Title: Cost-effectiveness of HIV screening in high-income countries: A systematic review

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Abstract

Introduction

Over 2 million people in high-income countries live with HIV. Early diagnosis and treatment present benefits for infected subjects and reduce secondary transmissions. Cost-effectiveness analyses are important to effectively inform policy makers and consequently implement the most cost-effective programmes. Therefore, we conducted a systematic review regarding the cost-effectiveness of HIV screening in high-income countries.

Methods

We followed PRISMA statements and included all papers evaluating the cost-effectiveness of HIV screening in the general population or in specific subgroups.

Results

Thirteen studies considered routine HIV testing in the general population. The most cost-effective option appeared to be associating one-time testing of the general population with annual screening of high-risk groups, such as injecting-drug users. Thirteen studies assessed the cost-effectiveness of HIV screening in specific settings, outlining the attractiveness of similar programmes in emergency departments, primary care, sexually transmitted disease clinics and substance abuse treatment programmes.

Discussion

Evidence regarding the health benefits and cost-effectiveness of HIV screening is growing, even in low-prevalence countries. One-time screenings offered to the adult population appear to be a valuable choice, associated with repeated testing in high-risk populations. The evidence regarding the benefits of using a rapid test, even in terms of cost-effectiveness, is growing. Finally, HIV screening seems useful in specific settings, such as emergency departments and STD clinics.

1. Introduction

In 2012, over 35 million people lived with human immunodeficiency virus (HIV) infection worldwide, and of these, approximately2.2 million lived in high-income countries [1]. Moreover, a large percentage of the infected population are unaware of their status; for example, in the US, 21% of people living with HIV ignore this condition [2]. Knowledge of the HIV-serostatus and early treatment can improve both the survival and the quality of life of infected subjects[3]. In addition to the individual benefits, the early identification of HIV may have a role in reducing the transmission from index patients to uninfected persons [4–6]. Indeed, people's knowledge of their condition substantially reduces their at-risk behaviours [4–6]. In addition, antiretroviral therapy (ART) effectively reduces the viral load [4–6]. Given the high burden of HIV infection worldwide [1] and the high number of people unaware of their serostatus [2], HIV disease represents a significant public health problem. Since highly sensitive and specific diagnostic tests are available and early treatment significantly alters the disease course, universal HIV screening may represent a valuable tool of secondary prevention [7]. Moreover, the progressive introduction of innovative rapid tests, promising to provide results in less than 30 min with extremely good sensitivity (from 95% to 98%) and specificity (99% with whole-blood specimens), represents a further resource for HIV-prevention [8]. Indeed, rapid tests may decrease losses to follow-up, a major issue of standard testing, which requires a second visit to communicate the results [9]. In this context, the "Centers of Disease Control and Prevention" (CDC) has recommended that all untested adults be screened, while high-risk populations should receive at least one test annually [10]. In particular, screening should be performed routinely for all patients aged 13–64 years, unless the prevalence of undiagnosed HIV infection is lower than 0.1% [10]. The main recognized risk groups are injecting-drug users (IDUs), sex workers, men who have sex with men (MSM), sex partners of HIV-infected persons and partners of at-risk subjects [11]. However, an interesting work of 2007 highlighted how the majority of the US states present HIV testing requirements inconsistent with the previously cited CDC recommendations [12].

In the literature, limited experience with universal HIV screening can be retrieved, particularly regarding emergency departments (EDs) [13,14].To effectively inform policy-makers and since accurate data regarding HIV prevalence are often lacking, screening programmes should monitor costs and effectiveness to avoid screening implementation causing increased health expenditures. In addition, these recommendations cannot be effectively implemented if patients with HIV diagnoses do not remain engaged in care [11,12]. The European Centre for Disease Prevention and Control (ECDC)has recommended repeated HIV testing for high-risk people. How-ever, economic modelling has not found annual testing to be cost-effective, even in populations with a high prevalence [15]. Conversely, the French Public Health Guidelines recommend HIV screening of the entire adult population [16]. In addition, the UK National Guidelines underline that universal HIV screening should be offered whenever the prevalence exceeds 2 in 1000 in the population [17]. An analysis regarding the cost-effectiveness of different HIV screening strategies is extremely important to effectively inform policy makers and consequently implement the most cost-effective programmes. Indeed, similar analyses effectively support decisions in the healthcare field [18]. These economic evaluations compare different programmes from the perspectives of both the cost and the consequences [19].

Recently, many studies have investigated the cost-effectiveness of HIV screening, considering different settings, target populations and screening frequencies [9,20–24]. Nevertheless, data

regarding this topic are often heterogeneous, considering both the screening strategy and the study methodology [20,22,24–28]. In public health, the cost-effectiveness analysis expresses costs in euros or dollars and health benefits in units of health, such as a life saved or a quality-adjusted life-year (QALY) gained [29].A cost-effectiveness ratio is calculated between money expended and health obtained [29]. The incremental cost-effectiveness ratio(ICER) is often used to compare the costs and effectiveness of health interventions and to provide an evident guide, for example, when policy-makers have established an explicit standard or threshold for what should be considered cost-effective [29]. Particularly, the thresholds based on per capita national incomes are one of the possible approaches to decide if a health programme represents a good investment for the national health-care system [30]. However, the exact cost-effectiveness threshold is still debated. Regarding this issue, the World Health Organization (WHO) guidelines identify as cost-effective an incremental cost-effectiveness ratio (ICER) lower than three times the per-capita gross domestic product (GDP) [30].

Therefore, in our analysis, we decided to adopt this threshold to assess cost-effectiveness; indeed, this threshold could be applied to countries with different incomes [30]. The cost-effectiveness of universal HIV screening is widely assessed in high-prevalence areas such as Sub-Saharan African countries [31,32]. However, increasing evidence has also out-lined the economic convenience of similar programmes among low-prevalence populations [21,22]. Indeed, the clinical benefits, deriving from the early diagnosis and the availability of highly active antiretroviral therapies, could make the screening not only acceptable and efficient but also economically suitable in such epidemiological settings [21,22].

To our knowledge, no previous review has investigated the cost-effectiveness of HIV-screening in developed countries. Therefore, we conducted a systematic review regarding the cost-effectiveness of HIV-screening, focusing on countries defined as high-income by the World Bank [33]. We decided to consider these countries in as much more comparable both in economic and epidemiologic terms. Aside from cost-effectiveness, we aimed to individuate the optimal testing frequency and the population to whom to actively offer HIV tests. Moreover, our review intended to investigate thecost-effectiveness of rapid tests compared to standard antibody tests.

2. Methods

For our systematic review, we employed Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statements [34]. We considered all papers reporting data about the cost-effectiveness of HIV screening, investigating the following three databases: Cost-Effectiveness Analysis Registry (CEA), PubMed and Scopus. From May to June 2016, two researchers (EC and MM) independently conducted a systematic search of the scientific literature employing the following strings: “HIV screening” AND cost effectiveness; “HIV test” AND cost effectiveness.

To select the eligible studies, we used the inclusion criteria reported below:

• Cost-effectiveness studies regarding HIV screening

• Papers written in English, French, Italian or Spanish

• Publication date from 2000

• Studies regarding high-income countries (considering the World Bank classification) [24].

We chose the time limit previously cited (from 2000 onwards) because it coincides with the wide introduction of effective ART regimens [35]. We considered both simulation models and clinical trials.

Furthermore, we stated the following exclusion criteria:

• Articles focusing exclusively on therapy cost-effectiveness

• Articles considering only cost analyses

• Articles assessing vertical transmission screening

• Articles considering blood donor screening or screening of healthcare professionals.

We decided to exclude the works regarding blood donors because the screening strategies for this group are already well-established [36,37]. Moreover, we decided to exclude the works regarding healthcare workers in order to focus on the general population and on the main at-risk groups, widely recognized in the literature as MSM and IDUs [11].

First, the investigators independently sorted the retrieved sources by title and abstract. This first procedure excluded irrelevant and duplicated results. Then, we collected the eligible studies available for a full-text review, completing our search through the reference list assessment. Finally, the researchers independently evaluated the retrieved articles using the above-reported inclusion and exclusion criteria.

2.1. Data extraction

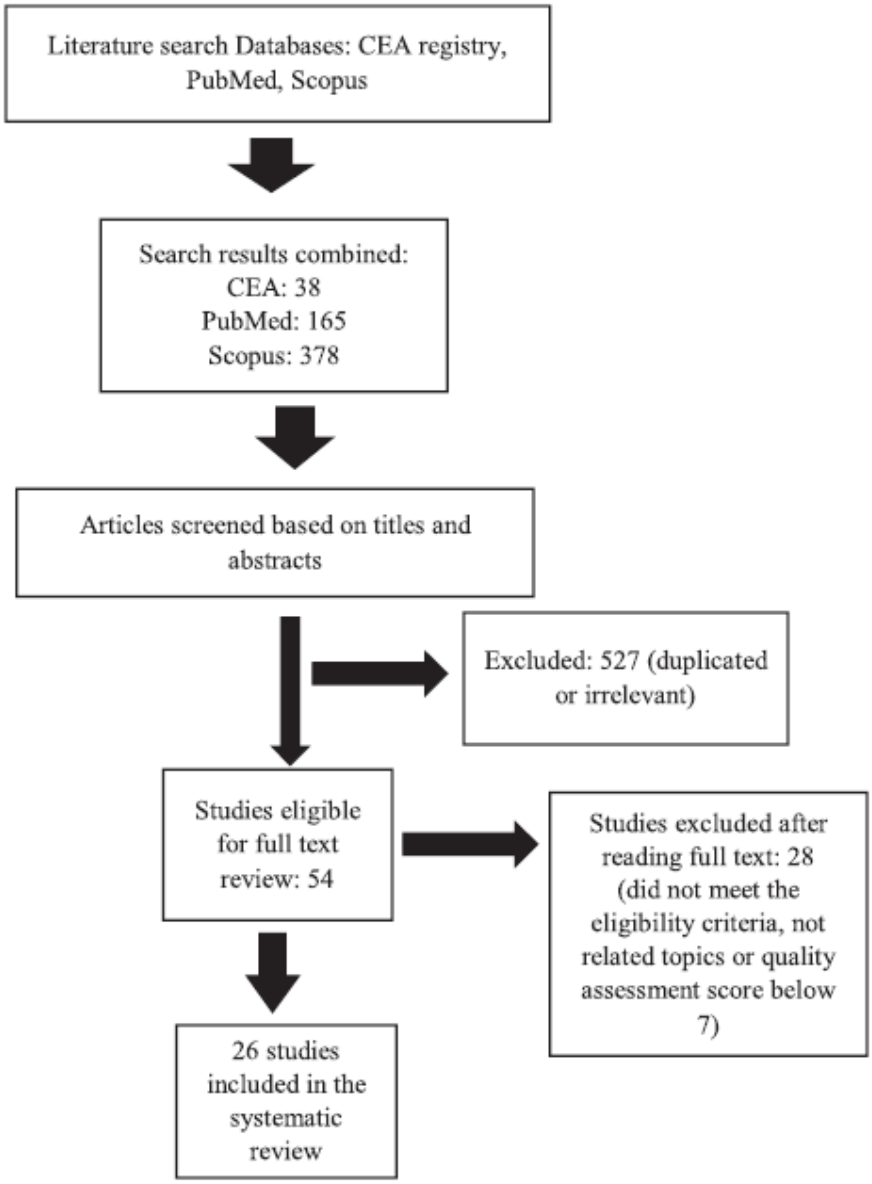
The researchers summarized the retrieved results independently, extracting the information of interest and solving any disagreement by consensus. For each article, we collected data about the country in the study, the intervention, the target population, the HIV prevalence or incidence, the setting, the outcome, the perspective, the time horizon, the costs and the results. Then, we analysed the retrieved studies in two groups: "HIV screening in the general population and high-risk groups" and "HIV screening in specific settings". We compared the studies in each group considering the methodological characteristics, HIV epidemiology in the considered setting/country, and the findings. We also found the potential source of heterogeneity.

2.2. Quality assessment

To limit the risk of introducing biases into our systematic review, the quality of these studies was assessed using the Drummond 10-item scale [38]. The scale is composed of 10 main questions, each further organized in sub-items. For example, the first item investigates the organization of the analysis, identifying the objective of the study. Most of the remaining questions consider the evaluation of the costs and consequences of the interventions in the study [38]. Two researchers (EC and MM) independently assessed the quality of the studies included in the review, using the afore mentioned Drummond scale. Then, the final score was obtained from the mean of the two partial scores. Each question of the scale was worth 1 point, with a potential score ranging from 0 to 10 points. We decided to exclude all the works with a score below 7. However, in the conclusions and

discussion of our work, we assigned a major weight to the deductions deriving from the studies with a higher quality assessment.

Figure 1 - Flow chart of the included and excluded studies. Information flow chart of the different steps of the systematic review.



3. Results

Our search obtained 581 results. After excluding duplicates and irrelevant sources, we collected 54 articles. Then, relying on full-text reading, we came to the conclusive number of 26 articles (see Fig. 1) [4,9,20–28,39–53]. The papers were excluded after a full-text reading because they did not meet the eligibility criteria previously mentioned, they referred to unrelated topics or they presented a quality assessment score below 7. Overall, the quality of the retrieved studies, as assessed through

the Drummond 10-item scale, was good (see Tables 1 and 3). Indeed, all the selected works scored at least 8 points on the considered scale, and over 73% of the studies presented a score greater than or equal to nine. Fourteen studies considered routine HIV testing in the adult population, considering the general population and high-risk groups (see Tables 1 and 2) [4,9,20–22,24,28,39,41–44,53]. The majority of the studies in the analysis adopted a societal perspective[4,22,24,28,39–41,43,44,53]. Two studies chose an intermediate perspective, called modified societal, not accounting for all indirect costs [20,21]. Nearly all the studies considered the long-term effects of HIV screening (lifetime or 20 years) [4,20–22,24,28,41–44,53], except for those of Farnham et al. (who considered in their mathematical model a 1-year perspective) [39] and Stevinson et al.(1-month perspective) [9]. In the latter case, the short-term analysis is justified by the study's aim of comparing two types of HIV testing (rapid or traditional testing) [9]. For the economic analysis, the reference year ranged from 2001 [44] to 2012 [20,22], with a discounting rate of 3% [4,21,22,24,28,39,41–44,53]. Four studies focused on European countries, specifically the UK [22], Portugal[20], France [21] and Russia [42]. Ten studies considered the screening implementation in the US [4,9,24,28,39–41,43,44,53]. Nearly all the studies compared universal screening of the adult population with current testing, considering different screening frequencies[4,20–22,39,41–43]. Moreover, the papers, with few exceptions[4,9,39,42,53], took into account targeted strategies towards high-risk groups. The authors agreed in identifying as high-risk groups MSM, IDUs and people from endemic countries [20–22,24,40,41]. Regarding the general population, the authors focused on adults(15–64 or 18–69 years) [4,20–22,24,40,41,43], except for Tole et al., who offered screening to a younger cohort (15–49 years) [42], and Sanders et al., who focused on older adults [53]. All the studies, except that of Stevinson et al. [9], employed a dynamic model simulating HIV progression, assessing the long-term consequences of HIV disease [4,20–22,28,39–44,53]. To assess HIV progression, these papers considered HIV viral loads, CD4 counts, ART therapy, opportunistic infections, morbidity and natural history data [4,20–22,28,39–43,44,53].

3.1. One-time routine HIV screening in the general population

France, the UK and the USA presented a comparable, low HIV prevalence [4,9,21,22,24,28,39–41,43,44,53], while Russia and Portugal presented a higher HIV burden [20,42]. Considering the undiagnosed HIV prevalence, which ranged in these countries from 0.03% [22] to 0.16% [20], a universal one-time screening was the best option in the UK, France and Portugal [20–22]. In the British study, the most cost-effective option was associating one-time testing of the general population with annual screening of high-risk groups [22]. The universal one-time screening yielded D 28,000/QALY (not considering secondary transmissions) and 7400D /QALY (accounting for secondary transmissions) in Portugal and D 57,400/QALY in France [20,21]. In the UK, a programme providing annual HIV testing to MSM, IDUs, and people from HIV-endemic countries coupled with one-time screening of all other adults reported an ICER of £17,500/QALY gained [22]. In Russia, the one-time universal screening resulted in $13,396/QALY, and accounting for the screening impact on secondary transmissions, the cost-effectiveness further improved [42].

Table 1
Studies characteristics for HIV screening in general population. The Table summarizes the main characteristics of the studies regarding the cost-effectiveness of HIV screening in general population, reporting the country in study, the screening strategies compared, the target population, the burden of HIV (as incidence or prevalence) and the outcome sought.

	Drummond evaluation	Country	Intervention	Target Population	HIV prevalence or Incidence	Outcomes
Long et al. [22]	10	UK	I. Status Quo (6125 annual new diagnosis) II. Universal strategy (all adults tested every one, two or three years) III. Targeted strategy (high-risk groups tested every year, general population one-time or every two years)	Adult population (15–64 years) and high-risk groups: MSM, IDUs, people from HIV endemic countries	**HIV prevalence**: General population: 0.033% MSM: 5.0% IDUs: 1.2% People from endemic countries: Men 2.5%, women 5.0%	HIV prevalence and incidence Lifetime Quality-adjusted life years Lifetime healthcare costs HIV averted infections Incremental cost-effectiveness ratio (ICER)
Yazdanpanah et al. [20]	10	Portugal	I. Routine HIV screening (one-time, every three years or annual) II. Targeted screening (regional screening, MSM or IDU) III. status quo (targeted and on-demand testing)	Adult population (18–69 years), and high-risk groups: MSM (mean age 34y) IDU (mean age 31y)	Overall prevalence: 0.53% Undiagnosed HIV prevalence: 0.16% Undiagnosed HIV in IDUs: 6.69% Undiagnosed HIV in MSM: 3.34% Annual HIV incidence: 0.03%	Quality adjusted survival Secondary HIV transmissions Cost and ICER (€/life year saved (LYS) and €/QALY)
Lucas et al. [28]	9	USA	To evaluate an increased HIV testing frequency versus CDC recommendations(one time to all adults and adolescents not previously tested, and annual test for high-risk groups)	General population (low, medium and high risk groups) (age not specified)	**Annual incidence**: Low-risk: 0.01% Medium-risk: 0.1% High-risk: 1%	QALY Optimal interval between tests ICER as $/QALY
Farnham et al. [39]	8	USA	HIV screening strategy versus absence of HIV testing programmes	General spopulation (age not specified)	HIV prevalence: 0.8% (in sensitivity analysis 0,1-2%)	Infections averted Total costs Cost per QALY saved and per infection averted
Juusola et al. [24]	10	USA	Viral load testing for individuals with influenza-like illness Expanded screening (antibody testing-only) Expanded screening (antibody + viral load) compared to no present rate of antibody testing	MSM aged 16–64 years	Undiagnosed HIV prevalence: 3.2%	New HIV infections Discounted quality-adjusted life years (QALYs) Costs and incremental cost-effectiveness ratios
Long et al. [24]	9	USA	HIV screening in different groups (including general population) with various screening frequencies (annually, or every 6 months), using fourth-generation immunoassay only or an immunoassay followed by pooled NAAT compared to current testing uptake (23% high-risk individuals tested in the previous year and 10% in general population)	General population (15–64 years), IDU + MSM or MSM only	**Undiagnosed HIV prevalence**: MSM: 4.3% IDU: males 4.4%, female 5.9% General population: men: 0.03%, women 0.07%	Number of acute infections identified HIV infections prevented QALYs gained ICER

Stevinson et al. [9]	8	USA	- Rapid test followed by confirmatory WB (standard care) - Rapid test followed by confirmatory second rapid test (Rapid test algorithm)	Users of public funded Counseling and Testing sites (in New Jersey) (age not specified)	New confirmed positive results in 2008:215/19,677	Percentage of positive clients notified Number of days between initial test and communication Cost per positive test
Long et al. [41]	10	USA	Expanded HIV screening, expanded treatment with ART, or the combination of these two interventions.	General population (15–64 years) and high-risk groups as IDU and MSM	**HIV prevalence**: General population: Men 0.1%, women 0.22% MSM: 12.6% IDU: men 12.9%, women 17.3% Overall undiagnosed HIV prevalence:0.11% **Annual incidence**: 0.03%	New HIV infections QALYs ICER
Yazdanpanah et al. [21]	10	France	Voluntary HIV screening (once, every five years or annually) in general population and targeted sub-populations compared to status quo (risk-factor based and symptomatic testing)	General population (18–69 years), high-risk groups: MSM, IDUs and people from French Guyana	**Undiagnosed HIV infection**: General population: 0.10% French Guyana: 0.41% IDU: 6.17% MSM: 1.7% **Overall HIV incidence**: 0.01/100 person-years	Life expectancy (LE) Cost and ICER (as €/QALY)
Tole et al. [42]	9	Russia	Voluntary HIV screening and counseling (with different frequencies) compared to no screening	General population (15–49 years)	HIV prevalence:1.2% (two third undiagnosed) Annual HIV incidence: 0.075%	Quality of life and survival Costs and cost per QALY gained
Sanders et al. [53]	9	USA	One-time voluntary HIV-screening in older individuals compared to current practice(testing in case of symptoms)	Patients aged 55–75 years with unknown HIV status	Unidentified HIV prevalence: between 0.1 and 1%	Life-expectancy QALYs Costs ICER ($/QALY)
Paltiel et al. [43]	9	USA	Different screening strategies (universal, targeted) and frequencies compared to current practice (no specific screening programme)	General adult population (mean age 33 years)	**Undetected HIV prevalence**: Low-risk: 0.1% Moderate-risk: 1.0% **Annual HIV incidence**: Low-risk: 0.084% Moderate-risk: 0.12%	HIV infections detected Secondary transmissions averted Quality-adjusted survival Lifetime medical costs Cost per QALY gained
Paltiel et al. [44]	8	USA	HIV expanded screening (frequencies: one-time, every five years, three years or annual) compared to current practice (non-routine background testing + clinical presentation with an AIDS defining illness)	Three target populations: high-risk, CDC threshold, US general population (age not specified)	High-risk: undiagnosed prevalence 3%, annual incidence 1.2% CDC: undiagnosed prevalence 1%, annual incidence 0.12% US population: undiagnosed prevalence 0.1%, annual incidence 0.01%	Life Expectancy Number of secondary transmissions averted Costs and ICER as $/QALY gained
Sanders et al. [4]	8	USA	Voluntary HIV-screening in healthcare settings compared with current practice (testing in case of symptoms)	General population with unknown HIV status (mean age: 43 years)	Prevalence of unidentified HIV: 1% Annual incidence: 0.03%	Quality of life and survival Costs ICER ($/QALY)

Abbreviations: MSM: men who have sex with men; IDUs: injecting drug users, ICER: incremental cost-effectiveness ratio, LYS: life years saved; QALY: quality-adjusted life years; CDC: Centers of Disease Control and Prevention; NAAT: Nucleic Acid Amplification Testing; WB: Western Blot; ART: anti-retroviral therapy; LE: life expectancy.

Table 2
Economical characteristics for HIV screening in general population. The Table summarizes the main economical characteristics of the studies regarding the cost-effectiveness of HIV screening in general population, reporting the adopted perspective, the time horizon chosen, the currency and reference year, the type of costs included in the analysis and the main results.

	Perspective	Time horizon	Currency and reference year	Costs included	Results
Long et al. [22]	Societal	Lifetime or 10-years	2012 £, discounting rate: 3%	All healthcare costs and savings (cost for asymptomatic HIV treated/untreated, for symptomatic HIV treated/untreated, AIDS treated/untreated, annual non-HIV related health costs, annual cost of ART, testing cost, counseling cost, annual costs of ancillary services)	Annual testing in general population would cost £67,400/QALY considering potential behavioural impact and £106,000/QALY with no behavior change. Targeted screening (+one-time general screening) would cost £17,500/QALY Targeted screening (+every two years general screening) would cost £36,000/QALY
Yazdanpanah et al. [20]	Modified-societal	Lifetime	2012 €, discounting rate: 5%	Indirect costs were excluded Cost included treatment cost until 6th line ART, Screening cost (HIV test, confirmatory test, counseling for HIV+)	One-time universal screening would cost €28,000/QALY (€30,000/QALY not accounting for secondary transmission) Annual screening for MSM would cost €21,000/QALY and every three years in high prevalence regions €34,000/QALY Among IDUs, all strategies are cost-effective (ICER from €26,000 to €30,000 per QALY)
Lucas et al. [28]	Societal	Lifetime	2010 US$, discounting rate: 3%	Societal costs of testing (monetary and health costs from both the individual tested and from preventing secondary infections)	Considering immediate ART initiation the optimal screening frequency was of 2.4 years for low-risk group ($36,342/QALY), every 3 months for high-risk ($45,074/QALY)
Farnham et al. [39]	Societal	1-year	2009 US$, discounting rate: 3%	The costs included only the marginal cost for HIV-rapid test (collecting specimens, test kits, confirmatory test and post-test counseling for HIV positive individuals)	In the base-case, HIV screening would cost $40,516 per infection averted and cost saving considering QALY saved (saving $50,772). In two-way sensitivity analysis, the cost per infection averted varied between $108,043 and 1,283,494 (with a HIV prevalence of 0.1% and higher test costs), while the cost per QALY saved ranged from −40,275$ to 142,447 in the worst scenario.
Juusola et al. [24]	Societal	20-years	2009 US $, discounting rate: 3%	Costs included testing, confirmatory viral load, Western Blot confirmation, follow-up visits and therapy	Expanding antibody screening of MSM annually cost $12,582/QALY, reducing of nearly 3% annually new infections. Symptom-based viral load cost $22,786/QALY. Combining these strategies cost $29,923/QALY.
Long et al. [24]	Societal	20-years	2009 US$, discounting rate: 3%	The costs included diagnostic services, confirmatory testing, counseling and future HIV-related and non-HIV-related healthcare costs, including ART, and annual cost of ancillary IDU services	Universal HIV screening with a fourth-generation immunoassay presented a cost of $100,000 to $580,000/QALY. A targeted screening for MSM and IDU would cost $6400/QALY at annual frequency and $17,800/QALY every 6 months. Annual NAAT would cost $4.7 million/QALY in general population. Annual NAAT for MSM+IDUs would cost 80,300$/QALY and 92,200$/QALY targeting MSM-only
Stevinson et al. [9]	Public funds	1-month	2008/2009 US$, no discounting applied	Testing and counseling costs	The cost of rapid algorithm compared to conventional strategy was of $30.46/additional percentage notified and 4.85$/additional percentage notified considering WB elimination. These findings translated in a saving of $14.86 per positive person.
Long et al. [41]	Societal	20-years and lifetime	2009 US$, discounting rate: 3%	The costs included HIV- and non HIV-related healthcare costs, ART, testing and counseling and ancillary IDU services costs.	One-time HIV screening of general population + annual screening for high-risk groups would cost $22,382/QALY. Increasing antiretroviral use to 75% of eligible patients would cost $20,300/QALY. An integrated strategy would cost $21,580/QALY.

Yazdanpanah et al. [21]	Modified-societal	Lifetime	2007 €, discounting rate: 3%	Cost of testing (pre-test counseling + blood draw + ELISA), confirmatory test (blood draw + Western Blot), counseling for HIV+, direct medical cost for routine care, ART and cost for opportunistic infections	One-time universal screening would cost 61,100€/QALY not accounting for secondary transmissions and 57,400€/QALY considering them. Annual testing would cost 51,200€/QALY for IDUs and 46,500€/QALY for French Guyana residents, both compared to screen every five years. One-time testing for MSM would cost 32,400€/QALY versus current practice, and annual screening 97,200€/QALY.
Tole et al. [42]	Not specified	Lifetime	2006 US$, discounting rate: 3%	The costs comprised testing (for negative and positive test)and counseling, cost for CD4 count, for viral test load, non HIV related healthcare costs, annual cost of HIV infection, ART therapy, second-line therapy, salvage therapy, additional support service, cost for ART side effect	One time screening cost 13,396$/QALY and every five years 27,696$/QALY. Adding benefits on secondary transmissions, one-time testing cost 6910$/QALY and every 5 years 7402$/QALY. In sensitivity analysis cost-effectiveness improved decreasing ART cost (once per-lifetime screening cost $4913 per QALY gained), while cost-effectiveness worsened considering a decrement in quality of life after the diagnosis ($11,942 per QALY gained for once-per-lifetime screening), or considering counseling as ineffective.
Sanders et al. [53]	Societal	Lifetime	2007 US$, discounting rate: 3%	Direct costs of medical care associated with HIV testing and counseling, follow-up, and treatment. Costs included age-specific medical expenditures unrelated to HIV care	In patients with partner at risk and prevalence of unidentified HIV 0.5%, the ICER was $30,020/QALY for the 65-years cohort and $41,520/QALY for 75 years. In individuals ($\leq$ 80 years) with no partner at risk, HIV screening costs less than $100,000/QALY if the prevalence of unidentified HIV $\geq$ 0.5%
Paltiel et al. [43]	Societal	Lifetime	2004 US$, discounting rate: 3%	Costs included rapid HIV testing, WB confirmation, counseling (pre- and post- test) and therapy	In case of moderate HIV prevalence and incidence, routine HIV screening cost $30,800/QALY (one-time screening), $32,300/QALY (every 5 years) and $55,500/QALY (every 3 years). In settings with lower HIV prevalence (0.1%) and incidence, one-time screening cost $60,700/QALY. The one-time screening stay below $50,000/QALY with HIV prevalence as low as 0.20%, while 5 year-screening with prevalence as low as 0.45%
Paltiel et al. [44]	Societal	Lifetime	2001 US$, discounting rate: 3%	Testing costs (ELISA, WB and counseling as pre- and post- test intervention),ART therapy	In high-risk groups, one-time screening cost $36,000/QALY, every five years $50,000/QALY, every three years $63,000/QALY. In CDC population, one-time screening cost $38,000/QALY, every five years $71,000/QALY, every three years $85,000/QALY. In US population, one-time testing cost $113,000 per QALY. In sensitivity analysis, the following influencing parameters were detected: background testing, adherence to ART, and rates of linkage to care. With the use of 5-year repeated testing, there would 49 fewer transmission in US general population
Sanders et al. [4]	Not specified	Lifetime	2004 US$, discounting rate: 3%	Costs included test (positive and negative), counseling, CD4 count, viral load, follow up and treatment(as three-drug therapy, four-drug ART or salvage therapy) and cost for ART side effects	At baseline prevalence, general screening would cost $15,078/QALY. Excluding HIV transmission benefit, the ICER increased to $41,736/QALY. The ICER stayed <$50,000/QALY until a 0.05% HIV prevalence. Repeated testing cost $57,138/QALY, but improve in case of higher incidence. In sensitivity analysis, the following influencing parameters were detected: the efficacy of behavior modification, the benefit of early identification and therapy, and the prevalence and incidence of HIV infection.

Abbreviations: QALY: quality-adjusted life years; ART: anti-retroviral therapy; MSM: men who have sex with men; IDUs: injecting drug users; NAAT: Nucleic Acid Amplification Testing; WB: Western Blot; ICER: incremental cost-effectiveness ratio; ELISA: enzyme-linked immunosorbent assay; CDC: Centers of Disease Control and Prevention.
Modified societal perspective: is an intermediate perspective (between societal and provider), including only some characteristics of the societal perspective (excluding the non-direct medical cost as participant time).

The US studies assessed the cost-effectiveness of one-time screening of the general population, considering the US prevalence [4,39,41,43]. In particular, in cases of lower HIV prevalence (0.1%), the one-time screening would cost $60,700/QALY [43]. Sanders et al. found a lower ICER of one-time HIV screening ($15,078/QALY), considering the additional sexual partner benefits, and 41,736$/QALY excluding HIV transmission. [4]. Incorporating costs and benefits, the authors estimated that one-time screening would cost $194 more than the current practice per patient [4]. A further analysis investigated the cost-effectiveness of expanded screening, expanded ART or the combination of these two interventions. The screening consisted of one-time testing for adults in addition to annual testing for high-risk individuals. The expanded ART programme increased the number of patients receiving appropriate therapy ($20,300/QALY), preventing 7,3% of new infections [41]. The screening intervention prevented 6.7% of expected infections (81,991 infections), at a cost of $22,382/QALY compared to the status quo [41]. Routine screening every three years among all risk groups had an ICER of $112,094/QALY gained compared to the status quo, while annual HIV screening of all adults was less cost-effective, at $143,930/QALY gained [41]. The combination strategy prevented 17.3% of expected infections, more than expected, summing up the two strategies benefits, with a cost-effectiveness rate of $21,580/QALY [41]. Another interesting study employed a mathematical model to assess how much policymakers should spend for HIV screening. Despite the main data derived from sexually transmitted disease (STD) clinics, the authors widely varied these parameters, adapting them to the general population. In the base case, the screening programme resulted in cost savings that remained until a prevalence of 0.09% and remained cost-effective until 0.03% [39]. In the base case, the cost per new HIV diagnosis was $2528, and the cost per infection averted was $40,516 [39]. Only one study determined a higher cost for general population screening with an ICER of$113,000/QALY [44]. This difference could be partially explained by the background characteristics considered (undiagnosed prevalence 0.1%, annual incidence 0.01%) and by other parameters such as background testing, adherence to ART, and rates of linkage to care. However, one-time screening significantly improved the average survival among HIV-infected patients [44]. Moreover, screening in the US population could avert up to 10 secondary transmissions per 100,000 [44]. All previous studies considered HIV screening for adults up to 65 years old, and only one study estimated the implementation of similar programmes targeted to older subjects. In this context, the screening cost-effectiveness depended mainly on age and HIV prevalence. In individuals with partners at risk and an HIV prevalence of 0.5%, the screening presented an ICER below $60,000/QALY in the entire age cohort (55–75 years). Instead, decreasing the HIV-prevalence to 0.1%, the screening would cost more, with an ICER of $91,410/QALY for 65-year-old patients, and exceeded this value in older people [53]. Considering the health benefits, the authors estimated the increase in survival deriving from the early identification of HIV. These benefits mainly depended on age and decreased for older patients. For a 65-year-old patient, screening increased the life expectancy by 0.58 years. These benefits reduced to 0.30 years for a 75-year-old HIV-infected patient. Considering current US population data, one-time screening could save over 120,000 life years [53]. In addition, the authors considered the potential role of abbreviated counselling. Including this counselling in the model was associated with better cost-effectiveness ratios. In a sensitivity analysis considering people up to 75 years old with no partner at risk, using a screen with abbreviated counselling would cost less than $100,000/QALY if the HIV prevalence is 0.1% and less than $50,000/QALY at a prevalence of 0.5% [53]. Moreover, the considered studies outlined the individual health benefits of HIV screening in terms of the CD4 count at diagnosis [20,21] and life expectancy [4,42,44]. In particular, screening identification and treatment resulted in

an increase in life expectancy of 1.52 years [4]. In addition, the authors assessed the public health role considering secondary transmissions [20,21,42,44] and the favourable impact on risk behaviours [22,42]. For example, one-time screening effectively reduced the lifetime numbers of transmissions to 0.95, 0.35, and 0.12 partners among men who have sex with men, heterosexual men, and heterosexual women, from 1.12, 0.42, and 0.14, respectively [4]. The main findings were robust across the sensitivity analysis [4,9,20–22,24,28,39,41–44,53]. However, the most influencing parameters were the impact on behavioural changes [22,42], HIV prevalence [20–22], and linkage to care [20,21,42]. Despite the influencing role of HIV prevalence, the one-time universal screening was considered cost-effective until a prevalence of 0.02% [42] or 0.05% in the USA [4]. Finally, the screening cost-effectiveness was equally assessed using standard ELISA antibodies [21,22,41] or HIV rapid testing [20,28,39,44]. Specifically, a study focused on this topic to individuate the optimal testing algorithm, comparing the standard algorithm (rapid test + confirmatory WB), requiring a second visit to communicate test results, to a rapid algorithm (rapid test + confirmatory rapid test), consenting to give same-day results. The first strategy presented a loss to follow-up exceeding 25%. The study outlined the benefits of a rapid algorithm, saving over $146 per positive person identified. Moreover, a confirmatory rapid test, aside from reducing loss to follow-up, correctly identified positive results as well as a standard Western blot [9]. There was a mean interval of 11.4 days until the test and notification of infection with the standard testing algorithm; by contrast, patients testing positive with the rapid test received the notification on the same day [9]. This study used a short-term perspective (one-month); how-ever, it gives interesting insights regarding the use of rapid tests in HIV screening [9]. Moreover, since several new infections are related to acute HIV infections, the detection of these individuals is important. A 2011 study analysed the cost-effectiveness of different screening strategies identifying acute infections. Indeed, the newer fourth-generation tests could significantly reduce the window period (average, 17 days) compared to the third-generation ELISA tests. Moreover, pooled nucleic acid amplification testing (NAAT) can detect HIV-RNA 11 days after infection. Then, the paper compared HIV screening using fourth-generation immunoassays to a screen for acute infection through pooled NAAT. Universal HIV screening with a fourth-generation immunoassay presented a cost variable from $100,000 to $580,000 per QALY, adding 2.3–2.7 million QALYs over 20 years [40].

3.2. Repeated HIV screening in general population

Several studies considered the opportunity of repeated screening in the general population [4,20,22,28,40,42]. For example, in the UK, although one-time screening was the more attractive strategy, annual testing of all adults would cost £67,400/QALY gained under the optimistic assumption, and £106,000/QALY in case of no partnership reduction [22]. In contrast, considering the French incidence and prevalence data, increasing the universal screening frequency exceeded any considered cost-effectiveness threshold [20]. Conversely, in Russia, with a prevalence of 1.2% and an incidence of 0.075%, 5-year universal testing would cost $27,696/QALY, and accounting for secondary transmissions, the cost-effectiveness further improved [42]. Furthermore, in the US, repeated screening could be a feasible choice for policy-makers [4]. Indeed, screening every five years, compared with a one-time screening programme, would cost 57,138 $/QALY, but the authors found an ICER below 50,000 $/QALY in settings with a higher incidence of infection [4]. Moreover, HIV screening significantly reduced HIV secondary transmission in all the considered groups (MSM, and heterosexual men and women) [4]. However, at the base-case incidence, screening every five

years, slightly affects the lifetime numbers of transmissions [4]. Another study clearly highlighted how repeated screening in the general population translated to increased costs and scarce incremental benefits [44]. Considering alternative types of tests, such as NAAT, the annual repetition of such an analysis in the general population would far exceed any proposed threshold (from $3.2 million to $4.7 million per QALY gained) [40]. Specifically, an additional study investigated the optimal screening frequency in HIV testing, assuming a test-and-treat scenario, in which each HIV-positive individual received ART immediately. In this scenario, the cost-effectiveness of HIV-screening was $36,342/quality-adjusted life-years (QALYs). Indeed, for low incidence (0.01%), the optimal testing uptake was approximately 2 years, considering 100,000$/QALY as the threshold, with an additional cost of $213.68 per person. Comparing these results with CDC recommendations, the higher frequency of screening for one million low-risk individuals would bring an additional health gain of 5880 QALYs at a cost of $213.7 million and $36,342 $/QALY. Decreasing the cost-effectiveness threshold to 50,000$/QALY, the optimal testing interval for a low-risk population increased to 5 years. Considering the traditional ART initiation, the optimal time interval almost doubled [28].

3.3. High-risk groups

Considering high-risk groups, the repeated screening became increasingly more interesting [20–22,24,28,43,44]. Despite the wide range of cost-effectiveness thresholds considered, the cost-effectiveness of repeated screening among IDUs and MSM was widely assessed [20–22,24,28,43,44]. As previously mentioned, the more cost-effective choice was providing annual HIV testing to MSM, IDUs, and people from HIV-endemic countries, coupled with one-time screening in the general population[20–22]. Indeed, in Portugal, screening every three years presented an ICER of 34,000D /QALY in high-risk regions, while amongst MSM and IDUs, even annual screening yielded D 21,000/QALY and D 30,000/QALY [20]. Similarly, in France, annual HIV screening resulted in 51,200D /QALY for IDUs and 46,500D /QALY for French Guyana residents [21]. Differently, while one-time testing for MSM was 32,400D /QALY compared to current practice, annual screening would be more expensive (97,200D /QALY) [21]. Lucas et al. investigated the optimal frequency of repeated screening in different groups highlighting the following results: screening every 9 months for medium-risk (0.1%) and 3 months for high-risk incidence [28]. Annual testing for medium- and high-risk groups would cost less than $100,000 per QALY, while testing every 5 years would cost less than 50,000 $/QALY [28]. Screening high-risk individuals every 3 months compared with annual testing presented a gain of0.03 QALYs with an additional cost of $1357 per person [28].In the high-risk groups (HIV-undiagnosed prevalence: 3.0%), the benefits of the screening were remarkable, increasing the mean count of CD4 at diagnosis, decreasing the rate of opportunistic infections and improving survival [44]. All the above mentioned benefits further increased using repeated testing [44]. For example, one-time screening presented a mean CD4 cell count at a detection of 210 rather than 154 per cubic millimetre with no screening; moreover, testing every five years further raised CD4 cell counts at detection among incident cases (347–397 per cubic millimetre)and significantly reduced to 16% the proportion of cases detected with an opportunistic infection [44]. Considering the threshold of $100,000/QALY, all the screening programmes (one time, every five years, every three years, annually) was cost-effective in high-risk communities [44]. Similarly, considering moderate prevalence and incidence, all screening strategies (one time, every five or three years) would cost less than 100,000 $/QALY [43]. Considering exclusively MSM, one recent study investigated the impact of different screening strategies as symptom-based viral load (VL), annual routine antibody testing

or the addition to routine antibody testing of viral load. Annual routine antibody screening effectively reduced new infections (reduction of 2,8%) at a cost of $12,582/QALY. The symptom-based VL yielded greater health benefits (reduction of 5,7% in new infections) at a cost of $22,786/QALY. The integration of these two strategies was associated with the greatest health benefits (averting nearly 40,000 new infections –7.2%) infections averted, at a cost of $29,923/QALY [24]. Similarly, another US study assessed the potential role of an alternative type of test such as standard testing or NAAT, assessing the optimal frequency utilization of this analysis [40]. In this case, choosing a standard targeted screening for high-risk groups (MSM, IDU) showed more favourable ratios (annual testing <$10,000/QALY, 6-months <$20,000/QALY). Moreover, annual targeted NAAT (MSM and IDU or MSM only) presented an ICER slightly under 100,000$/QALY; by contrast, semi-annual NAAT testing was far less economically efficient [40].

3.4. Particular settings

We retrieved 12 studies considering exclusively the cost-effectiveness of HIV-screening in specific settings (see Tables 3 and 4) [23,25–27,45–52]. The majority of the authors chose a societal perspective [23,25,26,46,47,48,50,52]. All studies adopted a long-term perspective [23,25–27,45–52]. For the economic analysis, the reference year ranged from 1999 [52] to 2009 [23,25,26,27,45–48,50], adopting a discounting rate ranging from3% [23,25–27,45–50,52] to 4% [51].

3.5. Healthcare settings

In this context, the most commonly studied setting was the emergency department (ED) [27,45,47,48]. Two studies assessed the cost-effectiveness of HIV screening for ED patients compared to the standard diagnostic approach [45,47]. Both studies outlined the health benefits of similar interventions, as additional cases individuated [45] or secondary transmissions prevented (preventing 2.1 HIV transmission events over 16 months) [47]. Economically, Haukoos et al. modelled the cost-effectiveness considering the intermediate outcome of additional new infections identified. In such terms, routine screening would cost $10,693 per additional new infection identified [45]. Conversely, Dowdy et al. used the direct outcome of quality-adjusted life-years, per patient screened, targeted screening saved $112 and resulted in 2.71 quality-adjusted life-days gained [47]. Both studies identified as more influencing parameters the testing costs and the undiagnosed HIV prevalence[45,47]. ED screening remained below $35,000/QALY even at a 0.1% prevalence ($35,000/QALY) [47]. In more detail, a recent study assessed the HIV screening carried out by ED staff (provider-based) or by HIV counsellors (counsellor-based). The key difference was the coverage rate of the testing, respectively 27% in the provider programme and 57% in the counsellor programme [48]. Considering costs, the provider and counsellor strategies presented an average cost of $8.10 and $31.00 per result received, respectively [48]. In the sensitivity analysis, the findings appeared sensitive to offer and acceptance rates but were robust considering variations in undiagnosed HIV prevalence and programmatic costs [48].

Table 3
Studies characteristics for HIV screening in special setting of high-risk population. The Table summarizes the main characteristics of the studies regarding the cost-effectiveness of HIV screening in particular settings or sub-population, reporting the country in study, the scre; ening strategies, the target population or setting, the burden of HIV (as incidence or prevalence) and the outcome sought.

	Drummond evaluation	Country	Intervention	Target Population	HIV prevalence or incidence	Outcomes
Haukoos et al. [45]	8	USA	Non-targeted opt-out rapid HIV screening in Emergency Department (ED) compared to diagnostic rapid HIV testing	All patients (≥ 16 years) in ED at Denver Health Medical Center	HIV prevalence: 0.2%	Total costs per HIV-patient identified ICER as additional cost per HIV-patient identified
Schackman et al. [25]	10	USA	- Off-site testing referral - On-site rapid test - On-site rapid test + counseling Compared to no intervention	12 community-based substance abuse treatment programmes in 2009 (n = 1281 participants) Mean age 39.2 ± 11.2 years	Undiagnosed HIV: 0.4%	Life expectancy Lifetime costs QALYs ICER ($/QALY)
Cipriano et al. [46]	9	USA	HIV and HCV screening of IDUs (one-time, annually or every 3 months) compared to no screening	IDU in opioid replacement therapy, age: 15–59 years	HIV prevalence: 0.47%	Number of HIV and HCV infections QALY Costs and ICER
Dowdy et al. [47]	9	USA	HIV screening in ED versus diagnostic testing	Patients in ED (all age categories as: <29; 30–39; 40–49: 50–59 and ≥60 years)	Undiagnosed HIV: 0.8%	QALYs gained
Prabhu et al. [27]	10	USA	HIV screening in three settings: sexually transmitted disease (STD) clinics, EDs and inpatient with clinical manifestations compared to no screening	STD clinics in urban areas with a large population of MSM, EDs or inpatients with clinical manifestations Age not specified	**Undiagnosed HIV**: STD: 0.8% ED: 0.7%	Incremental cost per QALY gained
Walenski et al. [48]	10	USA	HIV routine screening in ED offered by a staff member or by HIV counselors or no screening	ED patients (mean age: 37; range: 27–47)	Undiagnosed HIV: 0.4%	Survival Costs, and cost-effectiveness
Sanders et al. [23]	10	USA	- Traditional HIV counseling and testing - Nurse-initiated routine standard screening - Nurse initiated routine rapid test screening	Primary care patients with unknown HIV-status, age: 18–65 years (n = 251)	Undiagnosed HIV: 0.398%	Life-years, QALY Costs and ICER ($/QALY)
Wilson et al. [49]	8	Australia	HIV screening in sex workers (different frequencies) compared to current status (testing every three months)	Female sex workers (age not specified)	HIV incidence: 0.1/100	Expected number of transmissions to clients Costs and ICER (cost per infection averted and cost per QALY saved)
Coco et al. [26]	9	USA	Routine HIV testing for patients with viral symptoms versus no testing	Outpatients with fever or general viral symptoms (age not specified)	HIV prevalence: 0.66%	Number of cases identified Incremental cost-effectiveness ($/QALY)
Walenski et al. [50]	10	USA	Routine HIV screening in hospitalized patients	General inpatients in US hospitals (Mean age: 55.8 ± 11.9 years)	Undiagnosed HIV: 1%	QALY ICER (as $/QALY gained)
Bos et al. [51]	8	The Netherlands	Routine screening in STD clinics compared to no screening	General attenders of STD clinics in Rotterdam (age not specified)	HIV prevalence: 0.4%	Secondary transmission averted Life-years gained (LYG) ICER as €/LYG and €/averted infection
Phillips et al. [52]	10	USA	Routine HIV screening in Primary care practices or Targeted Screening to high-risk patients	New visits in Primary care(general and family practice and internal medicine); age: 15–65 years	Undiagnosed HIV: 0.15%	Cost per infection identified Costs and numbers of infections averted Additional years of life and QALY gained

Abbreviations: ED: Emergency Department; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; IDUs: injecting drug users; MSM: men who have sex with men; STD: sexually transmitted disease;LYG:Life-years gained.

Table 4
Economical characteristics for HIV screening in special setting of high-risk population. The Table summarizes the main economical characteristics of the studies regarding the cost-effectiveness of HIV screening in limited sub-population or in particular settings, reporting the adopted perspective, the time horizon, the currency and reference year, the type of costs included in the analysis and the main results.

	Perspective	Time horizon	Currency and reference year	Costs included	Results
Haukoos et al. [45]	ED perspective	–	2009 US$	Direct programmatic costs included: startup costs, labor for administrative, ED and laboratory staff, supplies and equipment	Confronted to diagnostic approach, non-targeted HIV screening identified 11 additional infections, costing $10,693 per additional infection identified
Schackman et al. [25]	Societal	Lifetime	2009 US$, discounting rate: 3%	Costs included counseling, testing, waiting and testing time, travel for off-site test, confirmatory testing and treatment. Research-related and startup cost were excluded	The off-site referral programme was dominated by on-site testing. Rapid test-only cost $60,300/QALY. The addition of counseling would cost 36$ per patient more, without further benefits. Cost-effectiveness decrease to $76,300/QALY reducing undiagnosed HIV prevalence (0.1%)
Cipriano et al. [46]	Societal	20-year	2009 US$, discounting rate: 3%	Costs included baseline general healthcare, ORT, death IDU-related, testing (antibodies + RNA amplification), counseling (pre- and post- test) and ART	Annual HIV-HCV antibody screening cost $35,100/LY and $80,800/QALY compared to no screening. The HIV-screening every 6 months cost $30,700/QALY-HIV antibody + HIV RNA every 6 months cost $65,900/QALY compared to screening annually. The addition of HIV viral RNA testing to standard testing would avert 14.8–30.3 new HIV in a population of 26,100 IDUs over 20 years, depending on screening frequency.
Dowdy et al. [47]	Societal	Lifetime	2009 US$, discounting rate: 3%	Costs included testing (test kit, laboratory and ED costs), confirmatory test, project management and treatment (ART and non-ART treatment)	In 16 months 2406 patients without symptoms were screened, with 19 (0.8%) new diagnosis). Screening prevented 2.1 secondary transmissions over 16 months. Assuming no transmission benefits, the screening cost $77,000/QALY. Cost-effectiveness improved increasing undiagnosed HIV-prevalence.
Prabhu et al. [27]	Provider	Lifetime	2009 US$	Costs included both treatment and programme costs. Treatment costs included healthcare resource use, ART, laboratory monitoring, diagnosis and therapy of opportunistic infections and costs incurred during the last month of life. Program costs included marginal costs associated with testing and counseling. The cost of administrative overhead and other costs were not included.	At ART initiation CD4 $\leq$ 350 cell/μL, the ED routine screening cost $34,597/QALY. Assessing for secondary transmissions, screening in ED and STD clinics were cost saving. At ART initiation CD4 $\leq$ 500 cell/μL, the two strategies stayed cost saving. Screening in STD clinics and EDs was always cost-effective compared to testing inpatients.
Walenski et al. [48]	Societal	Lifetime	2009 US $, discounting rate: 3%	Costs included testing, reviewing positive and negative results, CD4 test, HIV RNA test, and HIV medical costs (routine care, ART, opportunistic infections). All indirect costs were excluded	The Provider strategy (compared to no screening) cost $58,700/QALY and the Counselor strategy (compared to Provider) $64,500/QALY. In sensitivity analysis, the major influencing parameters were: relative offer and acceptance rates by strategy and the capacity of providers to target-screen, while results appear robust varying undiagnosed HIV prevalence and programmatic costs.
Sanders et al. [23]	Societal	Lifetime	2007 US$, discounting rate: 3%	All direct costs of medical care including physician and nurse time, testing, counseling, follow up and treatment. The patient time cost was not included. Age-specific medical expenditures unrelated to HIV care were included	The optimal strategy was nurse-initiated rapid testing ($36,390/QALY not accounting for transmission benefits and $10,600/QALY considering them). The results were robust across sensitivity analysis.
Wilson et al. [49]	Health-sector	Lifetime for male clients	Australian Dollars ($A), discounting rate: 3%	Costs included testing and treatment costs (for sex workers and male clients)	Considering a threshold of $A50,000/QALY, HIV testing should not be conducted at a frequency <40 weeks
Coco et al. [26]	Societal	39.9 years	2002 US$, discounting rate: 3%	All costs were included except for work loss and transportation. Costs included counseling, testing, and referral, including the cost of HIV counselors and nurses. Therapy included clinical visits costs and lifetime medical costs (as ART)	In baseline, p24 antigen EIA testing cost $30,800/QALY compared to no testing. In multi-way sensitivity analysis screening with p24 antigen EIA compared with no testing had a 67% probability of being cost-effective at baseline prevalence and of 71% at a prevalence of 1%.
Walenski et al. [50]	Societal	Lifetime	2001 US$, discounting rate: 3%	Costs included testing, counseling and therapies (ART and opportunistic infection therapy)	In base-case, routine HIV-screening for general inpatients would cost $35,400/QALY. At 0.1% HIV prevalence, screening would cost $64,500/QALY.
Bos et al. [51]	Not specified	Lifetime	€, discounting rate: 4%	Costs included testing, confirmation test, counseling and therapy	Routine screening would cost €2987/LYG, with an extremely worthwhile economic profile
Phillips et al. [52]	Societal	Lifetime	1999 US$, discounting rate: 3%	Costs included testing, risk history assessment, counseling, ART and viral load. Authors excluded patient time value, office visit charges, administrative and lost productivity costs.	Routine test is the most cost-effective approach ($22,000/QALY and $17,600/LYG). With a behavioural impact >10%, both routine and targeted testing were cost saving. Employing risk histories is less cost-effective than routine testing, but it appears similarly cost-effective in plausible ranges of sensitivity analyses.

Abbreviations: ED: Emergency Department; QALY: quality-adjusted life years; ORT: opioid replacement therapy;IDUs: injecting drug users; ART: anti-retroviral therapy; LY: life year; STD: sexually transmitted disease; EIA: Enzyme Immuno Assay; LYG: life years gained.

An additional study focused on routine screening in EDs, com-pared to diagnostic testing upon symptomatic manifestations. Assessing the screening impact on secondary transmissions, universal testing in EDs was cost-saving, adding an additional 2.5(2.3–2.6) QALYs [27]. Compared to standard diagnosis in inpatient settings, the cost per QALY for screening in the ED setting was$34,597 [27]. More broadly, Walensky et al. studied the implementation of routine HIV screening for all inpatients in US hospitals, assuming a moderate acceptance rate of 37%. This screening presented significant health benefits such as additional quality-adjusted life months, a higher CD4 count at diagnosis and reduction of opportunistic infections at diagnosis [50]. The screening was below $100,000/QALY both in cases of high HIV prevalence (1%) ($35,400/QALY) and considering the lower prevalence of 0.1% ($64,500/QALY). As expected, programmes with a higher acceptance rate were more economically attractive [50]. Another interesting healthcare setting is primary care (general, family practice and internal medicine). In this environment, Phillips et al. considered two approaches such as universal HIV testing or targeted high-risk testing. High-risk subjects were individuated through a behavioural assessment. It was assumed that approximately 31% of users presented at least one risk factor. Therefore, routine screening would cost $22,000/QALY gained. In the sensitivity analysis, the targeted strategy became more favourable when individuals at risk were below 23% or the cost of risk assessment decreased. Moreover, considering a behavioural impact higher than 10%, both routine and targeted testing appeared to be cost saving [52]. The behavioural impact of HIV screening consisted of a reduction of at-risk behaviour among tested people; in particular, it translated to a reduction of sexual transmissions [52]. Given the importance of HIV screening in primary care, in this setting, Sanders et al. investigated the role of different approaches, such as traditional HIV testing and counselling, nurse-initiated HIV screening or nurse-initiated screening through a rapid test. Both nurse strategies presented better test acceptance and result receipt compared to the standard approach. Precisely, the better option was nurse-initiated rapid testing [23]. Moreover, the implementation of HIV testing was assessed for outpatients presenting fever or other viral symptomatology. The authors investigated the impact of different tests, such as p24 antigen EIA, HIV-RNA or 3rd-generation EIA. The most cost-effective programme offered p24 antigen EIA with a cost-effectiveness ratio of $30,800/QALY, preventing over 400 new infections [26].

3.6. STD clinics

The implementation of HIV screening in STD clinics occurred in two studies [27,51]. The implementation of HIV screening in STD clinics, compared to diagnostic testing upon symptomatic manifestations, yielded, excluding the effect of HIV transmission, 34.597$/QALY at a CD4 cell count of 350 cells/L, similarly to ED screening, where treatment with HAART for the index patient was initiated at a CD4 count of 500 cells/L, whereas an ICER of approximately $60,000 per QALY was gained at a CD4 count of 500 cells/L in STD clinic settings. [27]. Similarly, a European study in this same setting reported D 2987/LYG with a similar screening. Likewise, assuming a lower behavioural impact (20%), the intervention presented an ICER of13,438D /LYG [51]. The authors also considered health benefits gained, such as CD4 count, opportunistic infections, the mean time from infection to the start of HAART and the avoidance of HIV infection in partners [27,51]. The difference of the results presented in the studies could be imputed to the different costs included in the analysis. For example, one study excluded the research-related and start-up costs from the model [27].

3.7. Substance abuse treatment programmes

One commonly identified high-risk group are IDUs. Two studies assessed the role of HIV screening in substance abuse treatment programmes [25,46]. The more recent study considered three different strategies, specifically, off-site referral for testing and on-site rapid test with or without counselling. The best option appeared to be on-site testing with an ICER of $60,300/QALY, dominating the off-site referral option. In the sensitivity analysis, offering a rapid test in this setting was <$100,000/QALY, even in case of low HIV prevalence (0.1%). In contrast, the addition of counselling did not bring any additional health benefit [25]. The second study considered HIV screening during opioid replacement therapy (ORT). Offering HIV screening in this setting averted up to 28 new infections, depending on the testing frequency. However, adding HIV-RNA testing, in order to identify acute infections, prevented more cases than simply increasing the screening frequency. Screening for HIV antibodies every 6 months cost $30,700/QALY gained, whereas screening for HIV antibodies and viral RNA every 6months had an ICER of $65,900/QALY gained compared to screening annually [46]. The present studies underlined the individual health benefits of HIV screening in terms of disease progression, mortality and transmission from sexual partnerships and injection equipment sharing through risk-structured mass action [46].

3.8. Sex workers

Even if most studies outlined the necessity to increase the screening frequency in specific settings, this is not always the case. Indeed, one paper regarding female sex workers highlighted an excess in testing under the current policy in Australia, where sex workers undertook HIV testing every three months. At the actual incidence rate (HIV: 0.1/100), the current screening strategy would cost over $A4,000.000 for every HIV infection averted and $A10,000.000 for each QALY saved. Screening remained under $A50,000 per QALY gained only with a testing frequency below 40 weeks [49].

4. Discussion

Given the well-established benefits, both individual and collective, of early HIV diagnosis, the implementation of HIV screening appears extremely important [3–6]. The scientific evidence regarding HIV screening is variegated, considering the screening approach, the type of test, the testing frequency and the target population [4,20–22,24,39,52]. To identify the most favourable strategy, policymakers have required accurate cost-effectiveness investigations. Then, the aim of our review was to summarize the available evidence regarding the cost-effectiveness of HIV screening, concentrating on high-income countries as more comparable. First, the cost-effectiveness of one-time screening for the general population was widely assessed in all the considered countries [4,20–22,28,39–43]. In their sensitivity analysis, these studies outlined the cost-effectiveness of similar programmes, even at an extremely low HIV prevalence [39–43]. In some countries with a higher HIV-burden, such as Russia or Portugal, even repeated screening in the general population was cost-effective [20,42]. Therefore, offering one-time screening to the general population appeared desirable, even in cases of an HIV prevalence lower than the CDC recommendations for screening implementation [10]. Moreover, the expansion of HIV screening to older cohorts seemed economically attractive in many circumstances, particularly whenever the prevalence exceeded 0.1% [53]. In addition, repeated screening of the general population could be useful in cases of a moderate

prevalence and incidence rate [42]. Furthermore, the repeated screening of high-risk groups appeared particularly interesting. Indeed, annual screening of IDUs or of people from endemic countries fell well within the cost-effectiveness limits [20–22,39,42]. The decision regarding the optimal testing frequency requires further studies and depends primarily on the HIV prevalence and incidence [20–22,39,42]. Indeed, with an increasing HIV burden, repeated screening has become increasingly more attractive [20–22,39,42]. Another important theme is the correct selection of high-risk groups and the individuation of effective strategies to reach them. Thus, information campaigns and appropriate counselling appear important in order to increase test acceptance. All the retrieved studies agreed about the importance of increase testing uptake [20–22,39,42]. In this sense, an important function could be carried out by stigma reduction. It must be taken into account that programmes proposed as routine testing reach higher acceptance than those presented as targeted towards at-risk sub-populations [54,55]. Another important parameter in determining cost-effectiveness is the impact upon behavioural changes [20–22,41,44]. Consequently, the efforts to minimize at-risk behaviours should be accentuated. Precisely, the programmes aiming to reduce risky behaviours appear to be a key component of HIV screening success. Moreover, the impact of HIV screening upon risk behaviours may be underestimated; indeed, some studies exclusively assessed the effect on sexual behaviours, ignoring the potential impact on other behaviours, such as needle sharing [20,42]. However, even in the worst-case scenario, the screening stayed cost-effective [21,22,25,42,47,50]. In particular, the attractiveness of screening was established using both standard and rapid testing [21,22,28,39,41]. However, some studies highlighted the advantages, even economic, of rapid testing [9,28]. Indeed, a rapid test, with its same-day results, maximizes the receipt rate. This is extremely important considering the influence of loss to follow-up on cost-effectiveness [20,21,42]. In addition, the impact of testing costs was investigated, highlighting the screening cost-effectiveness within a wide range of plausible costs. Another component of testing costs considered was counselling. The findings were heterogeneous. In particular, the addition of counselling to IDU screening did not present any additional benefit but was associated with a lower acceptance rate [25]. In older cohorts, the implementation of abbreviated counselling was linked with increased health benefits and a more-attractive ICER [53]. In EDs, counselling by HIV specialists is associated with higher acceptance [48]. In primary care, nurse counselling appears to be more favourable than the standard medical approach [52]. In summary, the optimal counselling strategy should be further investigated, also depending on different settings considered. In particular, it may be interesting to assess the exact impact of counselling on behavioural changes and secondary transmissions. One study outlined the importance of HIV screening as a component of a larger HIV prevention project. Indeed, integrative programmes work better than individual ones, presenting synergistic effects [46]. Therefore, it appears important to choose the most effective strategies to implement together, considering the potential complementary effects. The cost-effectiveness of HIV screening was assessed in a limited number of high-income countries. However, as several countries appear comparable in terms of resources and HIV burden, the retrieved results are widely applicable. Moreover, in the sensitivity analysis, a wide range of scenarios was tested, proving the robustness of the retrieved findings [4,20–22,28,39–43]. Another issue emerging from our review was related to HIV acute infections. The impact of acute infection on overall HIV transmission is not negligible. Therefore, some studies have focused on specific programmes to identify these infections [24,26,40]. The most cost-effective test, in this case, appeared to be a 4th generation ELISA test or more specific and expensive tests targeted towards high-incidence subpopulations [40]. Another cost-effective approach was testing outpatients reporting fever or viral symptoms [26]. In summary, the investigation of acute infections appeared

interesting, especially considering high-incidence groups. The most cost-effective strategy must be chosen depending on the HIV burden, specific setting and population. The main limitations consisted of the heterogeneity of the results and strategies tested. Indeed, the studies retrieved employed non-uniform values as cost-effectiveness thresholds. Inasmuch, some authors choose the traditional value of $100,000/QALY [21,44,53], while others set a lower limit of $50,000/QALY [4,26] or $75,000/QALY [23]. Furthermore, other studies have considered the suggested WHO thresholds [20]. Actually, the exact cost-effectiveness threshold is still debated [30]. Nonetheless, all the studies have outlined the economic and health attractiveness of these programmes. Moreover, HIV screening favourably compares with other screenings taking place in the considered countries [21,41,50]. Another source of heterogeneity is represented by the different types of costs included in the studies. In particular, it appeared difficult to correctly estimate all the indirect costs, such as losses of productivity. These issues are partially resolved by testing a wide range of costs in the sensitivity analysis. Additional limitations are attributable to the lack of accurate data; most were estimates of HIV prevalence and incidence, the costs of HIV testing and therapies. However, the cost-effectiveness of HIV screening appeared robust across various scenarios, even considering costs higher than the current value and an HIV prevalence lower than those experienced in most countries. Furthermore, the studies employed conservative estimates. Consequently, the real cost-effectiveness of HIV screening could be even underscored. Finally, most papers used mathematical models, therefore simplifying the real progression of HIV disease and estimating the long-term consequences based on multiple and heterogeneous sources. However, in this case, the wide assumptions used in the sensitivity analysis could effectively control this issue. One additional limitation of our review and, in general, of the literature available regarding the topic of interest, is the lack of observational studies of cost-effectiveness. Some direct experience of universal screening worldwide existed, but the economic analyses in this regard are scarce or have a very short time horizon. Possibly, in the next years, information regarding these experiences will grow, providing more direct data for economic and cost-utility analyses. Since the choice of the correct threshold may be difficult, we also compare HIV screening with other interventions in the field of HIV prevention. Interestingly, HIV screening favourably compares with this strategy and may be a part of a larger programme. For example, antenatal HIV screening has been considered cost-effective in several studies [56]. In addition, increasing antiretroviral use to 75% of eligible patients would be cost-effective ($20,300/QALY) [22]. Integrating this latter strategy with HIV screening would be very cost-effective ($21,580/QALY) [22].

5. Conclusion

In conclusion, the evidence regarding the health benefits and cost-effectiveness of HIV screening is growing, even in low-prevalence countries. The major determinant of cost-effectiveness remains the baseline HIV prevalence. In particular, in high-risk groups, repeated testing is especially attractive, while in the general population, one-time screening is worthwhile. From our review, both standard and rapid testing are cost-effective. However, increasing evidence outlines the benefits of rapid testing. Further studies are required to define the optimal screening frequency in both general and high-risk populations. However, despite the high heterogeneity of the retrieved studies, scientific evidence suggests the cost-effectiveness of HIV screening in multiple populations and settings. Another important, emerging topic is the impact of counselling. Further studies are required to exactly

define the best screening strategy considering the potential role of less-expensive, abbreviated counselling. Finally, our analysis highlighted the cost-effectiveness of HIV screening implementation even with higher frequencies and in populations with a lower prevalence than those recommended by the CDC [10]. The extension of HIV screening, even to older cohorts, is particularly interesting. However, the feasibility of similar choices should be weighed considering the available resources. Furthermore, the attractiveness of the screening programme was extensively outlined in specific settings such as EDs, primary care, STD clinics and substance abuse treatment programmes. In conclusion, our review may provide some useful directions to policy-makers, as follows:

• One-time screening offered to adult populations appears to be avaluable choice;

• Repeated testing in high-risk groups such as IDUs and MSM is an important tool in the field of HIV prevention;

• The evidence regarding the benefits of the use of rapid tests, even in terms of cost-effectiveness, is growing;

• Specific settings, such as STD clinics or EDs, may play an importan trole in offering HIV testing;

• HIV screening may be beneficial even in selected cohorts of older patients, according to the baseline prevalence in these groups.

Conflict of interests

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version.

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