



ORIGINAL ARTICLE

The impact of PrEP: results from a multicenter Health Technology Assessment into the Italian setting

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Keywords

Pre-exposure prophylaxis • HTA • Economic sustainability • Organizational impact • PrEP

Summary

Introduction. *The use of oral tenofovir/emtricitabine (FTC/TDF) for pre-exposure prophylaxis (PrEP) among high-risk people without Human Immunodeficiency Virus (HIV), is emerging as an innovative strategy to decrease HIV epidemic. The study aims at evaluating the implications related to PrEP introduction, from a multidimensional point of view, as required by Health Technology Assessment (HTA) approach, with a particular attention on sustainability and social factors, influencing PrEP implementation.*

Methods. *An analysis was conducted involving 35 Italian Infectious Disease Departments. The introduction of PrEP (applied both as “add-on” and “substitute” prevention strategy) into the clinical practice was compared with a baseline scenario, consisting of condoms among men who have sex with men, and serodiscordant couples, and the use of Needle Syringe Programme among injection drugs users. The above scenarios were analysed by means of a Health Technology Assessment (HTA) approach. The 9 EUnetHTA Core Model domains were assessed through comparative information, retrieved from literature evidence, and collection of qualitative and quantitative information, derived from real-world evidence, in particular from 35 Infectious Disease Departments and potential PrEP users involved. A final multi-criteria decision analysis approach (MCDA) was imple-*

mented to simulate the appraisal phase and providing evidence-based information with regard to the preferable technology.

Results. *Despite the improvement in patients' quality of life, PrEP would generate the development of other sexually transmitted and blood-borne diseases, with a consequent decrease of patients' safety in case of PrEP applied as a “substitute” prevention strategy. In addition, PrEP would generate an increase in staff workflow, with investment in medical supplies and training courses. PrEP would lead to significant economic investments both for the NHS (+40%), and for citizens (+2,377%) if used as an add-on strategy, assuming FTC/TDF patent cost. With the off-patent drug, the NHS would benefit from an advantage (37%), and a shrink of the patients' expenditure emerged (+682%). More economic resources are required if PrEP is applied as a substitute strategy, considering both the patent (NHS: 212%; citizens: 3,423%) and the off-patent drug (NHS: 73%; citizens: 1,077%).* **Conclusions.** *The most cost-containing strategy would be the use of PrEP, as an add-on strategy, with a consequent improvement in patients' safety, even if drug-related adverse events would be considered. The implementation of the off-patent drug would decrease the economic burden of the innovative prevention strategy. Hence, the organizational aspects related to its adoption would be deeply investigated, with the potential opportunity to create specific ambulatories devoted to PrEP users' especially for medium and big size hospitals.*

Introduction

The success achieved in the past few years in the HIV infection treatment has not been paralleled by remarkable improvements in the effectiveness of HIV prevention strategies [1, 2]. More than 1.8 million new HIV-1 infections were reported in 2017 worldwide, and an incidence rate equal to 5.7 new cases per 100,000 residents emerged in Italy [2].

As result, innovative and potent prevention strategies were required to reduce the risk of viral transmission from infected persons to healthy individuals, given the poor adherence to the traditional prevention strategy, as condoms and needle-syringe programs (NSPs). In the

last few years, the use of oral tenofovir/emtricitabine (FTC/TDF), for pre-exposure prophylaxis (PrEP) among high-risk persons without HIV, has emerged as an innovative strategy to decrease HIV epidemic.

PrEP was approved by the Food and Drug Administration in 2012, and the US Centers for Disease Control and Prevention (CDC) released clinical guidelines on its use in 2014, on the basis of the drugs' clinical effectiveness [3-6], thus recommending the use of PrEP, in addition to condoms and NSPs, for HIV negative individuals, with the following characteristics [7]: 1) serodiscordant sexual relationship; 2) anyone who is not in a monogamous relationship with an HIV negative person; 3) men who have sex with other men; 4) sexual risk in general,

including individuals who have had sex without using a condom; and 5) injection drug users. In 2016, also the European Medicines Agency (EMA) approved the use of the oral TDF/FTC for PrEP in adults at high-risk for contracting HIV infection, and guidelines were issued recommending that oral PrEP should be offered as an additional prevention choice, for people at substantial risk of HIV infection, as part of combination prevention approaches. EDCD's annual survey [8] revealed that by 2019, 14 of 53 reporting countries declared that their national healthcare service provided reimbursed PrEP (Belgium, Bosnia and Herzegovina, Croatia, Denmark, France, Germany, Iceland, Luxembourg, Moldova, the Netherlands, Norway, Portugal, Sweden, and Northern Ireland and Scotland within the United Kingdom - UK), either through insurance or from the public sector. The results show that progress has been made since 2016, when only France reported that PrEP was nationally available and reimbursed [9]. Despite the different behaviors of European Countries, the Italian provisions of PrEP remains limited, since, in the Italian setting, PrEP (as preventive strategy for high-risk people) is available only if totally paid by citizens.

Based on the above suggestions, while there have been a significant number of studies reporting the high potential efficacy of PrEP [3-6], its implementation is strictly related to significant economic and organizational concerns, as well as to the different behaviours and adherence of high-risk populations. Besides the high PrEP cost, there emerged an organizational difficulty to guarantee an adequate hospital pathway to the HIV negative individuals assuming PrEP [10], since specialist visits, cultural blood tests and treatment of other sexually transmitted diseases [11], could be ensured to the PrEP treated population, in particular, for whom not using condoms or NSPs. Furthermore, the ethical aspects related to the medicalization of a healthy person become an urgent pattern, in Countries characterized by limited economic resources, since the use of Highly Active Antiretroviral Therapy (HAART) is related to several monitoring activities for drugs toxicities [12].

Despite the relevance of the topic, no evidence has emerged with regard to the potential impacts associated to the introduction of PrEP in the Italian clinical practice. Thus, the aim of the present study was a multi-dimensional evaluation of PrEP adoption in Italy (as an "add-on" or a "substitute" prevention strategy), compared with the traditional HIV prevention strategies, in order to protect high-risk HIV-negative individuals, useful to support evidence-based decision-making processes, taking into consideration the individual's and the National Healthcare Service (NHS) perspectives.

Methods

An analysis was conducted involving 35 Italian Infectious Disease Departments in Italy, including 15 Italian Regions, in order to achieve a complete national landscape of the centers devoted to the enrollment

and treatment of these patients, in terms of regional distribution, centers dimensions and private/public ownerships.

A letter for participation to the study was sent via-mail to the Italian Infectious Disease clinicians, in order to gather information with regard to the number of potentially PrEP users, as well as to retrieve their perceptions with regard to the introduction of such preventive strategy. Thus, the introduction of PrEP (prescribed as an "add-on" or a "substitute" prevention strategy) into the clinical practice, was compared with a baseline scenario consisting of the use of condoms among men who have sex with other men (MSM), and serodiscordant couples (SCs), and the use of NSPs among injection drugs users (IDUs), thus being consistent with the guidelines available on the topic. The above scenarios were analysed by means of a Health Technology Assessment (HTA) approach, in order to cover all the domains required by the EUnetHTA Core Model according to real-life qualitative and quantitative information.

Since no sensitive and human data were collected, both the ethics approval and the compliance with the STROBE guidelines for reporting observational studies, were not applicable.

Because of the multi-dimensional nature of HTA [13], the present analysis considered several aspects of the medical technologies under evaluation, in accordance with the EUnetHTA Core Model [14]. Thus, the assessment of the EUnetHTA Core Model domains, was completed by a prioritisation phase, and a final multi-criteria decision analysis – MCDA [15-17], simulating the appraisal phase.

ASSESSMENT OF EUNETHTA CORE MODEL DOMAINS

Due to the multi-dimensional and multi-disciplinary nature of HTA, several aspects of the preventive approaches taken into account (PrEP and other alternatives, in add-on or not), were analyzed as suggested by literature [14]: i) health problem and current use of technology; ii) description and technical use of technology; iii) safety; iv) clinical effectiveness; v) costs and economic evaluation; vi) ethical analysis, in terms of access to care; vii) organizational aspects; viii) social aspects and ix) legal aspects.

The above domains were deployed, considering scientific evidence, economic evaluations (quantitative information) and qualitative approaches (expert opinion and potential PrEP's users perceptions).

LITERATURE REVIEW

With regard to the systematically searching medical literature, the PICO (Population, Intervention, Comparator and Outcome) was defined as follows: P – High-risk persons without HIV; I – FTC/TDF for pre-exposure prophylaxis; C – use of condoms among MSM and SCs, and use of NSPs among IDUs, to prevent HIV infection; O: HIV occurrence rate adverse events and sexually transmitted disease (STDs) incidence rate.

Literature evidence came from the systematic search of literature databases (Pubmed, Embase and Cochrane Library). The search terms were the followings: “pre-exposure prophylaxis”, “high-risk individuals”, “clinical effectiveness”, “HIV occurrence rate”, “drug-related adverse events”, “STDs”, “men who have sex with men - MSM”, “serodiscordant couples - SCs”, “injection drug users - IDU”.

Peer-reviewed papers that explicitly described the clinical effectiveness of the different preventive strategies under assessment, were consequently included, and synthesized according to a PRISMA flow diagram, thus mapping out the number of records (in terms of papers) identified, included and/or excluded, and the reasons for exclusion motivated [18].

The validation of the scientific evidence available on the topic, was performed through the ROBINS II Cochrane risk of bias tool [19], and the AMSTAR-Assessing the Methodological Quality of Systematic Reviews checklist, on the basis of the nature of the study included. Literature was used for highlighting efficacy profile in terms of HIV occurrence rate with or without PrEP, and safety profile (measured as drug-related adverse events rate). Since only primary evidence have been considered, the literature review proposed in the present paper, collected high-quality efficacy and safety information.

ECONOMIC EVALUATION

For the economic evaluation, both a process mapping technique [21] and a budget impact analysis [22] were conducted, comparing the clinical pathway costs of a PrEP user *versus* the ones related to an individual not using PrEP. Information was gathered according to the standard clinical pathway performed in the 35 Italian Infectious Diseases Departments involved in the study, by means of a Delphi approach [23], consistent with International and National HIV Guidelines, and Regional Clinical Pathways.

The following determinants of costs were deeply considered: i) cost of the prevention strategies; ii) cost of the drug-related adverse events; iii) cost of the other sexually transmitted infections; and iv) cost of the medical monitoring of PrEP users.

The pathways were valorized considering the reimbursement tariffs of the Italian NHS valid for the year 2018/2019 and assumed a 12-month time horizon. On the one hand, the cost supported by the NHS for the proper cure and follow-up of PrEP users, considered the following cost drivers, representing all the healthcare direct costs: specialist visits, diagnostic procedures, hematological exams, hospitalizations and drugs, all in terms of typology and quantity of healthcare services administered to the potential PrEP user. On the other hand, the cost supported by the PrEP users for the disease management, was calculated in terms of “out of pocket” healthcare expenditure, productivity loss (time spent in hospital valorized on the basis of the PrEP users average monthly gross salary), as well as the average transport costs (estimated according to the Italian Automotive Club - ACI tables price list), to reach the Infectious Disease

Department for outpatient procedures. It should be noted here that on the one hand, the average monthly gross salary derived from the most recent JP Salary Outlook for Italy [24], approaching with the Human Capital Method [25, 26] on the other hand, the average transport cost was calculated according to the average distance spent by the patient to reach the hospital of reference, that in the Italian setting is equal to 55.8 km [27].

After evaluating the management cost of the high-risk individuals, stratified by prevention technology, and including both the costs for the management of sexually transmitted infection and adverse events, a Budget Impact Analysis was developed considering a scenario in which PrEP is totally reimbursed by the NHS, and a scenario in which the drug, is directly purchased by the citizens (as happened in the Italian setting).

As mentioned before, all the economic analyses assumed both the NHS and the patient’s perspectives (in terms of “out-of-pocket expenditure” supported for the management and care of their clinical conditions), considering both branded and off-patent drugs costs (considering a 70% reduction in drug costs).

DOMAINS INVESTIGATED THROUGH QUALITATIVE APPROACHES

Qualitative questionnaires were administered to 35 clinicians referring to the 35 Infectious Diseases Departments involved in the study, who completed the questionnaire according to their own experience and perceptions.

The qualitative questionnaires were used for examining ethical, legal and organizational aspects, considering a comparative approach (use of PrEP as add on strategy *vs* not-use of PrEP in prevention activities), in accordance with a validated 7-item Likert scale ranging from -3 to +3 [28]. According to the above, the scenario consisting of the PrEP absence is always represented as a neutral situation, corresponding to zero value, and the perceptions related to the different domains, in case of PrEP adoption, were studied, with a comparative and incremental or decremental approach (the items studied are presented in Tab. I) It should be noted that all the items used for the deployment of each qualitative domain derived from the EUnetHTA Core Model issues [14], and were, then characterized and integrated, considering the specific topic of investigation.

The analysis of the social domain was conducted considering both the 35 clinicians and the potential PrEP users’ perceptions. For this last part of the sample, an online questionnaire, administered, using a Survey Monkey tool, was completed by a sexually high-risk population, representing potential PrEP users. In particular, the on-line questionnaire was sent to two different citizens’ association, where people voluntarily decided to complete the questionnaire. Data were collected anonymously, in accordance with the EU Regulation n. 679 of 04.05.2016, guaranteeing privacy and legal issues. In addition to information with regard their risk factor for HIV, their PrEP knowledge, attitudes and willingness-to-pay were deeply investigated

considering a 5-item evaluation scale, ranging from a minimum of 1 (completely disagree) to a maximum of 5 (completely agree).

Detailed information regarding the specific items related to each domain is shown in Table I.

STATISTICAL METHODS

Focusing on the statistical methods, qualitative data were first analyzed, considering descriptive statistics. The existence of statistically significant differences (according to a significance level lower than 0.05 p-value) was assessed in the comparison between

i) baseline scenario and innovative scenario, with regard to the qualitative assessment of the domains; ii) MSM and heterosexuals, with regard to the online survey conducted with the involvement of potentially PrEP users in the social domain deployment. In particular, independent sample t-test for either parametric or non-parametric variables were conducted.

MULTI-CRITERIA DECISION ANALYSIS

After the assessment of all the EUnetHTA Core Model domains, a Multi-Criteria Decision Analysis (MCDA)

Tab. I. Methods used for the deployment of the EUnetHTA dimensions.

Domains	Description of the domains	Quantitative and qualitative metrics for the evaluation	Scores and their related descriptions for the application of the MCDA
Health problem and current use of the technology	Target population eligible to PrEP administration	Definition of the high-risk population, potentially eligible for PrEP, in accordance with the Italian epidemiological data available and with real-life information retrieved by the 35 Infectious Disease Departments involved. Thus, information with regard to the overall number of adult MSM, SCs and IDUs, approaching the above 35 Departments were collected	1 – Small number of potentially eligible PrEP users 2 – Moderate number of potentially eligible PrEP users 3 – Significant number of potentially eligible PrEP users
Description and technical characteristics	Definition of evidence-based information and assessment of their quality	After the definition of the PICO guiding the literature review, the paper included in the HTA were synthesized according to a PRISMA flow diagram, thus mapping out the number of records (in terms of papers) identified, included and/or excluded, and the reasons for exclusion motivated. Furthermore, the validation of the scientific evidence available on the topic, was performed through the ROBINS II Cochrane risk of bias tool, and the AMSTAR-Assessing the Methodological Quality of Systematic Reviews check-list, on the basis of the nature of the study included	1 – Poor quality of evidence-based information 2 – Medium quality of evidence-based information 3 – High quality of evidence-based information
Safety	Rate of mild, moderate and severe adverse events	Identification of the possible adverse events for PrEP users, in terms of evidence-based incidence-rate data, with regard to drug-related adverse events, and sexually transmitted/blood borne infections, derived from literature evidence available on the topic. These events were also economically evaluated, in order to analyze their economic impact, considering both NHS and patients' perspective, in accordance with the standard clinical pathways, declared by the 35 hospitals involved in the study – according to the Delphi methods, consistent with international and National HIV Guidelines, and Regional Clinical Pathways	1 – The prevention strategy presents a significant decrease in PrEP user's safety 2 – The prevention strategy presents no impact in PrEP user's safety 3 – The prevention strategy presents a significant increase in PrEP user's safety
Clinical effectiveness	Efficacy indicators	Identification of the HIV occurrence rate related to the use of the three technologies (PrEP, condoms and syringes, as single prevention strategies or as add-on strategies), based on the evidence available, and validated in the Prisma Flow Chart	1 – The prevention strategy presents a significant increase in HIV occurrence rate 2 – The prevention strategy presents no impact in HIV occurrence rate 3 – The prevention strategy presents a significant decrease in HIV occurrence rate
Costs and economic evaluation	Activity based costing analysis	Clinical pathway economic evaluation, considering individual assuming or not assuming PrEP	1 – The prevention strategy presents a substantial economic impact on the clinical pathway 2 – The prevention strategy presents an insignificant and sustainable economic impact on the clinical pathway 3 – The prevention strategy presents a favorable and low economic impact on the clinical pathway
	Budget impact analysis	The above-mentioned clinical pathway cost per PrEP user was multiplied by the total number of patients potentially eligible to PrEP thus comparing a baseline with an innovative scenario and assuming different hypotheses: 1) PrEP used as an add-on or substitute strategy; 2) PrEP totally reimbursed by the Italian NHS or paid by the citizens; 3) administration of the branded or the off-patent drug	1 – The prevention strategy presents a substantial economic impact on both the NHS and individuals healthcare budget 2 – The prevention strategy presents an insignificant and sustainable impact on both the NHS and individuals healthcare budget 3 – The prevention strategy presents a favorable economic impact on both the NHS and individuals healthcare budget
Ethical aspects	Perceived aspects related to the access to care	The 35 clinicians involved in the analysis, completed a comparative qualitative questionnaire, based on a 7-item Likert scale (ranging from -3 to +3), considering the following items: 1) Access to care on local level; 2) Access to care for persons on a legally protected status; 3) Impact of the preventive strategy on the accessibility to care related to the management of adverse events; 4) Generation of healthcare migration phenomena; 5) Impact of the preventive strategy on the patients' willingness to pay; 6) General equity; 7) Accessibility to the prevention strategy, in case of full payment by the potential PrEP's users; 8) accessibility to the prevention strategy, in case of co-payment	1 – The prevention strategy presents a decrease in the access to care for PrEP users at local level 2 – The prevention strategy presents no impact in the access to care for PrEP users at local level 3 – The prevention strategy presents an increase in the access to care for PrEP users at local level
Social aspects	Social and ethical perceived aspects: the clinicians' point of view	The 35 clinicians involved in the analysis, completed a comparative qualitative questionnaire, based on a 7-item Likert scale (ranging from -3 to +3), considering the following items: 1) Ability of the drug to protect the patients' autonomy; 2) Ability of the drug to protect the human rights; 3) Ability of the drug to protect the PrEP users' integrity; 4) Ability of the drug to protect the PrEP users' dignity; 5) Impact of the drug on the PrEP users' willingness to pay; 6) Impact of the drug on PrEP users' religion; 7) Impact of the drug on social costs; 8) Impact of the drug on the citizens' medicalization; 9) Impact of the drug on the PrEP users' satisfaction; 10) Impact of the drug on the PrEP users' perceived quality of life; 11) Impact of the drug on the PrEP users' lifestyle; 12) Impact of the drug on sexual behaviours disinhibition	1 – The prevention strategy presents a decrease in individuals reported outcomes, considering the clinicians' perspective 2 – The prevention strategy presents no impact in individuals reported outcomes, considering the clinicians' perspective 3 – The prevention strategy presents an increase in individuals reported outcomes, considering the clinicians' perspective

continues

follows

Tab. I. Methods used for the deployment of the EUnetHTA dimensions.

	<i>Social and ethical perceived aspects: the PrEP users' point of view</i>	Definition of the PrEP users' awareness and knowledge with regard its adoption into the clinical practice, by means of an online questionnaire administration, filled in by potentially PrEP users	1 – The prevention strategy presents a decrease in individuals reported outcomes, considering the potential PrEP users' perspectives 2 – The prevention strategy presents no impact in individuals reported outcomes, considering the potential PrEP users' perspectives 3 – The prevention strategy presents an increase in individuals reported outcomes, considering the potential PrEP users' perspectives
Legal aspects	<i>Legal perceived aspects</i>	The 35 clinicians involved in the analysis, completed a comparative qualitative questionnaire, based on a 7-item Likert scale (ranging from -3 to +3), considering the following items: 1) Authorization level (national/European/international); 2) Legal impact on safety issues; 3) Infringement of intellectual property rights; 4) Impact on the production warranties; 5) Need to regulate the drug acquisition and costs; 6) The legislation covers the regulation of technology, for all categories of users; 7) Impact on the not-availability of PrEP in hospitals	1 – The prevention strategy presents the need to regulate its acquisition 2 – The prevention strategy presents no need to regulate its acquisition 3 – The prevention strategy presents an improvement of the related legal concerns
Organizational aspects	<i>Organizational perceived aspects</i>	The 35 clinicians involved in the analysis completed a comparative qualitative questionnaire, using a 7-item Likert scale (ranging from -3 to +3), in accordance with the following aspects: 1) Additional staff; 2) Training courses devoted to Infectious Disease clinicians; 3) Training courses devoted to healthcare professionals; 4) Training courses devoted to potentially PrEP users; 5) Internal hospital meetings; 6) Additional rooms and services; 7) Additional furniture; 8) Impact on the internal processes; 9) Impact on the processes between the Pharmaceutical Department and the Infectious Diseases Department; 10) Impact on the number of access; 11) Impact on the number of hematological exams, specialist visits related to the administration of the drug; 12) Impact on the management of other infectious diseases, different from HIV and HBV; 13) Organisational impact on the development of complications and adverse events; 14) Organisational impact on the development of drug toxicities and resistances; 15) Impact on the taking in charge of a higher number of users	1 – The prevention strategy presents a qualitative negative impact, since it requires important organizational efforts without any advantage for the hospital 2 – The prevention strategy presents no qualitative organizational impact 3 – The prevention strategy presents a qualitative positive impact, since it requires small organizational efforts with some advantages for the hospital
	<i>Organizational quantitative aspects</i>	Definition of the organizational ceasing or incremental costs related to the prevention strategies under assessment, considering additional persons, training courses, additional equipment, spaces or rooms	1 – The prevention strategy requires important and significant organizational investments 2 – The prevention strategy requires no or small organizational investment 3 – The prevention strategy presents the possibility to free-up organizational resources

approach [17] was implemented, thus simulating the appraisal phase.

At first, the domains were prioritized by the 35 clinicians involved, using a rating scale ranging from 1 (more important dimension), to 9 (less important dimension).

Furthermore, the quality of the information retrieved for the deployment of each EUnetHTA domain was evaluated by three Medical Directors, that assigned to each sub-dimension (listed in Tab. I), a three-level mark (ranging from a minimum of 1 – less performant – to a maximum of 3 – more performant –), after having carefully read a first draft of the evidence proposed in the present manuscript, in order to fully understand the potential impacts of the PrEP introduction or not introduction. Detailed information with regard the specific score assigned to each domain are reported in Table I.

This experiment was carried out to lead to a final concise result, useful in the choice of the “preferable” technology, supporting the appraisal phase and the policy-making process.

The final score was obtained by multiplying the normalized score, calculated for each domain, with the normalized value of priority, as suggested by scientific evidence [17]; the higher the score acquired, the more preferable is the technology.

Results

ASSESSMENT OF THE DOMAINS

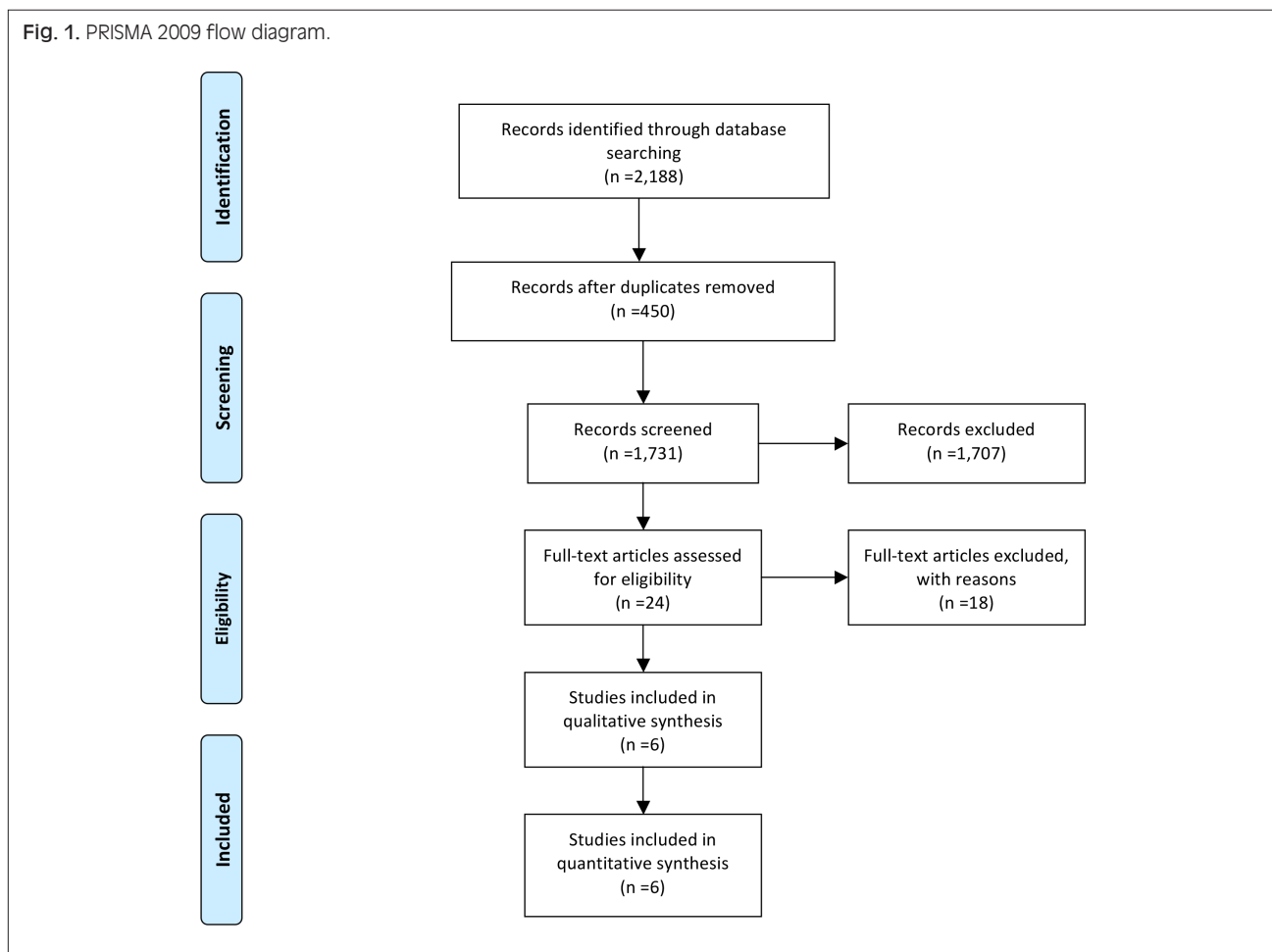
Results from literature review

Out of 2,118 papers identified through databases searching, according to the proposed PICO of the study, only six of them [3-6, 29-30] met the inclusion criteria, in accordance with the above-mentioned search strategy, focusing on the administration of PrEP for high-risk individuals as detailed in the Prisma Flow Chart for literature synthesis (Fig. 1). In particular, four of them [3-6] were RCTs investigating the effectiveness and the safety profiles within the target populations, and two of them [29, 30] were meta-analysis with regard to the effectiveness of the traditional preventive strategies. The rejected articles had different aims, without focusing the attention on efficacy/safety data, nor focusing on different populations than MSM, IDUs or SCs.

The literature review revealed the lack of scientific evidence concerning the head-to-head comparison of PrEP, as preventive strategy, used in add-on with the traditional preventive strategies (condoms or NSPs), or used alone, in particular observing the safety, and the efficacy profile of the alternatives.

Despite the above missing information, the articles included in the analysis presented quality and reliable data

Fig. 1. PRISMA 2009 flow diagram.



assessed, in accordance with the ROBINS II Cochrane risk of bias tool, the CASP checklist and the AMSTAR tool. Focusing on the RCTs included, useful for the retrieval of PrEP efficacy and safety profile, ROBINS II tool revealed that the risk of bias was not high.

All the studies were at low risk of bias since the classification of PrEP vs control was made clearly. The outcomes measurement proved to be relevant in most cases, and both positive and negative outcomes were determined and explained. According to scientific evidence [3-6], the innovative technology would lead to an increase in drug-related adverse events, whose incidence rates and economic evaluation are presented in Table II. Furthermore, since PrEP presents a protective effect only with regard to HIV infection, even if used as an add-on strategy, and considering the real-life adherence to condoms and NSPs strategies, individuals could acquire other sexually transmitted/blood borne infections [3-5], resulting in a final worst safety profile. The general population presents an HIV occurrence rate equal to 33% [2], with a consequent NHS resource absorption per patient of € 11,694.86 and an individual's "out-of-pocket" expenditure of € 751.94.

Focusing on the efficacy profile, the parameter used in the present HTA for this specific domain, was the ability of each strategy to prevent the individual from HIV infection and derived from literature evidence

available on the topic. With regard to the baseline scenario, condoms and the NSPs present an efficacy rate equal to 99% [29] and 17% [30], respectively. On the contrary, literature declares an efficacy rate of 86% for MSM [3, 4], 75% for SCs [6], and 48.9% for IDUs [5], strictly dependent from treatment adherence [31].

Results from the economic evaluation

Before conducting the economic evaluation, the number of HIV negative high-risk individuals, and, thus, individuals potentially eligible for PrEP treatment, was defined. Data derived from the number of individuals approaching the 35 Italian Infectious Disease Departments involved, for the conduction of the HIV test or for counselling were projected. Forecasting collected hospital data declared, considering the entire Italian potential population, it emerged that at least 16,577 individuals could be eligible for PrEP: 6,653 SCs, 5,943 MSM and 3,981 IDUs were considered and projected in the present economic analysis.

At first, as reported in Table II, the management cost of drug-related AEs and STDs developed by the PrEP population were considered.

Furthermore, the annual cost of each prevention strategy was accordingly investigated, assuming a 12-month time horizon and valorizing all the items of cost according to the reimbursement tariffs of the Italian NHS valid

Tab. II. Safety profile.

Drug-related adverse events: incidence and costs					
Drug-related adverse events	Men who have sex with other men [3, 4]	Serodiscordant couples [3, 4]	Injection drug users [3-5]	Cost for the NHS	Cost for citizen
Nausea	8%	8%	8%	€ 52.74	€ 22.15
Vomiting	2%	2%	5%	€ 52.74	€ 22.15
Diarrhea	4%	4%	11%	€ 1,822.21	€ 306.26
Abdominal pain	7%	7%	9%	€ 50.00	€ 21.00
Bone disease	2%	2%	2%	€ 661.44	€ 527.40
Creatinine Increase	18%	10%	7%	€ 1,474.61	€ 549.73
Headache	8%	8%	8%	€ 20.07	€ 8.43
Rash	8%	8%	8%	€ 760.13	€ 264.72
Other sexually transmitted/ blood borne infections	% PREP [3, 4]	% NO PREP [2]	Cost for the NHS	Cost for citizen	
HCV	1%	2%	€ 8,545.97	€ 950.89	
Syphilis	10%	9%	€ 117.75	€ 49.55	
Chlamydia	27%	22%	€ 76.00	€ 31.98	
Gonorrhoea	38%	37%	€ 88.67	€ 37.31	
Rectal or vaginal Infection	36%	32%	€ 267.72	€ 112.66	

for the years 2018/2019. The annual average cost (per person) of condoms was hypothesized equal to € 192.00; whereas the annual average cost (per person) of NSPs was equal to € 75.25, being consistent with literature evidence [31]. On the one hand, given an average value for each condom equal to € 1.00, the model assumed a use of this strategy four times a week [6]. On the other hand, the average cost for a clean and sterile syringe was equal to € 0.056, with on average 4 doses per day [32]. With regard to the branded drug, the model assumed a drug cost equal to € 5,339.95 and € 9,011.28 per year (per person), in case of NHS reimbursement and citizens purchased respectively. If the off-patent drug was used and introduced into the clinical practice, a cost equal to € 1,601.99 and to € 2,703.38 was hypothesized, considering the NHS and the citizen's perspective respectively.

In addition to the annual economic value of PrEP drug, its monitoring cost was evaluated. Patients should attend at least 2 specialist visits, and 2 follow-up medical controls, as well as conduct full blood test panels, with the inclusion of creatinine, phosphorus, urine, proteinuria, and tests for sexually transmitted diseases, such as HIV, HCV, HBV and syphilis. These procedures required on average € 306.40 and € 68.62 considering the NHS and the patient point of view respectively.

The following tables reported the budget impact analysis derived from the introduction of PrEP, both as an add-on, and as a substitute strategy to the traditional prevention technologies, considering branded (Tab. III) and off-patent (Tab. IV) drugs.

If PrEP is used as an "add-on" strategy, distributed and paid by the NHS, considering branded drugs, NHS investments would increase significantly (+40%),

Tab. III. Budget impact analysis, considering PrEP as an add-on strategy to condoms and NSPs.

	100% PrEP reimbursed by the Italian NHS, considering branded drugs				100% PrEP purchased by citizens, considering branded drugs			
	Italian NHS point of view				Italian NHS point of view			
	Baseline scenario	Innovative scenario	Difference	Difference %	Baseline scenario	Innovative scenario	Difference	Difference %
MSM and sexual risk	€ 47,049,798	€ 114,119,651	€ 67,069,852	143%	€ 47,049,798	€ 20,491,208	-€ 26,558,590	-56%
SCs	€ 52,670,757	€ 131,873,657	€ 79,202,900	150%	€ 52,670,757	€ 29,012,864	-€ 23,657,893	-45%
IDUs	€ 99,007,920	€ 31,559,987	-€ 67,447,933	-68%	€ 99,007,920	€ 24,948,467	-€ 74,059,453	-75%
Total high-risk population	€ 198,728,475	€ 277,553,294	€ 78,824,819	40%	€ 198,728,475	€ 74,452,539	-€ 124,275,936	-63%
	PrEP users' point of view				PrEP users' point of view			
	Baseline scenario	Innovative scenario	Difference	Difference %	Baseline scenario	Innovative scenario	Difference	Difference %
MSM and sexual risk	€ 5,183,416	€ 6,720,833	€ 1,537,416	30%	€ 5,183,416	€ 164,720,834	€ 159,537,418	3078%
SCs	€ 5,802,670	€ 7,120,791	€ 1,318,121	23%	€ 5,802,670	€ 180,700,582	€ 174,897,912	3014%
IDUs	€ 6,498,759	€ 2,778,990	-€ 3,719,769	-57%	€ 6,498,759	€ 87,616,622	€ 81,117,862	1248%
Total high-risk population	€ 17,484,846	€ 16,620,614	-€ 864,232	-5%	€ 17,484,846	€ 433,038,038	€ 415,553,192	2377%
	100% PrEP reimbursed by the Italian NHS, considering off-patent drugs				100% PrEP purchased by citizens, considering off-patent drugs			
	Italian NHS point of view				Italian NHS point of view			
	Baseline scenario	Innovative scenario	Difference	Difference %	Baseline scenario	Innovative scenario	Difference	Difference %
MSM and sexual risk	€ 47,049,798	€ 48,579,741	€ 1,529,943	3%	€ 47,049,798	€ 20,491,208	-€ 26,558,590	-56%
SCs	€ 52,670,757	€ 59,871,102	€ 7,200,345	14%	€ 52,670,757	€ 29,012,864	-€ 23,657,893	-45%
IDUs	€ 99,007,920	€ 16,772,989	-€ 82,234,931	-83%	€ 99,007,920	€ 24,948,467	-€ 74,059,453	-75%
Total high-risk population	€ 198,728,475	€ 125,223,832	-€ 73,504,643	-37%	€ 198,728,475	€ 74,452,539	-€ 124,275,936	-63%
	PrEP users' point of view				PrEP users' point of view			
	Baseline scenario	Innovative scenario	Difference	Difference %	Baseline scenario	Innovative scenario	Difference	Difference %
MSM and sexual risk	€ 5,183,416	€ 6,720,833	€ 1,537,416	30%	€ 5,183,416	€ 54,120,833	€ 48,937,417	944%
SCs	€ 5,802,670	€ 7,120,791	€ 1,318,121	23%	€ 5,802,670	€ 59,194,728	€ 53,392,058	920%
IDUs	€ 6,498,759	€ 2,778,990	-€ 3,719,769	-57%	€ 6,498,759	€ 30,040,415	€ 23,541,656	362%
Total high-risk population	€ 17,484,846	€ 16,620,614	-€ 864,232	-5%	€ 17,484,846	€ 143,355,976	€ 125,871,130	720%

Tab. IV. Budget impact analysis, considering PrEP as a substitute strategy to condoms and NSPs.

	100% PrEP reimbursed by the Italian NHS, considering branded drugs				100% PrEP purchased by citizens, considering branded drugs			
	Italian NHS point of view				Italian NHS point of view			
	Baseline scenario	Innovative scenario	Difference	Difference %	Baseline scenario	Innovative scenario	Difference	Difference %
MSM and sexual risk	€ 44,524,325	€ 126,062,875	€ 81,538,550	183%	€ 44,524,325	€ 35,401,844	-€ 9,122,482	-20%
SCs	€ 31,786,125	€ 150,349,598	€ 118,563,473	373%	€ 31,786,125	€ 52,557,382	€ 20,771,257	65%
IDUs	€ 45,636,657	€ 104,088,731	€ 58,452,074	128%	€ 45,636,657	€ 50,601,093	€ 4,964,435	11%
Total high-risk population	€ 121,947,108	€ 380,501,204	€ 258,554,096	212%	€ 121,947,108	€ 138,560,318	€ 16,613,210	14%
	PrEP users' point of view				PrEP users' point of view			
	Baseline scenario	Innovative scenario	Difference	Difference %	Baseline scenario	Innovative scenario	Difference	Difference %
MSM and sexual risk	€ 5,360,454	€ 6,149,260	€ 788,806	15%	€ 5,360,454	€ 159,141,693	€ 153,781,239	2869%
SCs	€ 3,826,853	€ 6,895,607	€ 3,068,754	80%	€ 3,826,853	€ 171,922,065	€ 168,095,212	4393%
IDUs	€ 2,995,535	€ 4,658,200	€ 1,662,665	56%	€ 2,995,535	€ 94,919,735	€ 91,924,200	3069%
Total high-risk population	€ 12,182,842	€ 17,703,066	€ 5,520,224	45%	€ 12,182,842	€ 425,983,493	€ 413,800,651	3397%
	100% PrEP reimbursed by the Italian NHS, considering off-patent drugs				100% PrEP purchased by citizens, considering off-patent drugs			
	Italian NHS point of view				Italian NHS point of view			
	Baseline scenario	Innovative scenario	Difference	Difference %	Baseline scenario	Innovative scenario	Difference	Difference %
MSM and sexual risk	€ 44,524,325	€ 62,600,238	€ 18,075,913	41%	€ 44,524,325	€ 35,401,844	-€ 9,122,482	-20%
SCs	€ 31,786,125	€ 81,895,138	€ 50,109,013	158%	€ 31,786,125	€ 52,557,382	€ 20,771,257	65%
IDUs	€ 45,636,657	€ 66,647,434	€ 21,010,777	46%	€ 45,636,657	€ 50,601,093	€ 4,964,435	11%
Total high-risk population	€ 121,947,108	€ 211,142,810	€ 89,195,703	73%	€ 121,947,108	€ 138,560,318	€ 16,613,210	14%
	PrEP users' point of view				PrEP users' point of view			
	Baseline scenario	Innovative scenario	Difference	Difference %	Baseline scenario	Innovative scenario	Difference	Difference %
MSM and sexual risk	€ 5,360,454	€ 6,149,260	€ 788,806	15%	€ 5,360,454	€ 52,046,922	€ 46,686,468	871%
SCs	€ 3,826,853	€ 6,895,607	€ 3,068,754	80%	€ 3,826,853	€ 56,403,471	€ 52,576,618	1374%
IDUs	€ 2,995,535	€ 4,658,200	€ 1,662,665	56%	€ 2,995,535	€ 31,736,620	€ 28,741,086	959%
Total high-risk population	€ 12,182,842	€ 17,703,066	€ 5,520,224	45%	€ 12,182,842	€ 140,187,013	€ 128,004,171	1051%

while NHS economic benefits (-63%) are found if PrEP is purchased by citizens (individuals' investment: +2,377%). As for off-patent drugs, the NHS would benefit from an advantage (-37%) and a shrinkage of the patients' "out-of-pocket" expenditure (+720%).

If PrEP is introduced as a "substitute" strategy, the economic burden would be higher, both for the NHS (+212%) and the citizens' (+3,397%). Even considering the off-patent drug, the NHS and patients face a relevant economic challenge, equal to +73% and +1,051% respectively.

Results from the qualitative approaches

As stated in the Method section, the qualitative assessment of the ethical, social and organisational dimensions was conducted through the involvement of 35 clinicians referring to different Italian Regions, giving a representativeness of the Italian landscape. With respect to the geographical origin, 49%, 31% and 20% of clinicians referred to north, south and islands, and centre of Italy respectively.

A synthesis of the clinicians' perceptions is reported in Table V, in terms of incremental or decremental value of PrEP (from -3 to +3), in comparison with the baseline scenario, without PrEP (always neutral, and equal to 0). While the use of traditional prevention strategies did not have an impact on the NHS accessibility, a critical impact on ethical aspects emerged in case of PrEP introduction (-0.50 vs 0.00, $p < 0.05$), in particular in case of full payment of PrEP by the potential users (-1.84 vs 0.00, $p < 0.05$), since this drug is expensive, thus limiting its accessibility to the different population categories.

However, the clinicians declared an improvement both in the PrEP users' quality of life (0.58 vs 0.00, $p < 0.05$) and in their satisfaction (1.52 vs 0.00, $p < 0.05$), even if professionals have the perception of disinhibition of

the sexual behavior of the individuals who assume PrEP (-2.20 vs 0.00, $p < 0.05$), thus being consistent with literature evidence [33-37].

From a legal point of view, investments are required to regulate the use of PrEP in hospitals (-1.21 vs 0.00, $p < 0.05$). Despite the EMA approval, in Italy the administration of this preventive strategy should be regulated and inserted in the clinical protocols.

With regard to the organizational impact, clinicians declared an increase in staff workflow (-1.62 vs 0.00, $p < 0.05$) due to the high number of HIV negative patients attending regular doctor appointments, and follow-up procedures, thus requiring additional clinicians (-1.44 vs 0.00, $p < 0.05$). The assessment of the quantitative organizational impact, assuming a 12-month time horizon, confirmed their perceptions, considering an Infectious Disease Department (taking in charge on average 745 HIV+ treatment-experienced and 32 HIV+ treatment-naïve individuals, 777 in total). There emerged the need to invest in additional working professionals, as well as to organize specific training courses devoted to individuals directly involved in the provision of PrEP to the citizens. At least 2 clinicians, 2 nurses, and 1 psychologist could be involved in the training activities, with an economic resources' absorption equal to € 1,750.00 only for the first year.

Ninety percent of the Infectious Disease Department involved in the analysis, required the creation of a new ambulatory devoted to the high-risk population potentially assuming PrEP, with a consequent additional investment in both medical supplies and equipment, for an average amount equal to € 666.26 and to € 1,158.7 respectively. At the 12-month time point of the base-case scenario for market penetration, a medium size hospital would invest on average a total amount of € 3,574.96, for organizational arrangements.

Tab. V. Clinicians' perceptions.

The clinicians' perceptions		
Ethical aspects	PREP	No PREP
Access to care on local level	0.25	0.00
Access to care for persons on a legally protected status	0.69	0.00
Impact of the preventive strategy on the accessibility to care related to the management of adverse events	-0.81	0.00
Generation of health migration phenomena	0.43	0.00
Impact of the preventive strategy on the patients' willingness to pay	-1.19	0.00
General equity	-0.44	0.00
Accessibility to the prevention strategy, in case of full payment by the potential PrEP users	-1.84	0.00
Accessibility to the prevention strategy, in case of co-payment.	-1.09	0.00
<i>Average value</i>	<i>-0.50</i>	<i>0.00</i>
Social aspects	PREP	No PREP
Ability of the drug to protect the potential PrEP users' autonomy	0.00	0.00
Ability of the drug to protect the human rights	0.00	0.00
Ability of the drug to protect the potential PrEP users' integrity	0.00	0.00
Ability of the drug to protect the potential PrEP users' dignity	0.00	0.00
Impact of the drug on potential PrEP users' religion	0.00	0.00
Impact of the drug on social costs	-1.76	0.00
Impact of the drug on the citizens' medicalization	-0.91	0.00
Impact of the drug on the potential PrEP users' satisfaction	1.52	0.00
Impact of the drug on the potential PrEP users' perceived quality of life	0.98	0.00
Impact of the drug on the potential PrEP users' lifestyle	0.19	0.00
Impact of the drug on sexual behaviors disinhibition	-2.21	0.00
<i>Average value</i>	<i>-0.20</i>	<i>0.00</i>
Legal aspects	PREP	No PREP
Authorization level (national/European/international)	-1.94	0.00
Legal impact on safety issues	-1.18	0.00
Infringement of intellectual property rights	-0.48	0.00
Impact on the production warranties	-0.79	0.00
Need to regulate the drug acquisition and costs	-1.48	0.00
The legislation covers the regulation of technology for all categories of patients	-1.00	0.00
Impact on the not-availability of PrEP in hospitals	-1.58	0.00
<i>Average value</i>	<i>-1.21</i>	<i>0.00</i>
Organisational aspects	PREP	No PREP
Additional staff	-1.44	0.00
Training courses devoted to Infectious Disease clinicians	-1.35	0.00
Training courses devoted to healthcare professionals	-1.41	0.00
Training course devoted to potentially PrEP users	-1.38	0.00
Internal hospital meetings	-1.35	0.00
Additional rooms	-1.00	0.00
Additional furniture	-0.59	0.00
Impact on the internal processes	-1.26	0.00
Impact on the processes between the Pharmaceutical Department and the Infectious Diseases Department	-0.76	0.00
Impact of the number of access for conducting HIV tests	-0.68	0.00
Impact on the number of hematological exams, specialist visits related to the administration of the drug	-1.68	0.00
Impact on the management of other infectious diseases, different from HIV and HBV	-2.06	0.00
Organisational impact on the development of complications and adverse events	-0.47	0.00
Organisational impact on the development of drug toxicities and resistance	-1.21	0.00
Impact on the taking in charge of a higher number of individuals	-1.62	0.00
<i>Average value</i>	<i>-1.22</i>	<i>0.00</i>

Focusing on the potentially PrEP users' perceptions, the on-line survey involved 129 individuals referring to two different citizens' associations. Individuals were well-matched in terms of homosexuals (MSM) and heterosexuals (54% vs 46%) risks factors. The sample

presented scarce knowledge of PrEP (2.78 ± 1.19), even if MSM reported a better awareness in comparison with heterosexuals (2.99 vs 2.54 , $p = 0.035$). Individuals also declared poor information sharing, both from healthcare agencies and medical providers (1.77 ± 0.72), and from

media information (1.51 ± 0.06). In this view, statistically significant differences emerged between MSM and heterosexuals, with regard to the perception concerning the quality of information from healthcare agencies and medical providers (1.60 vs 1.97 , $p = 0.010$).

A total of 69 individuals (only 53.48% of the entire sample), revealed their intention to pay for the administration of PrEP, by introducing the drug into their personal healthcare budget, showing no difference between MSM and heterosexuals (50.7% vs 49.3% , $p > 0.05$). Despite 70% ($n = 49$) of the individuals having the intention to pay for PrEP had a job, no relations emerged between the job category and the willingness to pay for PrEP ($p > 0.05$), thus leading to the fact that having a job is not a determinant of the individuals' willingness-to-pay.

The sample agreed that PrEP is not responsible of any modification of daily activities (1.82 ± 0.20), sexual behaviors (2.33 ± 0.11), as well as a possible accentuation of sexual disinhibition (2.18 ± 0.10), with no statistically significant differences between the two groups. In addition, they do not think that the development of drug-related adverse events could be a reason for PrEP discontinuation (2.78 ± 0.09), adhering to their treatment, in order to achieve clinical effectiveness. However, they felt slightly uncomfortable in going to the hospital to obtain PrEP (3.09 ± 0.09), and in conducting diagnostic and blood tests for PrEP (3.29 ± 0.09), as follow-up procedures.

APPRAISAL PHASE

The experimental appraisal phase required both a prioritisation of the domains (performed by the 35 Infectious Disease Clinicians), and the implementation of a multi-criteria decision approach (based on the above results and the marks proposed by three Medical Directors). The prioritization reported that the most important aspects were both safety and efficacy profiles, as well as the social domain. The MCDA revealed that the adoption of PrEP resulted in a score of 0.484, underlying a disadvantage for acquiring the new HIV prevention strategy, with respect to the baseline scenario (0.516), even if the alternative technology could present a positive impact from a safety and social perspective (Tab. VI).

Tab. VI. Appraisal phase.

Domains	Normalised score of the domains		Prioritisation	Final result	
	Baseline scenario	Introduction of PrEP		Baseline scenario	Introduction of PrEP
Health problem and current use of technology	0.471	0.529	0.044	0.021	0.024
Description and technical characteristics	0.500	0.500	0.022	0.011	0.011
Safety	0.438	0.563	0.178	0.078	0.100
Clinical effectiveness	0.545	0.455	0.200	0.109	0.091
Cost and economic evaluation	0.611	0.389	0.133	0.081	0.052
Ethical analysis	0.625	0.375	0.089	0.056	0.033
Social aspects	0.485	0.515	0.156	0.075	0.080
Legal aspects	0.375	0.625	0.067	0.025	0.042
Organisational aspects	0.538	0.462	0.111	0.060	0.051
Total	4.588	4.412		0.516	0.484

Discussion

PrEP is now established as a biomedical HIV prevention approach, with the potential to contribute significantly to global HIV prevention efforts and decreased HIV incidence rates, in several different populations considered at high-risk of acquiring HIV.

However, the population health benefits and costs of adopting PrEP remain unclear, since there are multiple barriers to worldwide provision of PrEP to all eligible high-risk populations [38]. Concerns around safety and potential side effects, effectiveness, cost, and adherence challenges become key issues to be considered. Thus, the present study paved the way to the determination of potential strengths and weaknesses of PrEP adoption into the clinical practice.

Accordingly, advantages include a reduction of HIV infection, if associated with the traditional prevention strategies (only if PrEP is used as an "add-on" strategy), as demonstrated in recent clinical trials with regard to the administration of PrEP to IDUs [5], MSM [3,4] and SCs [6]. This consideration would suggest that PrEP could substantially reduce the lifetime risk of HIV infection for individuals at high-risk also in Italy, thus protecting the community from HIV infection.

Results showed that PrEP would increase satisfaction and quality of life for its users, justifying the social acceptance and implications of the drug. Focusing the attention on the potential population eligible to PrEP, the study reported a limited knowledge of PrEP in Italy, suggesting the setting up and implementation of PrEP training programs, targeted at the eligible population through public health campaigns, in order to raise awareness and disseminate correct information. In this regard, efforts should be taken to challenge the stigma and marginalization of minority groups, such as IDUs and MSM, both within the community and at governmental level.

However, PrEP would also provoke safety and economic concerns that should be taken into consideration from the policy-makers point of view, and that significantly impact both on Italian healthcare expenditure and on the citizens' healthcare budget. The deployment of

the safety profile, derived from the HTA exercise, is consistent with scientific evidence available. Despite PrEP remaining significantly protective against HIV infection, its general safety is strictly related to the high-risk population behaviors, in terms of development of other sexually transmitted diseases if used as a substitute prevention strategy. In addition, some studies reported small, subclinical decreases in liver function [6, 39] and bone mineral density [40, 41].

Focusing on the economic impact, results revealed the impossibility for the Italian NHS to cover the cost of drugs, despite nowadays the off-patent drug is available. In particular, the acquisition of PrEP especially depends on its reimbursement and consumption, with the generation of financial problems, both in term of NHS investment and in terms of citizens' "out-of pocket" expenditure.

However, except for the cost of the preventive strategy itself, the management of the potential PrEP users', thus considering also the so-called risk compensation, require additional healthcare investments, since the need to intensively monitor the PrEP users, with a consequent negative organizational impact, due to the taking in charge of more patients.

At least, in the investigated setting, the best cost-containing strategy would be the use of PrEP with off-patent molecules, thus decreasing the economic burden of the innovative prevention strategy. Hence, in order to limit the need of the above-mentioned organizational investment, the potential opportunity to create specific ambulatories devoted to PrEP users' especially for medium and big size hospitals should be considered. Moving on from these elements, and considering the results derived from the MCDA approach, the decision to not implement PrEP into the clinical practice, with a public expenditure, could be the preferable option, at least, within the Italian healthcare setting. However, the quantitative difference between the baseline and the innovative scenario is not significant (0.516 vs 0.484, $p > 0.05$), thus leading to the consideration that the use of PrEP could be a positive solution devoted to high-risk patients given its high clinical effectiveness if applied as an "add-on" strategy considering the off-patent drug cost. The social, economic and organizational conditions of the Italian NHS could not be ready yet for the introduction of the prophylaxis, requiring the definition of proper clinical pathways to become sustainable. Given this fact, the preferable solution could be the adoption of PrEP as an "add-on" prevention strategy, but supposing also a co-payment, in order to guarantee the sustainability and affordability of the strategy. Considering a 50% co-payment, with the branded drugs, an economic burden emerged both for the NHS (+26%) and the patients (1,193%), whereas, with the off-patent drug the NHS would benefit from an economic advantage equal to -53% and patients would invest for 218%, in comparison with a baseline scenario consisted of the purchase of condoms and NSPs.

A future step of further research could be the integration of the present results, considering the innovative

molecules emtricitabine/tenofovir alafenamide (FTC/TAF), that has been recently approved for PrEP use, by the American Food and Drugs Administration (FDA). The introduction of TAF, instead of TDF, could thus improve the economic resources absorption of the innovative preventive strategy, but also the safety profile, in terms of management cost for drug-related side effect. TAF regimen has a reduced potential for causing kidney injury and thinning bones than TDF, with a consequent positive impact both on the economic pathway, and on the organisational aspects, with a lower impact of controls, laboratory exams and specialistic visits.

In conclusions, since the study was not design for the collection of PrEP users' reported outcome, in terms of quality of life, it could be interesting to investigate this topic thus examining the head to head differences between PrEP users and high-risk individuals, not assuming PrEP.

Conclusions

To the best of the authors' knowledge, this study could be considered the first attempt to fully evaluate the implications derived from the PrEP introduction into the clinical practice, with an holistic vision of all the impacts that could play an important role in the PrEP introduction' choice, offering new insights to advance the ongoing debate regarding the relevance and feasibility of its adoption, in contexts characterized by the paucity of economic and human resources.

On the whole, a proper stratification of the potential population eligible to PrEP could optimize the clinicians' choice and the correct use of PrEP, with a lower and more sustainable economic impact, and a maximization of both safety and efficacy profile. In particular, the individuals who are at risk, should identify themselves to their doctors, and every effort should be made, to ensure that a safe, stigma-free environment is created for them.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

EF, GC, ADB, GR, ME, RI, and DC made substantial contributions to conception and design. LF, EF, EG and VP acquire and analyzed data, and wrote the paper. GC, ADB, GR, ME, RI, and DC critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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