune Deficiency Syndromes*, vol. 55(1), September 2010, pp. 8-13.

II. PREP'S POTENTIAL CONTRIBUTION WITHIN THE EXISTING RANGE OF PREVENTION METHODS

II.1. THE PRINCIPLE OF PRE-EXPOSURE PROPHYLAXIS AND INITIAL RESULTS

AN APPROACH TRADITIONALLY USED IN INFECTIOUS DISEASE PREVENTION BUT NEW TO THE FIELD OF HIV

In the field of infectious diseases, drug treatments are already used as prophylactics for malaria or tuberculosis prevention, for example. Used against HIV, this is a new approach. PrEP consists of using the antiretroviral drugs normally used to treat people with HIV for primary prevention purposes i.e. to prevent uninfected people from contracting the virus.

Practically speaking, several methods of administration are currently being studied, corresponding to different potential uses:[20]

- ***Continued oral PrEP*** consists of taking a regular oral dose of[21] ARV treatment to permanently reduce the risk of infection. When the person treated is exposed to an infectious risk, the risk is "covered" by the ARV both prior to and following exposure. The first available results from trials investigating oral PrEP concern this continuous strategy. Numerous other trials are currently underway or planned.
- ***Intermittent "on demand" oral PrEP*** involves taking an ARV treatment solely to anticipate possible exposure. The ARV is first taken in the hours preceding the potential exposure, and a second time post-exposure, should this take place. There are currently no results on this strategy available from human clinical trials and its efficacy therefore remains unknown. The Ipergay trial (ANRS), which has recently started recruitment in France (January 2012), will investigate this type of strategy.[22]
- ***Topical PrEP***, also known as ***topical microbicides***, are ARV-based gels for local vaginal or anal application in the hours prior to sexual intercourse, followed by a second application shortly after intercourse, should this take place. The use of this type of gel therefore corresponds to the intermittent "on demand" strategy, to anticipate possible exposure to risk during a sexual encounter. The topical gel works through the action of the ARV which blocks the infection process in the mucosa in contact with the virus. The results of one trial investigating a vaginal gel are available, other vaginal gel trials are in progress. Studies looking at anal gels are planned.

In the trials initiated to date, the antiretroviral drugs investigated for use as PrEP have been limited to tenofovir (TDF, Viread®, Gilead Sciences) used alone, and a fixed-dose combination of emtricitabine and tenofovir (FTC/TDF, Truvada®, Gilead Sciences), both commonly used for therapeutic purposes. They have been selected from the various ARV available based on specific pharmacological characteristics which make them well-suited for use as PrEP, notably their high levels of safety and tolerance, long persistence of the active ingredients in the body (half life), making it possible to take a single daily dose, and the absence of interactions with tuberculosis and malaria treatments or hormonal contraception. There are however, other interactions which must be taken into account, notably with the antiviral treatments used to treat herpes, human cytomegalovirus infections or hepatitis B. Studies investigating other antiretroviral drugs that might be suitable for use as PrEP are underway, but are still in the preliminary stages. These notably concern the use of oral and topical maraviroc,[23] as well as rilpivirine in a long-acting injectable form.[24]

It is important to stress that whilst the ARV used for PrEP are the same as those used in certain combination therapies, PrEP protocols are not the same as therapeutic protocols. In terms of the combinations of ARV, PrEP

[20] For details of the clinical trials investigating PrEP currently underway or planned (updated January 2012), see http://www.avac.org/ht/a/GetDocumentAction/i/3113. For future updates, or to consult the trial history, see http://www.avac.org/ht/d/sp/i/3507/pid/3507.

[21] Current trial protocols consist of one tablet taken daily. The use of other molecules could however make it possible to administer the treatment by other methods and to space out the doses further.

[22] http://www.ipergay.fr/

[23] An trial investigating oral PrEP orale using maraviroc (MVC, Celsentri®, Pfizer) is currently being drawn up (Trial HPTN 069, http://www.hptn.org/research_studies/hptn069.asp). It will aim to compare the following PrEP oral strategies: MVC alone, MVC+FTC, MVC+TDF, FTC/TDF. Furthermore, given the properties of maraviroc which make it well-suited to topical application, research is also underway to develop vaginal and/or anal gels or vaginal rings using maraviroc.

[24] Rilpivirine (TMC278) is a recent ARV currently available in tablet form (Edurant®, Janssen-Cilag). A long-acting injectable form (TMC278LA) developed with a view to its use as PrEP is currently being studied in a phase I clinical trial (Trial NCT01275443 http://clinicaltrials.gov/ct2/show/NCT01275443).

protocols are designed to prevent infection and are unsuitable for therapeutic use. PrEP should therefore under no circumstances be offered to someone without first ensuring by means of initial screening that they are not infected. It is also important to subsequently regularly check the HIV status of people using PrEP, in order to interrupt the protocol in the event of infection and switch to a conventional comprehensive antiretroviral treatment strategy.

RESULTS FROM THE FIRST CLINICAL TRIALS DEMONSTRATE THE EFFECTIVENESS OF PREP USED IN ADDITION TO CONVENTIONAL PREVENTION METHODS

To date, four placebo-controlled trials investigating in one case a TDF-based vaginal microbicide gel, and in the other three continued daily oral TDF or combination FTC/TDF, have shown a significant reduction in the risk of contracting HIV in HIV-negative persons taking ARV. Within the context of these trials, these results constitute proof of concept, i.e. that ARV administered preventively have a protective effect on uninfected persons.

Two further trials however were respectively interrupted and modified whilst in progress. The first was studying the use of continuously administered FTC/TDF in women and was interrupted on the basis of the interim results which showed that ARV had no significant protective effect compared to the placebo. The second is a trial in progress which was initially comparing three approaches vs. placebo: 'oral FTC/TDF', 'oral TDF' and 'TDF vaginal gel'. However, the 'oral TDF' and 'TDF vaginal gel' arms were interrupted, again based on inconclusive interim results. These negative results would appear to contradict those obtained in the other studies. These discrepancies are currently being further investigated, but the results of this work are not yet available.

The table below summarizes the protocols implemented in a series of placebo-controlled trials currently underway or completed, for which results are available:

Simplified table of comparison of PrEP trials for which results are available

Type of PrEP	Trial *ARV used*	Target population (N° of participants) Country	Arm Reinforced "conventional" prevention + placebo *N° of infections observed / N° of participants*	Arm Reinforced "conventional" prevention + ARV *N° of infections observed / N° of participants*		Results
Daily oral PrEP	**iPrEx** [25] *Daily FTC-TDF (Truvada®) tablet*	**HIV-negative MSM** at high risk of contracting HIV (n=2499) USA, Brazil, Peru, Ecuador, South Africa, Thailand	**64**/1248	**36**/1251		- **overall reduction in incidence of 44%** - **high impact of adherence**: reduction › 70% in the sub-group reporting a high level of adherence and › 90% if ARV detected in the sub-group subjected to biological assays
	PARTNERS-PrEP [26] *Daily TDF (Viread®) tablet* *or* *Daily FTC-TDF (Truvada®) tablet*	**Heterosexual serodiscordant couples** (infected partner untreated) in a population with very high levels of prevalence (n=4758) Kenya, Uganda	**47**/1584	TDF arm **18**/1584	FTC/TDF arm **13**/1579	- **overall reduction in incidence of 62% to 73%** - - - according to the ARV used (difference between the two ARV arms non-significant) *Comment: Placebo arm interrupted in 2011 due to these positive interim results (unethical to continue), participants were reallocated to the two ARV arms and the trial continued with the aim of comparing the respective efficacy of the FTC/TDF strategy vs. TDF alone.*

[25] Grant, R.M., "Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men", *New England Journal of Medecine*, vol. 363, December 2010, pp. 2587-2599.

[26] http://depts.washington.edu/uwicrc/research/studies/files/PrEP_ResultsKeyMessages.pdf

Daily oral PrEP	**TDF2** [27] *Daily FTC-TDF (Truvada®) tablet*	**Heterosexual, HIV-negative men (55%) and women (45%)** in a population with very high levels of prevalence (n=1200) Botswana	**24**/599	**9**/601	- **overall reduction in incidence of 63%** - **high impact of adherence**: 77% reduction when participants having interrupted their treatment (or placebo) for 30 days or more are excluded
	FEM-PrEP [28] *Daily FTC-TDF (Truvada®) tablet*	**HIV-negative heterosexual women** in a population with high levels of prevalence (n=1951) Kenya, South Africa, Tanzania	The interim results showed that the trial could not demonstrate a significant difference between the oral FTC/TDF arm and the placebo arm.		→ **trial interrupted**
	VOICE [29] *Daily TDF (Viread®) tablet* *Or daily FTC-TDF (Truvada®) tablet*	**HIV-negative heterosexual women** in a population with high levels of prevalence (n=5029) South Africa, Zimbabwe, Uganda	The interim results showed that the trial could not demonstrate a significant difference between: - the oral TDF arm *vs.* placebo arm		→ **trial continued with the oral FTC/TDF arm vs. the placebo arm only** *(in progress, no results available).* → **interruption of the oral TDF arm**
Topical PrEP	*Or 1% TDF vaginal gel*		- 1% TDF vaginal gel arm *vs.* placebo arm		→ **interruption of 1% TDF vaginal gel arm**
	CAPRISA 004 [30] *1% TDF vaginal gel*	**HIV-negative heterosexual women** in a population with high levels of prevalence (n=889) South Africa	**60**/444	**38**/445	- **overall reduction in incidence of 39%** - **high impact of adherence**: Reduction of 54% in the sub-group using the gel (or placebo) on more than 80% of the occasions on which they engage in sexual intercourse

For both methodological and ethical reasons, all participants in PrEP trials, both those receiving the active treatment, and those receiving the placebo, benefited from reinforced "conventional" prevention measures including regular screening for HIV and other STIs, a regular, free supply of condoms and increased counseling[31] on HIV and STI transmission prevention methods. In a situation of dual uncertainty – uncertainty regarding the efficacy of ARV used as PrEP and uncertainty as to whether the participant is receiving an active treatment or the placebo – all participants were strongly encouraged to use the conventional protection methods available to them.[32]

[27] http://www.cdc.gov/hiv/prep/pdf/TDF2factsheet.pdf

[28] http://www.fhi360.org/en/Research/Projects/FEM-PrEP.htm, for more details on the interruption of the trial see http://www.fhi360.org/NR/rdonlyres/erjf6hevouwxddigldvcca6lvlybfolh4nedyfeo4yz2i7la53jknim6ex42bme2vyqf6xfzowyrkh/FEMPrEPFactSheetJune2011.pdf

[29] http://www.mtnstopshiv.org/news/studies/mtn003, for more details on the interruption f the oral TDF arm and the TDF 1 % vaginal gel, see http://www.mtnstopshiv.org/node/3619 and http://www.mtnstopshiv.org/node/3909 respectively

[30] Abdool Karim, Q., *et al.*, "Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women", *Science*, vol. 329, September 2010, pp. 1168-1174.

[31] C*ounseling*, is used in HIV prevention to denote all practices which aim to provide the personalised information, guidance, and psychological and social support that can help a person protect themselves effectively against the risk of contracting or passing on the HIV virus.

[32] Myers, G.M., Mayer, K.H., "Oral Preexposure Prophylaxis for High-Risk U.S. Populations: Current Consideration in Light of New Findings", *AIDS Patient Care and STDs*, vol. 25 (2), 2011, pp. 63-71. This point is specifically addressed on p. 67.

This means that the trials demonstrate the effectiveness of ARV protection in addition to, not as a substitute for, conventional means of protection. What is measured in current trials is not the level of risk reduction achieved using ARV alone, but the additional reduction in risk achieved using ARV in conjunction with the promotion of conventional means of protection.

The levels of protection obtained through the additional use of PrEP, may seem moderate, or even disappointing. However, two important points should be made regarding this initial assessment:

Firstly, it is no surprise that these results reflect the vital importance of treatment adherence. The two trials with the best overall efficacy, showing a reduction in incidence of 60 – 70%, are also characterized by high levels of adherence in the majority of participants. Conversely, the results from the other trials appear to be moderated by the non-compliance observed in some participants, whilst high levels of efficacy, at least for oral PrEP, are reported for the participants with the highest levels of adherence. PrEP thereby shows high theoretical levels of efficacy, in the sense that ARV, if used effectively, and under the strict framework of a clinical trial, can offer high levels of protection. However, the real effectiveness of PrEP clearly depends on how it is used by people and their ability to use it in a proper, coherent and consistent manner, a factor which refers back to the behavioral dimension inherent to any prevention intervention.

Secondly, in order to assess the potential practical benefits of PrEP, it is important to consider the efficacy results obtained in these trials with regard to contexts where conventional prevention has partially failed. The table above shows that a non-negligible number of infections occur in the "conventional prevention alone" arm. This highlights the limitations of a conventional prevention intervention even when optimized and reinforced for the purposes of the trial, in the high-risk populations targeted (high prevalence, high incidence, high levels of risk taking). From this perspective the protection provided by PrEP, even partial, constitutes a net benefit in terms of individuals' safety, and an additional means of reducing HIV incidence at collective level, on the condition that PrEP forms part of a comprehensive prevention package and is used in addition to conventional methods. PrEP can therefore be considered as a way of completing and improving the effectiveness of the prevention package available to the most at-risk populations.

MODELS TO IDENTIFY THE DETERMINANTS OF THE POTENTIAL COLLECTIVE IMPACT OF PREP ON THE EPIDEMIC

Alongside these clinical trials, to date eight studies have built mathematical models to test various hypotheses and scenarios on the use of PrEP. These aim to assess its expected impact in terms of the reduction in the number of infections in the target population.[33, 34, 35, 36, 37, 38, 39, 40] Three of these models also incorporate cost-effectiveness analyses. Without going into the detail of the different models, which differ widely in their methodology and hypotheses, it should be noted that five of these studies concern heterosexual populations in areas with high levels of prevalence (countries in Sub-Saharan Africa) and three focus on MSM (USA). Five of these studies have modeled the impact of an increase in at-risk behavior following the introduction of PrEP, and one explores the relationship between PrEP strategy and the concomitant development of a strategy to screen and treat infected persons (TasP strategy).

Despite their inherent diversity, these studies all show that the impact of PrEP is strongly dependent on:

- *the characteristics of the target population:* The impact of implementing PrEP is all the more significant if the target population has a high risk of infection, i.e. is characterized by high levels of HIV prevalence/incidence, and/or an inadequate use of other means of protection (inconsistent use of condoms, low rate of screening, or insufficiently frequent screening).

[33] Abbas, U.L., *et al.*, "Potential Impact of Antiretroviral Chemoprophylaxis on HIV-1 Transmission in Resource-Limited Settings", *PLoS ONE*, vol. 2 (9), September 2007, p. e875. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0000875

[34] Vissers, D.C.J., *et al.*, "The Impact of Pre-Exposure Prophylaxis (PrEP) on HIV Epidemics in Africa and India: A Simulation Study", *PLoS ONE*, vol. 3 (5), May 2008, p. e2077. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0002077

[35] Desai, K., *et al.*, "Modeling the impact of HIV chemoprophylaxis strategies among men who have sex with men in the United States: HIV infections prevented and cost-effectiveness", *AIDS*, vol. 22 (14), September 2008, pp. 1829–1839.

[36] Paltiel, A.D., *et al.*, "HIV Preexposure Prophylaxis in the United States: Impact on Lifetime Infection Risk, Clinical Outcomes, and Cost-Effectiveness", *Clinical Infectious Diseases*, vol. 48, March 2009, pp. 806-815.

[37] Van de Vijver, D.A., *et al.*, "Circulating HIV Type 1 Drug Resistance Will Have Limited Impact on the Effectiveness of Preexposure Prophylaxis among Young Women in Zimbabwe", *Journal of Infectious Diseases*, vol. 199 (9), May 2009, pp. 1310-1317.

[38] Supervie, V., *et al.*, "HIV, transmitted drug resistance, and the paradox of preexposure prophylaxis", *PNAS*, vol. 107, n°. 27, July 2010, pp. 12381-12386. http://www.pnas.org/content/107/27/12381.full

[39] Abbas, U.L., *et al.*, "Factors Influencing the Emergence and Spread of HIV Drug Resistance Arising from Rollout of Antiretroviral Pre-Exposure Prophylaxis (PrEP)", *PLoS ONE*, vol. 6 (4), April 2011, p. e18165. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0018165

[40] Pretorius, C. *et al.*, "Evaluating the Cost-Effectiveness of Pre-Exposure Prophylaxis (PrEP) and Its Impact on HIV-1 Transmission in South Africa", *PLoS ONE*, vol. 5 (11), November 2011, p. e13646. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0013646

- *the characteristics of PrEP and their implementation:* higher ARV performance (greater effectiveness of ARV treatment in reducing the risk of infection) and higher rate of antiretroviral coverage in the target population (proportion of the population using PrEP, actual rate of use/user compliance) are both factors which may increase the impact of PrEP. Conversely, this impact might be lowered if PrEP use leads to an increase in high-risk behavior (higher number of partners, decision to engage in high risk practices and frequency of these practices, frequency of unprotected intercourse).

Furthermore, one study specifically explored the complementarity or competition between PrEP and TasP strategies[41]. It highlighted the interconnections between the two which need to be taken into account in contexts where screening and treatment in the event of a diagnosed infection are generally accessible, as is the case in countries such as France. It would seem that the more the treatment coverage of the infected population increases, the more the impact of PrEP on incidence and its cost-effectiveness decreases and vice versa.[42]

In terms of strategy, in areas offering access to screening and treatment, PrEP should therefore specifically target the populations which are not only the most at risk, but in which the majority of transmissions originate from people unaware of their HIV status, meaning the impact of the treatment of infected persons as prevention strategy is suboptimal or hindered.

There are two possible scenarios:

- The first concerns a population in which the screening rate is low or the frequency of screening insufficient, in other words, with a high proportion of infected people diagnosed at a late stage. In this context, the development of PrEP, which requires both initial and regular screening, favors the earlier detection and provision of treatment to those infected. This therefore contributes to progressively improving the prevention strategy's performance by treating infected persons – and should therefore be promoted for a transitional period of variable duration.
- Conversely, the second possibility concerns a population in which, despite regular and frequent screening, a large proportion of transmissions originate from people who have been recently, or very recently infected (notably primary infections).[43] In this case, which notably concerns MSM with large numbers of partners[44], the strategy of prevention through screening and the early treatment of infected persons meets its limits. A non-negligible number of transmissions may indeed occur during the lapse of time, even if this only lasts a few weeks or months, between infection and screening,[45] and *a fortiori* the moment at which treatment is initiated and has met its objective of achieving viral suppression. In this context, the PrEP option would seem to constitute a long term complementary strategy.

[41] Pretorius, C. *et al.*, "Evaluating the Cost-Effectiveness of Pre-Exposure Prophylaxis (PrEP) and Its Impact on HIV-1 Transmission in South Africa", 2011, *op. cit.*

[42] Ibid., notably, with regard to the South-African situation studied, the authors conclude that : *"[…] The cost-effectiveness of PrEP relative to ART decreases rapidly as ART coverage increases beyond three times its coverage in 2010, after which the ART program would provide coverage to more than 65 % of HIV+ individuals. To have a high relative cost-effective impact on reducing infections in generalized epidemics, PrEP must utilize a window of opportunity until art has been scaled up beyond this level".*

[43] The high viral load in the body during the primary infection phase (the first weeks post-infection) means there is a far higher risk of transmission. A study investigating a Ugandan cohort, estimated that the risk of sexual transmission is 26 times higher for approximately three months following infection than for the subsequent asymptomatic chronic infection phase which lasts several years (Hollingsworth, T.D., *et al,* « HIV-1 Transmission, by Stage of Infection », *Journal of Infectious Diseases*, vol.198, September 2008, pp. 687-693). Various studies have highlighted the very important role of primary infections and recent infections in the epidemic's dynamic, for example, in Quebec (Brenner, B.G., *et al.*, "High Rates of Forward Transmission Events after Acute/Early HIV-1 Infection", *Journal of Infectious Diseases*, vol.195, avril 2007, pp. 951-959) and in Malawi (Powers, K.A., *et al.*, "The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study", *The Lancet*, vol. 378, n° 9787, July 2011, pp. 256-268). This impact can however be disputed in light of the results from another study, conducted in several European countries, as well as certain methodological considerations (Brown, A.E., et al., « Phylogenetic Reconstruction of Transmission Events from Individuals with Acute HIV Infection: Toward More-Rigorous Epidemiological Definitions », *Journal of Infectious Diseases*, vol.199, février 2009, pp. 427-431).

[44] For France see, Velter, A., *et al.*, « Prévalence du VIH et comportement de dépistage des hommes fréquentant les lieux de convivialité gay parisiens, Prevagay 2009 », *Bulletin épidémiologique hebdomadaire*, n°45-46, InVS, November 2010, pp. 464-467.

[45] *Ibid.* The Prévagay study, conducted in 14 Parisian gay bars and clubs of which 9 are equipped with specific areas for sexual encounters (backrooms, saunas), shows a high prevelance of HIV (18%) and that 20% of infected participants were unaware that they were HIV-positive at the start of the study. The fact that 62% of these had been tested in the last twelve months suggests that a large number of infections occured in the interim.

II.2. A POTENTIAL RESPONSE TO CONVENTIONAL PREVENTION FAILURE OR DIFFICULTIES

IDENTIFYING THE FACTORS LEADING TO HIGH EXPOSURE TO RISK

On the basis of the results currently available, to be confirmed by the trials planned or underway, the additional use of PrEP increases the level of protection for persons or groups of persons identified as highly exposed to HIV infection.

This notion of high risk exposure depends both on an epidemiological factor, i.e. a high probability of having one or more sexual partner(s) with untreated HIV, and a behavioral factor i.e. engaging in sexual practices without using adapted protection methods or using insufficient means of protection.

Regardless of the means of protection likely to be used, a person's risk of exposure to HIV is statistically higher when:
- they select their partners within populations particularly affected by HIV;
- they have a large number of partners;
- they engage in sexual intercourse with presumably at-risk partners who are unaware of, or who do not disclose their HIV status.

Finally, the risk is obviously present in the case of a relationship with a partner who knows they are HIV-positive but is untreated, notably in the case of "serodiscordant" couples.

In terms of the risk of exposure due to the non-use or misuse of sexual means of protection, it is important to differentiate between *non-consensual exposure* and *consensual exposure:*

- Non-consensual exposure refers to risk taking forced upon a person by one or more partners in a social, cultural, economic and/or personal context which does not allow, or does not always allow, the person to negotiate effective protection, notably condom use: An unbalanced economic or emotional relationship, gender relations which create vulnerability notably for women, situations of inequality or dependence of one partner in a couple etc.
- Consensual risk taking by the person themselves depends on a variety of determinants. People may make the informed choice to accept the high level of risk associated with their practices. However, not all of this form of risk taking is necessarily willful, conscious or informed. Engaging in at-risk practices may be the result of the person's lack of understanding of prevention which means they misunderstand or underestimate the risks to which they are exposing themselves, are unaware of effective means of protection or use risk reduction methods or strategies which are ineffective, unsuitable or insufficient. This may also be the result of difficulties in "mastering" preventive behaviors, for a number of reasons: Sexual or emotional barriers to using adapted protection methods in certain situations, difficulties in maintaining a high level of protection over the long term, difficulties in reconciling the use of protection and inclusion in a group or sexual culture whose codes do not encourage its use, difficulties due to the alteration of the person's physical and cognitive faculties through the consumption of drugs or alcohol.

IDENTIFYING POTENTIAL PREP USERS IN FRANCE: DISTINGUISHING BETWEEN THE COLLECTIVE AND INDIVIDUAL BENEFITS

Metropolitan France is characterized by a concentrated epidemic. The epidemiological data on HIV prevalence and incidence show that most transmissions occur within the MSM population[46], and within migrant populations[47]. In the latter, transmission is highest between heterosexual partners, and notably in populations of Sub-Saharan African origins[48]. Within this group, the epidemic affects a large proportion of women[49]. Looking beyond metropolitan France, the cases of French Guiana and to a lesser extent Guadeloupe, constitute a specific challenge given that both of these territories are suffering from generalized epidemics.[50]

The benefit of making PrEP available in France and which specific populations it should target should be examined from two perspectives. These depend on whether the aim is to have a significant collective impact on the epidemic

[46] In 2010, 40% of new HIV-diagnoses in France were due to male homosexual transmission and 57% to heterosexual transmission of the virus.(French Institute for Public Health Surveillance (InVS) mandatory notification of HIV-cases, data on 31/12/2010)

[47] In 2010, migrants (in the sense of persons born in a foreign country) contaminated through heterosexual intercourse represented 39% of all new HIV-diagnoses and almost 70% of heterosexual infections. Furthermore, it should be noted that 17% of cases of homosexual infections concern men born in a foreign country. (French Institute for Public Health Surveillance (InVS), mandatory notification of HIV-cases, data on 31/12/2010)

[48] 68% of migrants who discovered they were HIV-positive in 2008 came from Sub-Saharan Africa. (French Institute for Public Health Surveillance (InVS), mandatory notification of HIV-cases, data on 31/12/2008).

[49] In 2008, in the sub-group of migrants originating from Sub-Saharan Africa, 58% of people finding out their HIV-positive status were women as opposed to 41% for heterosexuals born in France. Furthermore, 75% of women who found out they were HIV-positive in France were born in a foreign country. (French Institute for Public Health Surveillance (InVS), mandatory notification of HIV-cases, data on 31/12/2008)

[50] The WHO considers an epidemic to be generalised when HIV prevalence in pregnant women is higher than 1%.

or to assess the benefit of PrEP as an individual means of protection, capable of meeting the needs of persons who have experienced prevention failure using other existing methods.

It is important to consider on the one hand the epidemiological criteria for populations in which PrEP trials have had a significant impact on incidence and, on the other hand, the efficacy factors for PrEP interventions as shown in the impact models and cost-efficiency studies carried out. On this basis, only the MSM population with an average estimated incidence of 1.01 – 1.04% would be eligible for an intervention aiming to significantly impact incidence. The other groups mentioned, despite having levels of prevalence or incidence that are well above the national average, remain well below the reference criteria for impacting the dynamic of the epidemic.[51]

However, in terms of *human rights*, access to PrEP cannot be restricted based on sexual preference, something which in itself is difficult to delineate. The individual benefits of using PrEP justify making it available to a broader population, i.e. all those for whom it is likely to constitute an adapted response given the level of risk to which they are consensually or non-consensually exposed. In this context, a person's access to PrEP should not depend on belonging to a given group, but on their individual risk of contracting HIV.

PREP CAPABLE OF REINFORCING AUTONOMY AND RESPONDING TO SPECIFIC PREVENTION CHALLENGES

The main benefit of PrEP resides in the fact that it is implemented prior to the sexual encounter and is controlled by the person wanting to protect themselves rather than their partner. It could therefore constitute a precious means of increasing people's autonomy, either in situations of non-consensual risk exposure or, as previously mentioned, for people identified as lacking the self-discipline required to protect themselves effectively and systematically in at risk sexual situations.[52] The different forms of PrEP – topical, continued and "on demand" - could contribute to developing differentiated and adapted responses offering a range of prevention methods closely adapted to individual needs, according to each person's specific constraints and difficulties.

It is clear, for the aforementioned epidemiological reasons, that PrEP can constitute a specific response to the high levels of risk taking in MSM populations. Data from the numerous qualitative studies and research projects have made it possible to highlight and analyze the regular increase in at-risk sexual behavior since the end of the 1990s[53]. This increase is observed regardless of HIV-status, but is proportionally higher for men who are HIV-positive or those who are unsure of their status. One of the indicators of this trend, the proportion of MSM declaring *at least one unprotected anal penetration* during the last 12 months with an occasional partner has increased from 15% HIV-negative and 26% HIV-positive in 1997[54] to approximately 30% HIV-negative and 50% - 70% HIV-positive in the second half of the 2000s.[55] Almost 13% of HIV-negative and 57% of HIV-positive MSM declared in 2009, *regular unprotected anal intercourse* with occasional partners[56]. Numerous explicative and/or predictive factors for risk taking have been studied. The diversity in lifestyles, identities, ways of meeting people and socializing and specific sexual cultures covered by the term MSM makes an overall analysis of prevention issues impossible. The potential contribution of PrEP can therefore only be assessed by means of a detailed analysis of behavior and risk factors which cannot be developed herein.

We can however suggest several avenues for further exploration.

Within the population of HIV-negative MSM declaring at-risk behaviors, a large proportion reported occasional but not regular or systematic risk taking. This suggests that prevention remains their fundamental objective but is sometimes abandoned in specific circumstances. This is either due to an inability to keep to this objective in a given circumstance, or a conscious decision to make an exception.[57] The different forms of PrEP, used in addition to

[51] The estimated rate of incidence in migrant populations of Sub-Saharan African origins in France is 0.25 % and appears well below the rates of equal to or above 1% which characterise the populations studied under the different PrEP trials. As regards the epidemiological situation in French Guiana, there is no incidence data available, but we know that HIV prevelance is around 1% for French women and up to 3.5% for Haitian women, the worst affected population (2003 data). In the populations studied under PrEP trials, the prevelance of HIV in pregnant women is around 20 – 50%.

[52] Regarding potential users' perception of PrEP as an opportunity for building their autonomy see Eisingerich, A.B., *et al.*, « Attitudes and Acceptance of Oral and Parenteral HIV Preexposure Prophylaxis among Potential User Groups: A Multinational Study », *PLoS ONE*, vol. 7(1), January 2012, p. e28238. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0028238

[53] In France, the main sources documenting this trend are the regular surveys *Enquêtes Presse gaie* (EPG*), Baromètre gay* (BG) and *Net-baromètre gay* (NBG), carried out since 1985, 2000 and 2003, respectively. For a comprehensive analysis, see also Bozon, M. and Doré, V. (dir.), *Sexualité, relations et prévention chez les homosexuels masculins : Un nouveau rapport au risque*, Agence nationale de recherches sur le sida et les hépatites virales (ANRS), coll. Sciences sociales et sida, Paris, 2007. For further documentation regarding these phenomena at European and international level, see the references provided in section IV.1 of this opinion.

[54] Data EPG 1997.

[55] Convergent data EPG 2004, BG 2009 et NBG 2009.

[56] Data NBG 2009

[57] CNS Hearings

conventional prevention practices to cover this type of occasional risk taking, may well constitute an interesting response to this individual prevention issue.

In the case of men declaring regular or even systematically unprotected practices, the conditions for using PrEP are less favorable as protection seems to be a low priority for this group. However, an analysis of sexual practices in this group shows that risk taking is closely associated with constructions of sexual desire and pleasure in which anal penetration, oral contact with sperm, and the exchange of fluids, associated with group practices, large numbers of partners or the consumption of psychotropic drugs play an important role.[58] The motivation for choosing to prioritize the quality of their sex life and personal pleasure may therefore be due to the incompatibility between condom use and the practices that constitute their sexual desire, rather than mere indifference as regards their protection. It is therefore possible to emit the hypothesis - currently unsupported – that PrEP may also be beneficial for persons who do not, or no longer seek to protect themselves by providing them, not with optimal protection, but at least a means of reducing the risks when no protection is used.

Another potential target population for PrEP, in addition to MSM, are heterosexual women, many of whom are faced with particular difficulties concerning their sexuality due to their social relationships and/or gender inequalities[59]. PrEP offers them a means of increased protection over which they have total control and which they can use entirely autonomously.[60] To date, the female condom was the only method which could be used independently of the male partner, but with the significant limitation that the male partner would be aware of its use, which they may reject. As a form of protection which can be used without the partner knowing, PrEP offers a solution which bypasses these constraints, something conventional protection has failed to do.

PrEP is therefore likely to significantly improve the safety of all populations, and most notably specific groups of women or men, who are exposed with greater or lesser regularity to unprotected practices with one or more partners whose HIV-status is not known or who have a high risk of carrying HIV - whether this is within a couple, with occasional partners, or, in the case of sex workers with certain clients.[61]

Finally, serodiscordant couples constitute a specific case as they are keen to have access to solutions which reduce the constraints of systematic protection using condoms. This may either be due to a desire to procreate without resorting to reproductive technologies, or for emotional reasons, to generally improve the quality of their sex life. The benefits of PrEP for serodiscordant couples immediately appear limited, as it would be paradoxical to treat the uninfected partner with ARV rather than the infected partner. In terms of prevention, the treatment of the infected person is proven to significantly reduce the risk of transmission[62]. The preliminary results obtained from studies into PrEP provide no evidence that it offers the same levels of protection as the therapies used to treat infected persons. There is therefore a clear imbalance in terms of the benefit-risk analysis between on the one hand, an infected person for whom the treatment is a therapeutic necessity which should be initiated as soon as possible, and on the other hand, an uninfected person for whom the benefit is purely preventive.

That said, whilst serodiscordant couples should always be offered a TasP solution, PrEP could be used in certain specific cases, notably for temporary and/or complementary use in the event of specific situations which could hinder the treatment of the infected person, or diminish its efficacy. This could also provide a means of taking into account the emotional and psychological aspects which lead the couple, and in particular the HIV-negative partner to request this solution.[63] In either case, requests for PrEP from serodiscordant couples constitute very specific cases in which the doctor needs to take into account individual circumstances and the couple's emotions and intimate concerns when making their decision.

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[58] CNS Hearings

[59] See notably Garcia-Moreno, C, *et al.,* « Prevalence of intimate partner violence: findings from the WHO multi-country study on women's health and domestic violence », *The Lancet*, vol. 368, n° 9543, octobre 2006, pp. 1260-1269 ; The Gender and Development Group [Poverty Reduction and Economic Management (PREM)], *Integrating Gender Issues into HIV/AIDS Programs*, World Bank, Washington, DC, 2004, http://siteresources.worldbank.org/INTGENDER/Resources/GenderHIVAIDSGuideNov04.pdf.

[60] Eisingerich, A.B., *et al.*, "Attitudes and Acceptance of Oral and Parenteral HIV Preexposure Prophylaxis among Potential User Groups: A Multinational Study", *PLoS ONE*, 2012, *op.cit.*, p. e28238-7.

[61] On issues specifically related to prevention in the sex trade, see National AIDS Council, *HIV and the sex trade. Guaranteeing universal access to prevention and health care. Opinion and recommendations*, 16 September 2009. http://www.cns.sante.fr/spip.php?article349

[62] Cohen, M.S., *et al.*, "Prevention of HIV-1 Infection with Early Antiretroviral Therapy", *New England Journal of Medecine*, 2011, *op. cit.*

[63] CNS hearing. In this context, certain instances of self-medication by the HIV-negative partner, using the drugs prescribed for the treated partner, with a view to natural procreation, have been reported.

III. PREP MEDICAL MONITORING REQUIREMENTS AND COST CONSTITUTE A NEW CHALLENGE FOR PREVENTION POLICY

III.1. MEDICAL PRESCRIPTION AND MONITORING REQUIREMENTS FOR PREP

For the types of PrEP currently being contemplated and given current knowledge, developing a prevention program that offers ARV to uninfected persons introduces a series of new constraints. This is because the individual must see a doctor in order to access ARV treatments on prescription[64] and comply with a number of vital usage and monitoring requirements to ensure the health and safety of both individuals and the community.

A first major challenge is to combine PrEP and screening, so that PrEP is only offered to people who are HIV-negative, and in order to stop the treatment if they become infected. As previously stressed, although PrEP protocols include the same ARV used for therapeutic purposes, they do not constitute effective combination therapy, neither in terms of the combinations of ARV used nor their efficacy. When administered as a topical gel, ARV have a localized rather than systemic effect. PrEP protocols for continued oral or intermittent oral administration are insufficiently effective mono or combination therapies and are not recommended as treatment strategies for people with HIV.[65] Indeed, this sort of treatment plan does not achieve viral suppression and may even increase resistance, i.e. reduce the individual's therapeutic chances if they are infected whilst on PrEP and continue to take it (increased risk of therapeutic failure and reduction of future treatment options). Collectively, there is a risk that it will contribute to the spread of viral strains resistant to the most widely ARV. Prescribing PrEP therefore requires initial screening and regular monitoring of the person's HIV status at yet to be defined intervals.

A second medical monitoring issue is that these treatments, at least when taken orally, have a potentially significant risk of medium or long-term adverse effects. The risks of taking tenofovir, in particular, which is the basis for all the PrEP protocols currently being trialed, are well known and require regular monitoring of a number of biological parameters, particularly with regard to bone and renal risks.

A third challenge is patient adherence to the PrEP protocol and prescription compliance. Prophylaxis trials have shown that the level of adherence to the protocol and of prescription compliance have a major impact on the level of protection achieved.[66] On this point, the different forms of PrEP currently being trialed have advantages and disadvantages. In the case of daily oral PrEP, taking medication on a daily basis in the long term, particularly for a healthy individual, can prove difficult, as suggested by the compliance problems documented in fields other than HIV. Intermittent oral 'on demand' PrEP (only taken before a potential sexual encounter) has the advantage – if the efficacy of this still theoretical strategy is confirmed – of avoiding the constraints of taking medication every day and of linking preventive behavior to its actual objective. However, the main drawback of the treatment plans to be trialed in the near future, is that actually taking the medication is complicated (it must be taken within the 12 hour period leading up to sexual intercourse and a second dose must be taken within the hour following it). Another disadvantage is the inherent difficulty of planning or scheduling sexual intercourse several hours in advance. Finally, the use of topical gels causes similar problems relating to forward-planning and their application can also be more inconvenient than taking tablets. The constraints involved in using the different forms of PrEP, to which monitoring constraints must also be added, may constitute significant obstacles to their acceptance and to their proper and sustainable long-term use.[67]

COMPLEX IMPLEMENTATION PROCEDURES WILL BE REQUIRED

In light of the aforementioned HIV status monitoring, biological monitoring and pre-exposure treatment support issues, the monitoring of PrEP users seems to constitute a major challenge when moving out of the strict framework of clinical trials and developing 'real-life' PrEP programs.

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[64] As well as stipulating that a hospital specialist must prescribe ARV when being used for the first time, current regulations also require the user to see a specialist at least once a year.

[65] With regard to ARV treatment objectives and currently approved treatment plans, see Yeni, P. (dir.), *Rapport 2010 du groupe d'experts sur la prise en charge médicale des personnes infectées par le VIH*, 2010, *op. cit.*, pp. 57 *sqq.*

[66] See chapter II.2 of this opinion.

[67] Eisingerich *et al.*'s large-scale study evaluating PrEP acceptance conducted in seven countries with different potential target groups concluded that there is strong interest in PrEP despite the various obstacles and constraints. The hypothesis of developing ways of administering the medication that would enable it to be taken at less frequent intervals (bimonthly or monthly injections, in particular) does however seem likely to encourage the use of PrEP (Eisingerich, A.B., *et al.*, "Attitudes and Acceptance of Oral and Parenteral HIV Preexposure Prophylaxis among Potential User Groups: A Multinational Study", *PLoS ONE*, 2012, *op. cit.*

Current research will help to build knowledge and clarify certain issues.[68] However, it must be acknowledged that experimental data will not be able to address in advance all the difficulties related to PrEP use. In light of these uncertainties, the rollout of the first PrEP programs must include a comprehensive monitoring system which will be demanding in terms of user adherence and in terms of the prevention structures' ability to provide the human and technical resources required.

However, this observation should not stop us taking a longer-term view and hoping that progress will make it possible to streamline the system in the future. Some of the current uncertainties, constraints and reservations are due to the specific characteristics of tenofovir. It is not unreasonable to hypothesize that the development of new ARV molecules and new formulations could lead to the production of second and third-generation PrEP, which would be more effective, better tolerated and less binding in terms of use and monitoring.[69]

III.2. MONITORING AND EVALUATING THE IMPACT OF PREP THROUGHOUT IMPLEMENTATION

Ensuring user safety, preventing the potential risks for the community and contributing to the progress of research are three overlapping requirements which mean that the deployment of a PrEP program needs to be accompanied by an effective monitoring system covering several fields. This is the only means of resolving some of the uncertainties which subsist and of assessing the medium and long-term effects of PrEP.

Concerns about the possible adverse effects of the ARV medication used for PrEP obviously require the implementation of all the standard post-marketing authorization measures for drug-related risks (pharmacovigilance) as well as epidemiological and virological (resistance monitoring) measures. Furthermore, the proper authorities should ensure that ambitious phase IV studies[70] are designed and implemented by the pharmaceutical companies in question.

A process of reflecting on both the need for, and the best way of designing, a user data collection system, incorporating prescription and HIV status and biological monitoring data and, if possible, compliance and behavioral data, must also be set in motion and must involve the relevant research bodies.

Finally, it seems necessary to promote ad hoc research projects, in particular those looking at the behavioral aspects of PrEP use, such as its impact on risk-taking, actual PrEP use and the impact of use on other prevention methods. In these areas, it seems particularly important to encourage social and human sciences research and multidisciplinary approaches.

III.3. WHO WILL COVER THE COSTS OF PREP?

The possible future implementation of PrEP comes up against economic constraints of an unprecedented scale in the field of prevention. Offering medication to healthy people, especially a long-term treatment in the case of daily oral PrEP, involves allocating substantial resources, due to the cost of ARV therapies and the human and technical resources required to prescribe and monitor PrEP. In terms of resource allocation, developing a PrEP program therefore raises both ethical and strategic issues.

Internationally, in a context of limited resources, providing people without HIV with PrEP would be hard to justify at a time when almost 8 million eligible people living with HIV are unable to access treatment[71] and only 2% of those treated benefit from second-line drugs.[72]

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[68] Extension under the open format of trials such as iPrEX (*iPrEX-Open Label Extension,* see http://www.iprexole.com/1pages/aboutus.html), in which all participants who do not have HIV at the end of the placebo controlled trial are given the option of continuing with PrEP with the certainty of receiving the medication and with full awareness of its effectiveness, and pilot trials *(demonstration projects)* that are closer to reality, should help to better evaluate the challenges involved in rolling out PrEP on a wider scale. A first pilot project of this type aimed at MSM is currently being developed and should be launched in the US during 2012. (http://www.ebar.com/news/article.php?sec=news&article=6032)

[69] Apart from the above mentioned research on PrEP that can be injected on a bimonthly or monthly basis, methods for administering the treatment, such as patches, that would help to facilitate compliance, are also being considered. Topical PrEP, if highly effective formulations are developed, would have the advantage of limiting problems of toxicity and resistance, particularly if users are not being monitored.

[70] As an extension of the pharmacological clinical trial phases leading to the approval of a new drug or the validation of a new purpose for an existing drug, IV phase studies, which are also known as post-marketing studies, are long-term monitoring studies of the drug once it has obtained marketing authorization. They aim to identify rare side effects or long-term complications and any misuse related risks. The pharmaceutical company is responsible for this phase.

[71] UNAIDS, *World AIDS Day, 2011 report, op.cit*

[72] World Health Organisation (WHO), UNAIDS and United Nations Children Fund (UNICEF), *Toward universal access: scaling up priority HIV/AIDS interventions in the health sector: progress report 2010*, World Health Organisation, 2010. http://www.who.int/hiv/pub/2010progressreport/summary_en.pdf

In a country such as France, given the current cost of ARV therapies the prospect of rolling out a PrEP program either raises concerns regarding unequal access or, if state-funded, the ethics of choosing to invest in this rather than other health needs or in under-funded existing prevention programs.

Without state cover or a dramatic reduction in the cost of ARV drugs, access to this new prevention method would automatically be limited to the wealthy[73], thwarting the efforts made to reduce health inequality. This would be compounded by the fact that some of the PrEP target groups are people whose risk of contracting HIV is high because they are very economically and socially vulnerable and/or are economically dependent on their partner(s).

However, it does not seem likely that the state health insurance scheme would cover the cost of PrEP in current circumstances. A significant drop in the price of the ARV treatments used in PrEP would be a prerequisite for possible state funding but would in itself still be insufficient. Indeed, it would still be difficult to justify due to the needs of numerous under-funded diseases and the fact that other HIV prevention methods, such as condoms, and more generally other health risk reduction measures, for example for smoking and alcohol consumption, are not covered by the state. Apart from the contingent question raised by PrEP, this absence of funding would justify a more wide-ranging debate on the level and objectives of public investment in health risk prevention.[74]

[73] For the purposes of information, based on current retail prices in France, a daily oral TDF-based PrEP would cost €375.85 a month (box of 30 Viread® tablets) and €520.90 a month if the combined TDF/FTC is used (box of 30 Truvada® tablets).

[74] See the Economic, Social and Environmental Council, *Les enjeux de la prévention en matière de santé,* 2012. http://www.lecese.fr/travaux-publies/les-enjeux-de-la-prevention-en-matiere-de-sante

IV. A NEW STEP TOWARD CHANGING THE PREVENTION PARADIGM

IV.1. UNCERTAIN IMPACT ON BEHAVIOR: THE RISKS OF DISINHIBITION AND RISK COMPENSATION

The possible introduction of a new method offering a certain level of risk protection legitimately leads us to consider the impact it may have on the use of other existing prevention methods and on the risk-taking behavior of potential users. In the case of HIV prevention, the possible future use of PrEP has already raised questions[75] in the field of science and amongst community-based organizations, leading on from the already very heated debate concerning the promotion of the preventive effect of treatment for infected persons (TasP).

As demonstrated above, clinical trials have proven the efficacy of PrEP when combined with the intensive promotion of conventional protection methods, particularly condoms. Modeling, however, shows that in terms of collective impact, the benefits of developing PrEP are likely to be reduced, cancelled out and even counterproductive when we hypothesize that PrEP may induce, to varying degrees, behavioral disinhibition and risk compensation. However, it is difficult to predict the occurrence of such phenomena and their potential scale. Placebo-controlled clinical trials cannot, due to their inherent nature, document any behavioral changes due to PrEP use.

Disinhibition and risk compensation effects that could be caused by PrEP once they have been approved and made available in 'real-life', are therefore unknown and subsequent observation is the only way of fully resolving the issue. Nevertheless, some theories and analyses regarding disinhibition and risk compensation can be presented. Whilst they may not provide unequivocal answers, they do clarify some of the key factors and mechanisms.

CONCERNS THAT PREP MAY HAVE A COUNTERPRODUCTIVE EFFECT ON SEXUAL AND PREVENTIVE BEHAVIOR

The concepts of disinhibition and risk compensation are frequently used in the literature to describe situations in which individuals, once they feel protected from a health risk, engage in other high risk behaviors which make them vulnerable again to the initial risk or another health risk. Both terms define the same set of behaviors in a complementary fashion. Disinhibition is a concept taken from psychology and describes an individual who stops to take steps to protect themselves or others from risk. In practice, they reduce their level of vigilance and stop taking precautionary measures. Risk compensation is a more cognitive concept that designates risk adjustment mechanisms. Action taken to prevent a given risk is used to justify taking new and different risks.[76]

In this case, both concepts encompass the idea that individuals who feel protected by PrEP (or TasP) may have an altered perception of risk, and feel they can:

- Increase their number of partners.
- Choose behaviors more likely to result in transmission (e.g. penetration vs. fellatio).
- Stop using condoms or at least increase the frequency of unprotected sexual practices.

Concerns expressed on this issue by a certain number of researchers and prevention stakeholders are based on the self-evident observation that using conventional protection methods – i.e. condoms - is seen by many as a constraint and that a given individual's prevention practices are the result of them balancing out the associated costs and benefits[77]. Why would people not take advantage of a method seen as means of removing constraints, simplifying their protection and giving free rein to indulge in unsafe sexual practices? Taking this rationale one step further, it could be said that methods such as TasP and PrEP would catalyze previously observed trends towards the abandonment of prevention practices and thereby undermine the fragile achievements of conventional prevention methods based on the exclusive and systematic use of condoms.

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[75] See, amongst other references, Leibowitz, A.A., *et al.*, "A US Policy Perspective on Oral Preexposure Prophylaxix for HIV", *American Journal of Public Health*, vol. 101 (6), juin 2011, pp. 982-985; Myers, G.M., Mayer, K.H., "Oral Preexposure Prophylaxis for High-Risk U.S. Populations: Current Consideration in Light of New Findings", *AIDS Patient Care and STDs*, 2011, *op. cit.*; Nguyen, V.-K., Bajos, N., *et al.*, "Remedicalizing an epidemic: from HIV treatment as prevention to HIV treatment is prevention", *AIDS*, vol. 25 January 2011, pp. 291-293; Gregson, S., Garnett, G.P., "Antiretroviral treatment is a behavioural intervention: but why?", *AIDS*, vol. 24 November 2010, pp. 2739-2740; Giami, A., *La prevention bio-médicale est une prévention comportementale*, vih.org, 13 October 2010, http://www.vih.org/reseau/alain-giami; TRT-5 umbrella organisation, *Projet d'essai de traitement antiretroviral en prophylaxie pré-exposition chez des homosexuels masculins : rapport de consultation communautaire*, 2010, http://www.trt-5.org/IMG/pdf/TRT-5_-_Rapport_Consultation_communautaire_PrEP_FINAL_.pdf

[76] Hogben, M., Liddon, N., "Disinhibition and Risk Compensation", *Sexually Transmitted Diseases*, vol. 35 (12), December 2008, pp. 1009-1010.

[77] With regard to the concept of 'balancing risk', see Eaton, L.A., Kalichman, S.C., "Risk compensation in HIV prevention: Implications for vaccines, microbicides, and other biomedical HIV prevention technologies", *Current HIV/AIDS Reports*, vol. 4 (4), December 2007, pp. 165-172, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2937204/pdf/nihms230735.pdf, and Adam, P.G.C., *et al.*, "Balancing risk and pleasure: sexual self-control as a moderator of the influence of sexual desires on sexual risk-taking in men who have sex with men", *Sexually Transmitted Infections*, vol. 84, November 2008, pp. 463-467

HOWEVER, IT IS UNLIKELY THAT THIS NEW METHOD WILL HAVE A MAJOR IMPACT ON BEHAVIOR

The hypothesis of a widespread negative impact on behavior caused by the introduction of new TasP and/or PrEP prevention methods has not to date been corroborated by the research. In particular, it should be noted that:

- An increase in at-risk behavior has been observed and widely documented over many years, notably in the gay community, or at least in certain subgroups. However, this very progressive phenomenon has not been caused by a shift in the prevention paradigm. It actually started with the development of effective treatments in the late 1990s, suggesting that there was a change in risk perception caused by an overall change in perceptions of the disease and the seriousness of its consequences.[78]
- The extensive literature (of which it is impossible to present a detailed review here) describes the development and analyzes the multiple determinants of sexual behavior, risk taking and prevention strategies used by individuals or in the social groups to which they belong.[79] Many factors that explain increased risk taking have been brought to light, showing that there are multiple determinants of risk exposure and preventive behaviors. It has also been shown that these change for individuals depending on their circumstances and over time. [80]
- There is no available data demonstrating mass changes in behavior since the introduction of new prevention methods. For instance, the long-established option in France (1998) of using a post-exposure prophylaxis (PEP) protocol once a sexual risk has been taken is still not widely taken up. According to the small number of international studies available, PEP does not have a measurable disinhibitive effect. It has a neutral or even rather favorable effect on the sexual and preventive behaviors of those who use it.[81] Albeit in a context that is very different in many ways, male circumcision trials conducted in several African countries have not led to a large increase in at-risk behaviors nor have they significantly reduced condom use. In some cases, condom use actually increased following the operation.[82] Finally, data on the behavioral impact people's awareness of TasP (protective effect of the treatments administered to people with HIV), could be a better point of comparison as the behavioral issues raised by PrEP correspond closely to those raised by TasP. However, this cannot be accurately estimated due to the relatively recent implementation of TasP and the fact that awareness of this information remains very patchy depending on the country and group in question.
- Some research is attempting to assess attitudes towards PrEP, factors that determine the intention to use or not use the future treatment[83] and its impact on sexual behavior and on condom use, amongst high-risk MSM who may be interested in using PrEP.[84] Despite the numerous limitations, these surveys evidence widespread interest in PrEP, particularly among people engaged in the most at-risk behavior, who find it hardest to protect themselves using condoms. The study that most comprehensively explored

[78] For a summary and extensive bibliographical references about epidemiological changes and changes to at-risk behaviour since the advent of ARV therapies, see Crepaz, N., *et al.*, "Highly Active Antiretroviral Therapy and Sexual Risk Behavior: A Meta-analytic Review", *Journal of the American Medical Association*, vol. 292 (2), July 2004, pp. 224-236. For studies on behavioral changes among MSM in industrialised countries, see Jaffe, H.W., *et al.*, "The Reemerging HIV/AIDS Epidemic in Men Who Have Sex With Men", *Journal of the American Medical Association*, vol. 298 (20), November 2007, pp. 2412-2414, and Grulich, A.E., Kaldor, J.M., "Trends in HIV incidence in homosexual men in developed countries", *Sexual Health*, vol. 5 (2), June 2008, pp. 113-118; Bezemer, D., *et al.*, "A resurgent HIV-1 epidemic among men who have sex with men in the era of potent antiretroviral therapy", *AIDS*, vol. 22, 2008, pp. 1071-1077; Likatavičius, G., Devaux, I., "Augmentation du nombre de nouveaux diagnostics d'infection à VIH chez les hommes homosexuels en Europe, 2000-2007", *BEHWeb*, 2009 (2), http://www.invs.sante.fr/behweb/2009/02/pdf/a-3.pdf. For a focus on the situation in France, see Bozon, M. and Doré, V. (dir.), *Sexualité, relations et prévention chez les homosexuels masculins : Un nouveau rapport au risque*, ANRS, Paris, 2007, *op. cit.,* and Lert, F. et Pialoux, G., *Rapport de la mission RDRs : Prévention et réduction des risques dans les groupes à haut risque vis-àvis du VIH et des IST*, December 2009, http://www.anrs.fr/VIH-SIDA/Sante-publique-Sciences-sociales/Actualites/Rapport-Prevention-et-reduction-des-risques-dans-les-groupes-a-haut-risque-vis-a-vis-du-VIH-et-des-IST (19 March 2010 version).

[79] A large number of references about these different aspects are listed in the bibliography of Lert, F. et Pialoux, G., *Rapport de la mission RDRs : Prévention et réduction des risques dans les groupes à haut risque vis-àvis du VIH et des IST*, 2009, *op.cit*, pp. 208-238.

[80] CNS hearings

[81] Martin J.N., *et al.*, "Use of the postexposure prophylaxis against HIV infection following sexual exposure does not lead to increases in high-risk behavior", *AIDS*, vol. 18 March 2004 pp. 787–792; Schechter M., *et al.*, "Behavioral impact, acceptability, and HIV incidence among men with access to postexposure chemoprophylaxis for HIV", *Journal of Acquired Immune Deficiency Syndrome*, vol. 35, April 2004, pp. 519–525.

[82] Auvert B., *et al.*, " Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial", *PLoS Medicine*, vol. 2 October 2005, pp. 1112–1122; Bailey R.C., *et al.*, "Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomized controlled trial", *The Lancet*, vol. 369, n°9562, February-March 2007, pp. 643–656 ; Gray R.H., *et al.*, " Male circumcision for HIV prevention in men in Rakai, Uganda: a randomized trial", *The Lancet*, vol. 369, n°9562, February-March 2007, pp. 657–666.

[83] Eisingerich, A.B., *et al.*, "Attitudes and Acceptance of Oral and Parenteral HIV Preexposure Prophylaxis among Potential User Groups: A Multinational Study", *PLoS ONE*, 2012, *op.cit.* ; Mimiaga, M.J., *et al.*, "Preexposure Antiretroviral Prophylaxis Attitudes in High-Risk Boston Area Men Who Report Having Sex With Men: Limited Knowledge and Experience but Potential for Increased Utilization After Education", *Journal of Acquired Immune Deficiency Syndrome*, vol. 50, January 2009, pp. 77-83; Liu, A.Y., *et al.*, "Limited Knowledge and Use of HIV Post- and Pre-Exposure Prophylaxis Among Gay and Bisexual Men", *Journal of Acquired Immune Deficiency Syndrome*, vol. 47, March 2008, pp. 241-247.

[84] Golub, S.A., *et al.*, "Preexposure Prophylaxis and Predicted Condom Use Among High-Risk Men Who Have Sex With Men", *Journal of Acquired Immune Deficiency Syndrome*, vol. 54, August 2010, pp. 548-555.

> the risks of changes to sexual and preventive behavior did not yield clear-cut results, predicting the absence of counter-productive effects in over 60% of potential users but nevertheless identifying a significant segment (35.5%) who might reduce condom use. However, analysis of the factors used to predict reduced condom use shows that these are people who are already finding it difficult to use condoms given their current lifestyles. The authors note that the strong interest in PrEP displayed by these people is encouraging in the sense that they see PrEP as being a possible solution to these difficulties. However, the identification of a substitution risk highlights the need to incorporate PrEP into a comprehensive prevention approach and to combine tailored behavioral and psychosocial support with PrEP.[85]

In light of this information, it would seem reasonable to suppose that the introduction of PrEP may constitute a pretext for some people to take fewer prevention measures. However, the new method is not the root, nor the sole, reason that certain people abandon their preventive behaviors. Indeed, it is more likely to reveal this behavior or act as the final trigger cause.

Furthermore, regarding the idea that PrEP would free individuals from the constraints of using condoms and/or would allow them greater sexual freedom, the restrictions for using PrEP should not be underestimated. PrEP involves different but nevertheless significant constraints: compliance and forward-planning, the complexity of initial (screening and medical prescription) and continued access (regular biological testing and screening for prescription renewals), and the potentially high financial cost.

More fundamentally, the view that PrEP is in direct competition with condoms is overly simplistic. Indeed, PrEP is intended to form part of an overall prevention approach. It is a complex and demanding method which requires the individual to be more actively involved in the prevention approach rather than abandoning their preventive practices. Using PrEP involves going through compulsory phases. The positive impact of these phases on prevention behaviors has been proved: screening, counseling, knowledge and know-how acquisition, repeated contact with a prevention structure and/or at least with the prescribing physician.

PrEP seems poorly suited to those solely seeking to reduce their own contribution to prevention efforts to ensure their protection. Instead it is aimed at people who fundamentally want to protect themselves, but are aware of the difficulties of systematically using and maintaining conventional prevention methods in the long term. PrEP can therefore constitute one element of their prevention strategies, used as a last resort or as an opportunity to step up their level of protection. PrEP can be used as a safety net to protect against occasional or regular conventional prevention "accidents". Its use would make these situations less frightening and objectively safer for the individuals involved when compared to the absence of any kind of protection. Others may develop a form of use built on their desire to release themselves, under certain circumstances, from the constraints of conventional prevention. PrEP is then a means of reducing the risk when changing practices and is a way of managing rather than abandoning prevention efforts.

RELYING ON PEOPLE'S ABILITY TO USE APPROPRIATE PREVENTION METHODS ACCORDING TO THEIR PRACTICES, DESIRES AND CONSTRAINTS

This information collected on the potential impact of PrEP on sexual and preventive behavior, calls for prudence but not inaction.

Certain negative effects of disinhibition and risk compensation, whilst not directly caused by the new method may at least be encouraged or accelerated by its introduction. This possibility of such effects cannot be ruled out nor assessed or quantified in advance. Nevertheless, certain elements suggest that PrEP alone would have a limited impact in comparison with the wide range of factors that influence preventive behaviors. Conversely, the new method clearly has the potential to be adopted and used by individuals in the target groups to increase the individual and collective level of protection. Admittedly, it is impossible to anticipate and quantitatively or qualitatively determine how potential target groups will actually use PrEP. However, the success of risk reduction strategies in other areas, such as those promoting risk reduction tools amongst injection drug users[86], shows people's capacity to adopt available prevention methods as long as they are compatible with their practices or constraints.

There are some purely hypothetical concerns that PrEP may have an overwhelmingly negative impact on preventive behaviors. These should not however limit the provision of a method that may well offer some high risk individuals or groups who have difficulties with conventional prevention methods an adapted means of reducing the risks to which they are exposed. It is possible to count on people's ability to adopt and develop the reasoned use of PrEP, adjusted to their personal prevention challenges, as long as they benefit from a full package of prevention services

[85] *Ibid.*, p. 552.

[86] Promotion of clean injection techniques, stopping sharing of needles and paraphernalia, over-the-counter sale or free supply of needles or Steribox injection kits and development of schemes offering access to opioid replacement therapies.

and they are given the means to find out about the advantages and limitations of PrEP, and of the other methods available.

IV.2. THE NEED TO GO BEYOND THE ISSUE OF MEDICALIZATION AND PROMOTE A COMPREHENSIVE APPROACH

Both PrEP and "treatment as prevention" for infected people may be seen as 'prevention on prescription', which is a cause for concern for some prevention stakeholders. These new tools give the physician a key role in terms of access to prevention (on prescription) and use (monitoring). This constitutes a significant change from conventional prevention strategies based on condom use.

Screening, however, is an established means of prevention that already makes use of a medicalized system. Experience in this area and analysis of the obstacles to screening have demonstrated the importance of diversifying services in order to reach out to different groups, in particular those most at risk. The development of complementary screening services outside of traditional healthcare system settings, such as not-for-profit community schemes and 'outreach' screening initiatives run by some "CDAG" (free and anonymous screening centers) demonstrate the benefit of offering screening in an environment which incorporates the lifestyles, settings and the cultural or sexual, social or leisure practices of the target public.

However, using ARV-based prevention, as per current PrEP trials, does require a more medicalized approach. The involvement of a physician capable of developing a long-term relationship with the patient is crucial and means that people wanting to use this method must agree to being examined by a doctor and talking about the intimate subject of their sexual behavior, which they may feel compromises their autonomy. This relationship with a 'medical third party' is necessary but cannot be neutral. Although it is not necessarily imbalanced, conflictual or unilateral, it does confront the individual's intimate requirements and laymen's knowledge with the doctor's medical expertise and instructions. The medical mediation of this prevention method may have a negative impact if the user feels that they are being dispossessed or alternatively sees it as the opportunity to abdicate their responsibilities and give up their independence and control over their own protection.

GIVING THOSE REQUESTING PREP THE MEANS TO MAKE AN INFORMED DECISION

In the case of PrEP, the concern that the use of treatments for prevention purposes may lead to doctors 'taking control' of the prevention and exposing patients to forms of medical interventionism appears unfounded. Unlike a patient with HIV in a TasP setting, the potential PrEP user is and remains a 'healthy' person and does not 'depend' on the doctor or the treatment in the same way as an infected person. Furthermore, the only risk involved is the patient's risk of acquiring HIV, there is no risk for other people. The risk of the doctor pressurizing the patient is therefore low, as treatment is initiated at the patient's request. If they feel that the doctor is too intrusive, judgmental or prescriptive with regard to his or her sexual behavior, they can withdraw their request or change doctor.

Nevertheless, when discussing a PrEP request, there is a need for a proper dialogue and real transparency:

- In the medical information provided on the objective compliance and monitoring requirements, possible inconveniences and potential health risks resulting from the treatment. This comprehensive information is needed to allow the potential user to make an informed choice and to ensure adherence with the protocol.
- Dialogue and transparency are also vital when conducting the risk-benefit analysis. This requires a comprehensive approach to individual sexual risks and prevention issues which goes beyond the medical approach in the strictest sense of the term and requires in-depth discussion of the person's sexuality and practices, the risks to which they are exposed or they take and the steps they take or don't take to protect themselves, in order to establish what PrEP can offer them in this context. Rather than an information session on the advantages and drawbacks of PrEP, people considering using PrEP should be offered a real "prevention consultation".

The multiple dimensions that need to be taken into consideration when dealing with a request for PrEP demonstrate the limitations of a purely medical approach. Some doctors thanks to their natural disposition, commitment or specialization may already have or can develop the special skills and dedication needed to offer a more comprehensive approach. However this cannot legitimately be expected of all doctors nor constitute standard practice. It is therefore advantageous for both doctors and potential users to involve other resources and partners who can work in partnership with the doctor in order to offer a comprehensive package of prevention services.

GIVING THOSE REQUESTING PREP THE MEANS TO MAKE REASONED AND CONTROLLED USE OF THE TREATMENT

Ensuring that PrEP provision takes into account more than just the medical and technical aspects is also the key to making sure PrEP is not pigeonholed as a 'separate' prevention method, in competition with, or a possible replacement for, conventional prevention.[87] Partly due to the aforementioned disinhibition and risk compensation issues, it is vital that PrEP services are not limited to the simple prescription of drugs. In this case it could be seen by potential users as a 'magic pill' allowing them to relinquish their responsibilities, no longer take precautions regarding their sexual practices and preventive strategies, and rely entirely on the promise of a purely technological solution, using science and medicine as a pretext for surrendering their autonomy.

In a medium to long-term, if PrEP are provided outside a research setting, i.e. once the supplemental New Drug Application (sNDA) allows certain ARV to be used as PrEP, it is crucial that PrEP prescription forms part of a comprehensive prevention package. This package should be constituted after carefully listening to and dialoguing with the individual to ensure it meets their prevention requirements and allows them to use the treatment option in conjunction with other available prevention methods, thus optimizing their protection. However, relying on potential users' own intelligence and ability to use the methods provided requires resources if it is to be truly effective. This means the quality of the PrEP package offered is a key factor in determining its actual effectiveness.

Firstly, incorporating the use of ARV for PrEP into a comprehensive prevention approach means a clear distinction must be made between the preventive and therapeutic use of ARV. This means the drugs should presented differently according to the intended purpose, even if the same drug is used for both purposes. Therefore, a specific brand name, packaging and patient information leaflet should be created for the preventive indication. The patient information leaflet for the preventive version should include clear information about other prevention methods, in particular condoms, to be used in combination with PrEP. The suggestion of making preventive ARV therapies available as part of a prevention kit that also includes condoms, is worth considering.

Secondly, and most importantly, it is vital to ensure the package of prevention services remains truly comprehensive. The necessary medicalized access to PrEP should not lead to approaches being segmented and access to services compartmentalized, with the existing range of conventional prevention services and methods on the one hand, and the separate and unconnected development of a medicalized PrEP service, on the other.

BUILDING ON PILOT PROJECTS INTEGRATING PREP INTO THE COMPREHENSIVE PREVENTION APPROACH

Combining different approaches to create a comprehensive prevention package which includes these new medicalized tools, requires a close collaboration between medical structures and the non-medical prevention stakeholders. It is therefore important that the doctors – including general practitioners – and/or medicalized structures (CDAG – Free and Anonymous Screening Centers, CIDDIST – STI screening, diagnosis and information centers, health centers and hospital departments) working specifically with at-risk populations, develop and strengthen partnerships with NPOs with close working or cultural ties to communities and patients. These associations are more likely to be effective in providing information and counseling services and are better placed to address private matters. Conversely, it is also important that the highly diverse structures and associations involved in providing HIV and STI information and prevention services (both prevention associations or associations that do prevention work as part of their wider social remit) take on board these new issues and prevention tools, including screening, TasP and PrEP. They must also be capable of advising, acting as intermediaries for and supporting their beneficiaries with regard to the medical resources needed to make these methods available.

It is currently too early to predict the precise form and role that PrEP may take in a preventive capacity and therefore too early to define practical service delivery procedures. Nevertheless, the specific and targeted nature of PrEP (which potentially only concerns those with a high risk of contracting HIV) and the challenge of incorporating PrEP prescription and monitoring into a comprehensive approach and package justify limiting PrEP delivery to prevention structures bringing together experienced HIV healthcare professionals (doctors, nurses and potentially psychologists) and sex and prevention counselors and advisors.

These different resources and skills do exist in the French prevention system but are highly fragmented. The benefits of bringing them together in order to improve coordination achieves the overarching aim of developing combination prevention and goes beyond the very limited and as yet uncertain aim of developing a PrEP program.

This objective justifies trialing and developing Sexual Health Center type structures. This sort of structure does not really exist under the current French prevention system, apart from the recent *Le 190* not-for-profit sexual health center founded in Paris in 2010 by Sida Info Service.[88] The center primarily targets the gay community but is open to all groups and offers a package of services using an approach that is personalized, non-judgmental and tailored to

[87] Nguyen, V.-K., Bajos, N., et al., "Remedicalizing an epidemic: from HIV treatment as prevention to HIV treatment is prevention", *AIDS*, 2011, *op. cit.* ; Giami, A., *La prevention bio-médicale est une prévention comportementale*, vih.org, *op. cit.*

[88] http://www.le190.fr/

its users' lifestyles. This includes information and counseling on sex, sexual risks and prevention methods, an STI screening and treatment service, a HIV screening service and hospital referral when required, as well as monitoring and treatment for infected persons once an initial prescription has been delivered by the hospital. The constant cross-referencing between health and sex issues has enabled the center to develop special packages such as sexual check-ups adapted to the individual's sexuality and HIV status, guidance on sexuality for people who are HIV-positive, consultations for couples and/or the uninfected partner in a serodiscordant couple.

In the event of a PrEP program being developed in the long term, innovative Sexual Health Center type structures could prove to be the most appropriate delivery setting as they bring together all the technical and human resources required to meet the medical needs of PrEP as well as needs in terms of sex and prevention counseling, advice and support services all at a single location. This is favorable to a community-based approach whilst remaining open to all.

The existence of just one experimental Sexual Health Center (which furthermore is in a financially precarious situation) is insufficient given the ambition to promote a combination prevention offering – of which PrEP would only constitute a minor component – aimed at the different target groups. In addition to renewed support for the *Le 190* project, other innovative structures capable of offering a comprehensive approach to sexual health should also be piloted.

In this respect, the currently proposed reform of the public health networks dedicated respectively to HIV-screening (free and anonymous screening centers (CDAG)) and to STI screening and care (STI screening, diagnosis and information centers (CIDDIST)) should be taken into consideration. This reform, which plans to merge these structures both administratively and financially[89] should be viewed as an opportunity to rethink their remit and implement innovative experiments. Admittedly, not all of these structures have the vocation nor the human and financial resources required to become Sexual Health Centers. However, in line with the recommendations made in 2010 by the *Inspection générale des affaires sociales* (General Inspectorate of Social Affairs)[90] some of these structures, taking into account the specificities of their users' profiles, should be encouraged to voluntarily develop projects offering a more complete package of services as part of a comprehensive approach to prevention and sexual health.

In any case, it is within the framework of structures offering Sexual Health Center type services that pilot prevention projects with a PrEP component should be developed, in limited numbers in the first instance. These projects should be approved based on quality and using yet to be defined specifications which would notably set out a methodological and scientific framework for the system. This sort of pilot project could therefore be authorized in order to evaluate the system prior to the ARV in question obtaining the sNDA for use as PrEP.

IV.3. COHERENT INFORMATION ABOUT COMBINATION PREVENTION MUST BE PROVIDED

THE PREVENTION MESSAGE MUST INCORPORATE COMBINATION PREVENTION OR RISK BECOMING UNCLEAR

The prospect of introducing PrEP into the existing range of prevention measures raises fears that this will complicate and confuse prevention messages. This is a particular concern as the prevention message already struggles to include screening and the benefits of early treatment. However, this concern should also serve as a catalyst to accelerate the reconstruction of a prevention message capable of promoting combination prevention strategies, rather than encourage the use of a model that has already demonstrated its limitations.

In the early years of the epidemic the prevention message was legitimately build around a simple message strongly promoting condom use, the universal means of avoiding infection and infecting others. It has since diversified and developed both with customized messages targeting different groups (general population, young people, MSM, migrants, the communities from France's Overseas Departments), and with the progressive introduction of initiatives to promote screening. However, the initial unequivocal message continues to structure HIV prevention messages. In this sense, the prevention message now seems overly simplistic and based on out-dated perceptions of the infection and those affected, as well as being out of sync with modern-day issues and prevention and treatment methods.

Whilst there is no intention to question the promotion of condom use, which of course must be pursued, the means of promotion and its objectives must continue to evolve and create a message with greater emphasis on the links between prevention methods, the benefits of screening and the benefits of treatment. The general public's overall perception of prevention issues and methods needs to move in this direction, both to ensure that new screening objectives are met, and more widely to change how people view HIV and people living with the virus. Establishing

[89] Art. 33 of the white paper on simplifying the regulations applicable to local authorities, number 779, presented by the senator Eric Doligé and filed with the Office of the President of the Senate on 4 August 2011.

[90] *Evaluation de la mise en œuvre de la recentralisation de la lutte contre les infections sexuellement transmissibles (IST). Rapport.* Inspection générale des affaires sociales, August 2010. *(non-public report).* The French *Inspection générale des affaires sociales (IGAS)* is the inter-ministerial audit and evaluation office for social and health, employment and labour policies. Its role is to assist public stakeholders to make informed decisions. See: http://www.igas.gouv.fr/spip.php?article164

this new conceptual framework is also vital in a context in which the development of new dedicated tools requires more complex and personalized prevention strategies. While some of these methods, such as PrEP, are not aimed at the general population but target specific groups, it is important that targeted promotion of these approaches does not become an alternative prevention message that competes with or contradicts the general prevention message.

THE URGENT NEED TO REDEFINE THE PREVENTION MESSAGE TO LINK SCREENING, PREVENTION AND TREATMENT

Efforts made over the past few years to promote screening, notably via a number of campaigns aimed at the general public, need to be extended and further developed. The aim is to make it clear that it is beneficial to everyone to be aware of and regularly monitor their HIV status in order to be able to adjust prevention methods in response to the risks posed by the HIV/AIDS epidemic. These risks include that of becoming infected but also the risk of developing the disease and complications if it is not diagnosed early enough, and the risk of transmitting the virus.

This notably involves placing appropriate emphasis on providing information on the interest and benefits of early access to treatment via early screening. This provision is currently wholly inadequate. There is a need to widely inform the public about the tangible improvements to modern-day treatments in order to change the negative image of the first generations of treatments and, more profoundly to change and de-dramatize the idea people have of living with HIV and/or living with infected persons. People need to be made aware that early treatment can give the person with HIV a life expectancy comparable to that of uninfected persons and allow them to live an almost normal life. They also need to be told that a person receiving effective treatment has a very reduced risk of transmitting the virus. Changing the message in this way could help to change society's perception of people with HIV, which has not really evolved over time.

The prevention message and the means of communication used to promote it must therefore seek to effect two major changes. Firstly, the aim is to switch from messages that primarily focus on the use of a specific prevention tool (condoms, screening) to messages that promote the range and complementary nature of methods offering different conditions of use, aims and strategies according to people's life circumstances[91]. Secondly and as a result of this, the aim is to move from general, prescriptive messages to messages that encourage individuals to consider which approaches, uses and strategies are right for them, i.e. which are feasible and adapted to their specific situation, constraints, desires and practices. This sort of communications drive would aim to give individuals the information they need to develop their own prevention strategy and to make their own decisions. More complex than universal, unequivocal prescriptive messages, this type of message focuses on reinforcing individuals' ability to exercise their freedom and responsibility. By doing so, it would help to create a favorable context for intelligibly and coherently linking the different levels of the prevention message, ranging from messages targeting the general population to more targeted messages, and for encouraging the reasoned use of new prevention methods, including the most sophisticated, by the groups to which they are best suited.

[91] For example, a 2008 TV campaign tackled head on the issue of couples wanting to stop using condoms and how to get screened in order to ensure that both partners were safe. http://www.inpes.sante.fr/70000/cp/08/cp080617.asp

GUIDELINES FOR USE OF PREP IN FRANCE

The French National AIDS Council is keenly aware of the diversity and importance of the challenges that the hypothetical implementation of a new prevention method raises at this very preliminary stage in the knowledge acquisition process. However, in light of the potential benefits PrEP offers in terms of improving prevention performance and given the promising initial clinical research results, we believe that **the framework and terms for the potential implementation of antiretroviral treatments as PrEP should be defined so as to meet all the following requirements:**

- **The PrEP program should form part of a comprehensive approach and package** that combines prevention, screening and treatment so PrEP can be integrated into the existing range of prevention methods to complement the other methods available. This means that the prevention message will need to be redesigned according to the situations and target groups in question;
- **The use of ARV for PrEP as part of a combination prevention strategy needs to be clearly distinguished by delivering the drugs used under a different brand name and packaging,** with a patient information leaflet indicating that it is a preventive treatment. Packaging that includes condoms should be promoted;
- **The structures delivering PrEP need to provide a comprehensive package of services combining prevention, screening, access to medical care, information, counseling and psychosocial support.** It is important that people who are likely to include PrEP in their prevention strategies make an informed decision. Adherence to the PrEP protocol must be based as far as possible on an understanding of the benefits, limitations and constraints of the method and on the individual analyzing of the circumstances in which they expose themselves and/or are exposed to risk and how they can use different prevention methods, including PrEP, according to these circumstances;
- **The impact of the new prevention method needs to be evaluated from a medical and public health perspective** (pharmacovigilance and virological and epidemiological monitoring), and from a **behavioral and social perspective** (sociodemographic characteristics of users, changes in behavior in response to risk, screening practices and use of other prevention methods, observation of how users use PrEP in reality).

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