The Epidemiology of HIV Infection Among People Who Inject Drugs in the Middle East and North Africa

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STATEMENT OF OWN WORK

I, Ghina Riad Moumtaz, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:  Date: January 10, 2017

ABSTRACT

This thesis aims to address a major knowledge gap in understanding the epidemiology of HIV infection among people who inject drugs (PWID) in the Middle East and North Africa (MENA) by 1) assessing HIV epidemic state, 2) estimating HIV epidemic potential using hepatitis C virus (HCV) prevalence, and 3) estimating HIV incidence and impact of interventions on incidence. Methods included systematic review and data synthesis, mathematical modelling, and ecological analysis of systematic review data.

There was evidence of HIV epidemics among PWID in at least one-third of countries, most being emerging concentrated epidemics with HIV prevalence of about 10-15%. The overall high injecting risk environment suggests potential for further spread.

Mathematical modelling indicated, across a range of HCV prevalence, overall acceptable precision in predicting endemic HIV prevalence among PWID. Ecological analysis on PWID MENA data also indicated a positive, statistically significant association between HCV and HIV endemic prevalence. Of nine MENA countries with data, five have high and three medium HIV epidemic potential, based on current HCV prevalence.

The estimated HIV incidence rate among PWID ranged between 0.7% per person-year (ppy) and 7.8% ppy. Further, substantial number of HIV infections in the general population were estimated to be due to the dynamics of injecting drug use, namely among ex-PWID and sexual partners of current/ex-PWID. It was predicted that scale-up of antiretroviral therapy and harm reduction services could avert up to 90% and 70% of incident infections among PWID and their sexual partners, respectively.

In conclusion, this thesis identified recent emerging HIV epidemics with high HIV incidence rates among PWID in multiple MENA countries. A novel method for estimating HIV epidemic potential using current HCV prevalence was demonstrated. In MENA, further HIV epidemic growth among PWID is predicted in most countries. Scale-up of HIV/drug interventions is needed to halt the growing epidemics.

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ACRONYMS AND ABBREVIATIONS

ART	Antiretroviral therapy
FSW	Female sex worker
GBD	Global Burden of Disease
HCV	Hepatitis C virus
IBBSS	Integrated bio-behavioural surveillance survey(s)
IQR	Interquartile range
KP	Key population at increased risk
MENA	Middle East and North Africa
MSM	Men who have sex with men
NGO	Non-governmental organization
NSP	Needle and syringe programmes
OPT	Occupied Palestinian Territories
$OR_{HCV/HIV}$	Odds ratio of HCV prevalence to HIV prevalence
OST	Opioid substitution therapy
PLHIV	People living with HIV/AIDS
ppy	Per person year
PWID	People/person who inject(s) drugs
ROB	Risk of bias
$RR_{HCV/HIV}$	Risk ratio of HCV prevalence to HIV prevalence
STI	Sexually transmitted infection
UI	Uncertainty interval
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization
WHO/EMRO	Eastern Mediterranean Region Office of the World Health Organization

1. INTRODUCTION

1.1. MENA DEFINITION

The definition of the boundaries of the Middle East and North Africa (MENA) varies between different regional and international organizations. In this thesis, MENA includes countries that are part of the MENA definitions of all three United Nations agencies leading most HIV/AIDS efforts in the region; the Joint United Nations Programme on HIV/AIDS (UNAIDS), the Eastern Mediterranean Region Office of the World Health Organization (WHO/EMRO), and the World Bank. Since the goal of this research is to impact policymaking and facilitate evidence-informed HIV prevention and intervention programming in the region, having an operational definition of MENA that falls into the mandates and catchment areas of these organizations is essential. The definition includes the following 23 countries that share historical, socio-cultural, or linguistic similarities:

Afghanistan, Algeria, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan (including South Sudan), Syria, Tunisia, United Arab Emirates, West Bank and Gaza (Occupied Palestinian Territories (OPT)), and Yemen.

Figure 1.1. Map of the Middle and North Africa.

1.2. OVERALL AIM AND OBJECTIVES

Rationale

MENA is one of the region where knowledge of the HIV epidemic continues to be limited. Yet, based on scattered available data, the region is thought to have one of the fastest growing HIV epidemics despite overall low HIV prevalence [1, 2]. Much remains to be known about HIV epidemic dynamics in MENA, particularly among key populations at increased risk (KPs) where most HIV infections appear to be happening [3]. One of these KPs is people who inject drugs (PWID), who bear a disproportionate burden of HIV infections globally.

Emerging HIV epidemics have been recently documented among men who have sex with men (MSM) in MENA [4]. There could be similar epidemic trends among the other KPs, namely PWID in a region that is at the centre of major drug production and trade routes. MENA has also a number of social and structural drivers of risk and vulnerability for injecting drug use and HIV such as a political instability, refugee population movements, a large youth population, high unemployment rates, and high levels of stigma and non-supportive policy responses, among others. Fortunately, the recent nature of the documented epidemics in the region means that there is a window of opportunity for prevention that should not be missed to halt the growing epidemics.

Following investments by global donors such as the Global Fund, there has been a remarkable increase in the number of integrated bio-behavioural surveillance surveys (IBBSS) in MENA, particularly among KPs. This large volume of data that became available in the last few years is yet to be analysed and synthesized within a country-specific or a regional context to characterize the HIV epidemics in this region. A critical understanding of the status, scale, and epidemic potential of the epidemic in MENA is critical for evidence-informed political advocacy to control the epidemic and increase commitment to HIV surveillance, prevention, and treatment.

Aims and objectives

The overall aim of this thesis is to address a major gap in knowledge and understanding of the epidemiology of HIV infection among PWID in MENA, by assessing the status of the HIV

epidemic, estimating HIV epidemic potential, and estimating HIV incidence and the impact of interventions on HIV incidence at country-level among this population group.

Specific objectives are as follows:

Objective 1

To provide a critical description of the epidemiology of HIV infection among PWID in MENA through a systematic review, synthesis, and analysis of biological and behavioural data.

Objective 2

To explore, through mathematical modelling, the use of hepatitis C virus (HCV) prevalence as a proxy biomarker of future HIV prevalence, as a novel and practical tool to estimate HIV epidemic potential among PWID in resource-limited settings such as MENA.

Objective 3

To analyse, through ecological analysis of systematic review data, the epidemiological association between HCV and HIV prevalence among PWID in MENA, and to estimate HIV epidemic potential in this population across MENA countries using HCV prevalence data.

Objective 4

To estimate, through mathematical modelling, at country-level in MENA: HIV incidence among PWID that is due to sharing non-sterile injecting equipment, HIV incidence among PWID sexual partners that is due to heterosexual sex with infected PWID, the role of injecting drug use as a driver of the HIV epidemic in the population, and the impact of select interventions on HIV incidence.

1.3. BACKGROUND

This section provides background information on the global epidemiology of injecting drug use and of HIV and HCV among PWID. A discussion of the epidemiological links between HIV and HCV infections among PWID, and an overview of HIV and HCV prevention interventions among PWID are provided. This section also highlights the significance of conducting this research work in MENA, by describing in this region: the context of risk and vulnerability, overall understanding of HIV epidemiology, and, briefly, the status of HIV response.

1.3.1. Global epidemiology of injecting drug use and associated HIV and HCV infection burden

PWID are typically one of the most hidden and hard-to-reach KPs. They face criminalization, stigma and discrimination, and are marginalized by family members and society [5]. This makes population size estimates for PWID challenging to ascertain; and hence global estimates for injecting drugs use have wide ranges. It is estimated that there are 11-21 million PWID worldwide, with a middle estimate of 16 million, with China, the USA, and Russia carrying the largest numbers [6]. The population prevalence of injecting drug use across all countries is estimated at 0.36%, and ranges from 0.06% in South Asia to 1.50% in eastern Europe [6]. These estimates by the Reference Group to the UN on HIV and Injecting Drug Use, are based on extrapolations using injecting drug use estimates identified in 61 out of 148 countries where this practice has been documented [6, 7].

Injecting drug use is a major global health issue and contributor to the global burden of disease due to associated morbidity and mortality, largely caused by the transmission of blood-borne viral infections - namely HIV and HCV - through unsafe drug injection [8]. The Reference Group to the UN on HIV and Injecting Drug Use estimates that about 3.0 million PWID worldwide are infected with HIV (range 0.8-6.6 million), leading to a global HIV prevalence of 19% among PWID [6]. HIV prevalence among PWID varies considerably between and within countries and ranges between less than 0.01% to 72% (Estonia) [6]. It is overall highest in countries of Southeast Asia, eastern Europe, and Latin America where it has been reported to exceed 40% among PWID subpopulations [6].

HCV infection burden among PWID is even more substantial, due to more efficient transmission than HIV via the parenteral route [9]. It is estimated that about 10.0 million PWID are anti-HCV positive (range: 6.0-15.2 million) [10]. With the estimated 16 million PWID globally, this leads to an HCV prevalence of 63% among PWID [10]. Out of 77 countries with HCV prevalence data among PWID, anti-HCV prevalence is in the range of 60-80% in 25 countries, and over 80% in 12 countries [10]. It is reported lowest in Paraguay at 10% and highest in Mexico at 97% [10].

1.3.2. HIV and HCV epidemiological links among PWID

Because HIV and HCV are transmitted along the same parenteral route among PWID, they often co-infect the same individuals. HCV is however 4-10 times more transmissible per percutaneous injection than HIV [11-14], and therefore is usually acquired before HIV at the individual level. This also explains why HCV prevalence among PWID is larger than HIV prevalence, and why HCV is hyperendemic among PWID globally but HIV is not [6, 10]. A recent meta-analysis identified that 82% of HIV-infected PWID globally are co-infected with HCV [15]. HIV-positive PWID were found to have a six-time increased odds of HCV infection compared with HIV-negative PWID [15], a finding consistent with the fact that both infections are caused by the same injecting risk behaviour. Although HIV and, in specific situations [16], HCV can be transmitted sexually, sharing of needles/syringes is their main transmission mode among PWID [17].

1.3.3. Overview of prevention interventions among PWID

A number of prevention interventions have proven to be successful in curbing HIV transmission among PWID [18]. Harm reduction strategies include primarily the provision of sterile injecting equipment through needle and syringe programmes (NSP), and opioid substitution therapy (OST) - the supervised administration of psychoactive medications that aim at reducing opioid dependence and withdrawal symptoms [19]. Recent systematic reviews and meta-analyses have documented a reduction in HIV transmission by up to 58% associated with exposure to NSP [20] and by 54% to OST [21]. OST was also associated with improved ART-related outcomes (recruitment onto ART, ART coverage and adherence, and viral suppression) among PWID living with HIV [19].

Evidence on the prevention benefit of ART in reducing HIV parenteral transmission among PWID appears to be confined to one cohort study in Vancouver where a temporal association was observed between PWID community viral load and reduced HIV incidence [22]. However, ART has been proven to reduce heterosexual HIV transmission by up to 96% due to decreased viral load [23, 24], and recent evidence suggested also prevention benefit among MSM [25]. It is therefore plausible and likely that ART could similarly reduce HIV parenteral transmission through the same biological mechanism.

While unsafe injection is the main mode of HIV transmission among PWID, sexual transmission can occur and might not be insignificant among specific sub-populations of PWID who are also MSM or FSWs [26, 27]. Therefore, ART, coupled with sexual-risk reduction strategies including

condom provision and education, play a role in reducing sexual HIV transmission among PWID, and also, importantly, transmission to their non-injecting sexual partners [18, 28].

Each of these prevention interventions, however, may achieve modest reductions in HIV transmission if implemented alone. The evidence indicates that efficient strategies for prevention of HIV infections in PWID need comprehensive packages and combined approaches, in addition to high coverage, especially in settings with high prevalence and substantial levels of risk behaviour [18, 19, 28, 29]. Such comprehensive approaches would include NSP, OST, voluntary counselling and testing, ART, prevention of sexually transmitted infections, education programs, in addition to hepatitis diagnosis and treatment [28].

Although the use of ART for pre-exposure prophylaxis was significantly associated with a 49% reduction in HIV incidence among PWID in a randomised, double-blind, placebo-controlled trial [30], more research is needed to establish, not only effectiveness, but also strategies for large-scale implementation of this intervention among PWID [30]. Currently, pre-exposure prophylaxis is not included as part of WHO's recommendations of HIV prevention packages among PWID [31].

While reduction of HCV transmission is also expected with harm reduction services in view of the associated reduction in injecting risk behaviour, there is overall insufficient evidence of these services impact on HCV incidence [32]. However, recent epidemiological and mathematical modeling analyses have suggested that high coverage NSP and OST can reduce HCV incidence and prevalence, especially if in combination [33, 34]. These reductions, nevertheless, are overall modest in scale and would require a long time to materialize, mainly due to high background HCV prevalence among most PWID populations globally [33]. Combining harm reduction services with current HCV treatment were shown to enhance their impact [35], and potentially more so with the new direct-acting antivirals to treat HCV [36].

Despite the prevention benefits of harm reduction services among PWID, coverage remains insufficient globally. In 2014, NSP and OST were implemented respectively in about half of all countries where injecting drug use has been documented [37]. Generally, coverage is lower in low- and middle-income countries, though it varies widely among and within regions and countries [37]. Between 2012 and 2014, the greatest increase in NSP provision was seen in Malaysia, Iran, and Australia, while the most striking scale-up of OST was implemented in

Vietnam [37]. A decrease in provision of services was seen in a few countries including Pakistan and Oman, two MENA countries [37].

1.3.4. Context of risk and vulnerability in MENA

Similar to other regions, MENA has several vulnerability factors for HIV. Overall, the social determinants of health in terms of political conflict, limited resources, and gender inequity continue to challenge the region [38]. Youth constitute a major proportion of MENA populations, with one-fifth of the population aged 15-24 years [39, 40], normally the age of sexual debut [40]. It is estimated that in 2015, the average median age across the 23 MENA countries was 24.0 years [41]. The recent Arab spring revealed the frustrations and challenges youth are experiencing, including high unemployment rates, widening gap between rising aspirations with mass education and lack of political reforms, poverty, and oppression.

MENA has the highest number of refugees and internally displaced persons in the world [42]. In 2015, over half of refugees worldwide came from three MENA countries (Syria, Afghanistan, and Somalia), and 39% of the world's displaced people were hosted by MENA countries [42]. The Arab Middle East has received more than 10% of the world's migrants [43]. The overwhelming majority of these are males, and about half are single or without their spouses [44, 45], and therefore may be vulnerable to practices that increase the risk of exposure to HIV [46].

Denial that HIV exists in society or is an important challenge remains widespread. KPs including PWID, MSM, and female sex workers (FSWs) are highly stigmatized and lack access to comprehensive and confidential services. Despite the emergence of community organizations serving vulnerable groups, their efforts are in most instances not well coordinated and remain insufficient to meet current needs. Health promotion approaches remain didactic, prescriptive, largely non-participatory, and divorced from behavioural theory.

PWID are one of the central KPs in MENA, a region with several vulnerability factors for injecting drug use. For example, 83% of the global supply of heroin is produced in Afghanistan [47], and over 75% of this is trafficked through Iran and Pakistan, which contributed to opioids dependence epidemics in these neighbouring countries [48]. In 2014, Iran bore the highest fraction of the global opium and heroin seizures (75% and 17%, respectively) [49]. Increased

availability and purity of heroin at lower prices in MENA appears to have led to a subsequent rise in injecting drug use [50]. In 2010, one gram of heroin in Afghanistan could be purchased for about US$4 compared with up to US$100 in West and Central Europe, US$200 in the United States and Northern Europe, and US$370 in Australia [47]. The pattern of heroin dependence epidemics fuelling heroin injection epidemics; in turn fuelling HIV epidemics among IDUs, has been previously documented in settings with a similar risk environment of drug production, trafficking, and use such as Uzbekistan, Tajikistan, and European Russia [50].

The region has also several vulnerability factors for sexual risk behaviour. Within prevailing socio-economic conditions, it has been difficult for youth to start sanctioned sexual activity, and the age at first marriage has increased in most countries by as much as 8 years in 20 years [51]. There appears to be an ongoing socio-cultural transition in multiple countries leading to increased tolerance of practices such as premarital and extramarital sex [52]. This is accompanied by accelerated modernization - including mass education and urbanization, exposure to different cultures, and enhanced communication and technology means [52-54].

1.3.5. Understanding of HIV epidemiology in MENA

MENA is one of the regions where knowledge of the HIV epidemic continues to be limited, and there is a widespread belief that the region is "a real hole in terms of HIV/AIDS epidemiological data" [55]. When this thesis was planned, UNAIDS stated in their 2010 Global Report that "data on the epidemics in MENA remain in short supply" [1], and that the available data suggest that despite overall low HIV prevalence, MENA is one of the regions with the fastest growing HIV epidemic [1, 2]. They estimated that the number of new infections and AIDS-related deaths in their definition of MENA (excluding Afghanistan and Pakistan) increased by almost two-folds between 2001 and 2010 when they reached 84,000 and 39,000 people respectively [2]. More recently, MENA was found to be one of the few regions where the number of new HIV infections increased between 2010 and 2015; and the vast majority of these infections seemed to be happening among KPs and their sexual partners [3].

The apparent lack of data has stimulated an intense debate on the status of the epidemic in MENA [56]. One viewpoint, prominent in the earlier years of the epidemic, was that the region is protected from HIV because of its conservative socio-cultural traditions, including strong prohibitions against premarital and extramarital sex, homosexuality, and alcohol and drug use

[57, 58]. This perhaps has incited a radically opposing view that considered “cultural immunity” a form of denial of a major public health crisis “behind the veil”, predicting a severe health burden and mortality among the 15 to 49 year age group if immediate action was not taken [59, 60]. In truth, much of these assumptions seemed to be fuelled by preconceived notions and none were substantiated by scientific evidence [56].

This thesis work comes in the context of a large effort to provide a scientific and data-driven characterization of HIV epidemiology in MENA. As part of this endeavour, an earlier in-depth study was conducted among MSM in the region [4]. This systematic review and data synthesis documented for the first time emerging HIV epidemics among MSM in about half of MENA countries, with a risk environment suggesting potential for further spread [4]. These findings further motivated the need for detailed and in-depth analyses for a better understanding of the HIV epidemic and HIV transmission patterns among the other KPs, including PWID, and to assess the drivers of HIV incidence in this region.

1.3.6. Context of HIV response in MENA

The timid leadership and political commitment to address the sensitive HIV issue remain an important challenge in the region. After years of denial that HIV exists in MENA, there is an increasing recognition in the public sphere that HIV is a domestic public health concern [61]. Nevertheless, most HIV programming efforts are small-scale, not well coordinated, and insufficient to meet current needs. With a median antiretroviral therapy (ART) coverage of 17%, MENA has the lowest ART coverage of all regions globally [62]. Also, HIV response among KPs is still largely the province of non-governmental organizations (NGOs) [63]. Political leaders are often reluctant to even acknowledge the existence of KPs. PWID, MSM, and FSWs continue to be stigmatised and lack access to comprehensive and confidential services [63, 64]. While it is widely perceived that political and socio-cultural sensitivities are behind this lagging response, in truth political leaders are not confronted with concrete data to warrant a sense of urgency to address the epidemic. The low HIV prevalence observed among blood donors and other select general population samples is feeding a culture of complacency towards the epidemic [63, 64]. Most prevention and health promotion efforts remain didactic and geared to the general population, rather than the populations most affected.

The findings of this research work will provide a scientific assessment of the status, scale, and epidemic potential of the HIV epidemic among PWID in MENA, and accordingly will inform HIV policy and programming in the region.

1.4. THESIS STRUCTURE AND RESEARCH PAPERS OUTLINE

This thesis follows the *research paper* style and has resulted in five research papers. Four of these papers have been published, while one is nearly ready to be submitted for publication. Each research paper constitutes an independent chapter, or is incorporated into a broader chapter. Published papers are included in their published formats, which inevitably results in some inconsistencies in formatting, referencing style, and terminology. Research papers are supplemented as appropriate by additional material to provide further methodological information, results, and linking material with other chapters. In most cases, additional methodology details and results pertaining to research papers were published as part of extensive supplementary online material, and they are included as such, in their published format. The supplementary online material of each research paper is included in a separate Appendix to this thesis.

Each research paper includes its own list of references within its corresponding chapter, while references pertaining to all other material in the body of the thesis (excluding appendices) are included together at the end of the thesis. Files in the appendices include their own references each.

The thesis structure is as follows:

Chapter 2 corresponds to **Research paper 1**, which was published in *PLoS Medicine*. This paper provides a first time in-depth characterization of the state of the HIV epidemic among PWID across MENA countries, through a comprehensive systematic review and data synthesis (objective 1). This paper is a basis for the subsequent research papers. The emerging HIV epidemics and the high injecting risk environment it identified motivated the need to estimate HIV epidemic potential (research papers 2 & 3) and how interventions could halt the growing epidemics (research paper 4). It also provided the epidemiological data to conduct the ecological analysis for the HCV-HIV association (research paper 3), and provided the MENA-

specific data needed to parameterize the HIV incidence study using mathematical modelling (research paper 4).

Chapter 3 corresponds to **Research paper 2**, which was published in *BMC Public Health*. This is a mathematical modelling study that theoretically explores the association between HCV and HIV among PWID, and provides the foundation for the concept of using HCV as proxy biomarker of future HIV epidemic spread (objective 2). The main importance of this study is that it provides a practical tool to predict the future size of HIV epidemics using existing data (HCV prevalence). This has important policy-implications as it can inform prioritization and resource allocation for prevention interventions, which is especially valuable in resource-limited settings such as most of MENA.

Chapter 4 corresponds to **Research paper 3**, which was published in *AIDS*. This chapter includes an applied epidemiological analysis of the concept of using HCV as proxy for future HIV epidemic spread demonstrated in Chapter 3. The study is an ecological analysis of the HCV-HIV association in PWID using the epidemiological data extracted in research paper 1. This association is then applied in MENA to predict HIV epidemic potential among PWID at country-level using current HCV prevalence (objective 3).

Chapter 5 corresponds to **Research paper 4,** which is nearly ready to be submitted for publication at the *Journal of the International AIDS Society* (*JIAS*). This is a mathematical modelling study that estimates, at country-level in MENA, HIV incidence that is due to injecting drug use (objective 4). The study not only provides estimates of HIV incidence among PWID, but also delineates the role of injecting drug use as a driver of HIV infection in the wider population, namely through history of past injection and onward transmission to sexual partners. It also estimates impact of select interventions on HIV incidence. Quantifying HIV incidence among PWID in MENA is timely and warranted, as it provides baseline data to track progress towards the global and regional targets of reducing the number of new HIV infections, as part of UNAIDS 90-90-90 scheme [65].

Finally, **Chapter 6** summarizes the findings of the previous chapters, describes their implications for HIV/drug use policy and programming, and makes recommendations for future research. This chapter includes **Research paper 5**, which provides a high-level summary of HIV and HCV epidemiology among PWID in MENA, with a focus on the response and ways to move forward in

the context of the thesis findings. This paper is an invited, peer-reviewed, viewpoint that was published in the *Journal of the International AIDS Society* (*JIAS*) on the occasion of the World Hepatitis Day - July 28, 2015.

1.5. ROLE OF CANDIDATE

The research work undertaken as part of this thesis falls under the *MENA HIV/AIDS Epidemiology Synthesis Project* [63] which was funded in its initial phase by the World Bank, WHO, and UNAIDS, and, in its subsequent phases, by the Qatar National Research Fund (NPRP 04-924-3-251 and NPRP 9-040-3-008). The *MENA HIV/AIDS Epidemiology Synthesis Project* was conceptualized, proposed, and awarded to my co-supervisor on the thesis, Dr. Laith Abu-Raddad. I was the lead scientist working on the sub-project that addresses HIV epidemiology among PWID in MENA, and which led to this thesis.

I am first and corresponding author on all research papers in the thesis. For all papers, I co-conceptualized the studies, conducted the vast majority of the analyses, wrote the first draft, and revised and finalised the paper based on feedback from co-authors.

I wrote the protocol of the systematic review (Research paper 1), devised the search criteria (guided by colleagues), conducted database searches, screened all titles and full-texts, extracted data on a computerized database, devised the quality assessment methodology, and analysed the data.

Research papers 2 and 4 include co-authors who provided technical assistance in Matlab codes pertaining to the mathematical modelling. Research paper 2 includes a co-first author who conducted all the Matlab coding in this study that has a complex dynamical mathematical model. I led the conceptualization of the plan of analysis and interpretation of findings, and along with the co-first author, conducted the analyses. In Research paper 4, I coded the mathematical model and conducted all analyses, while receiving technical programming assistance from a co-author who helped me solve some of the coding issues.

I conducted all the statistical analyses in Research paper 3. The mathematical modelling used in the conceptual framework of this study is based on the same model used in Research paper 2 and hence was developed and coded by my co-authors.

Part of the research work undertaken in this thesis was conducted in partnership with the WHO, UNAIDS, and the World Bank. These organizations were co-authors on two of the research papers (Research papers 1 & 4) where they provided or facilitated access to key data, access to which is otherwise difficult. They facilitated communication with national stakeholders and provided strategic data and information pertaining to HIV epidemiology and response in the region.

Further details on my contribution and the role of all co-authors are described in the research papers.

2. HIV EPIDEMIOLOGY AMONG PWID IN MENA

2.1. INTRODUCTION

This chapter aims to provide a critical and systematic assessment of the status of the HIV epidemic among PWID at country-level in MENA. The rationale for this study came from signs of a growing HIV infection burden, in particular among MSM where emerging HIV epidemics were recently documented [4], in a region with several vulnerability factors for HIV and injecting drug use, and where scientific evidence was critically needed to inform an overall limited and non-supportive policy response.

This aim was addressed by conducting a systematic review and data synthesis of all available PWID-related data in the region. The study analysed all aspects of HIV epidemiology among PWID to draw a comprehensive understanding of the status of the HIV epidemic in each country and in the region as a whole. These aspects included the prevalence of injecting drug use; HIV prevalence level, trend, geographical distribution, and quality of data; HIV incidence; injecting and sexual risk behaviour; mixing with other KPs; and prevalence of proxy biomarkers of risk.

2.2. EPIDEMIC STATE CLASSIFICATION

This section provides details on the approach used for the HIV epidemic state assessment and classification, which was described briefly in the published manuscript. Based on the extent of HIV transmission and prevalence in the different population groups in a given country/setting, HIV epidemics can be classified into three different states: low-level, concentrated, and generalised - a classification devised by UNAIDS/WHO to guide surveillance and policy-making at country level [66].

In low-level HIV epidemics, HIV has not spread to significant levels in any sub-population including KPs. In concentrated HIV epidemics, HIV transmission has taken roots in one or more KPs but HIV is rarely transmitted outside of these KPs and their sexual partners. In generalized HIV epidemics, HIV is established in the general population where there is sustainable HIV transmission [66].

I adapted the HIV epidemic state definitions devised by UNAIDS/WHO and applied them to describe the epidemic level in PWID. In addition to the "low level" and "concentrated" states, I added a third category, "at least outbreak-type", to describe a pattern of HIV transmission where the level of evidence is not sufficient to categorize the epidemic into either of the low-level or concentrated epidemic states, but there is evidence for tangible transmission. The classification and definitions of the different epidemic states among PWID are in Figure 2.1 and Table 1, and can be visualized on the epidemic curve of a prototype KP in Figure 2.2.

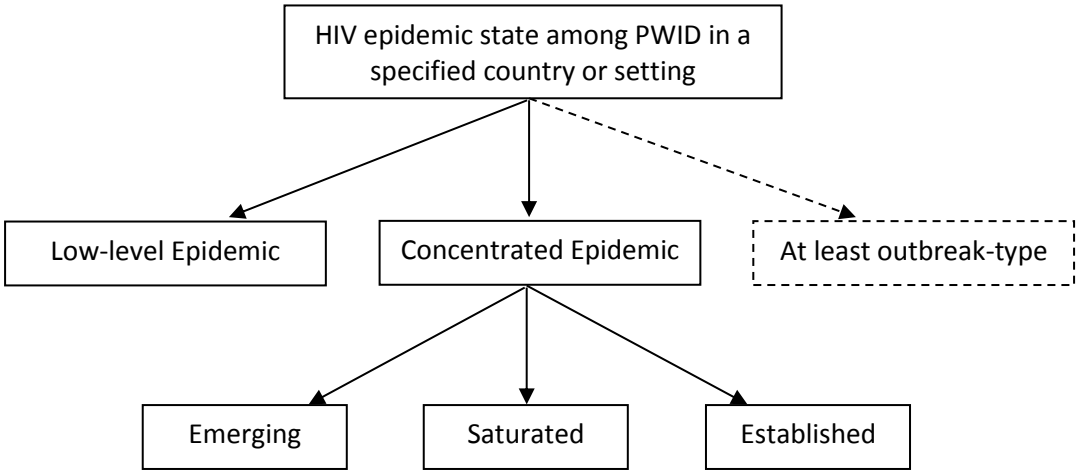

Figure 2.1. Flow chart of the classification of HIV epidemic states among people who inject drugs in the Middle East and North Africa.

Table 2.1. HIV epidemic states definitions among people who inject drugs.

Low-level HIV epidemic among PWID
Definition: Based on the extent of available evidence, HIV has not reached considerable levels among PWID. In a low-level epidemic, HIV may not have been introduced to the PWID population, may have been recently introduced, or may have been spreading for some time but slowly and inefficiently. The latter may reflect infrequent and few repeated transmission contacts among members of the PWID population to sustain higher HIV prevalence, or could be a consequence of stochastic effects where the small number of individuals who introduced HIV to the population happened by chance not to have transmission links that can sustain large transmission chains.
Concentrated HIV epidemic among PWID
Definition: Based on the extent of available evidence, HIV has reached considerable levels and taken root among PWID through transmission chains between members of this population. With no sufficient behaviour changes or introduction of interventions, HIV transmission among members of PWID will continue to take place. *Concentrated* epidemics can be further categorised into the following categories based on trends of HIV prevalence: Emerging epidemic: HIV started its initial growth among this HRP and continues in a trend of increasing HIV prevalence. Saturated epidemic: The emerging epidemic has reached its peak and HIV prevalence is stabilizing towards its endemic level. Established epidemic: The saturated epidemic has reached endemic equilibrium.
"At least outbreak-type" transmission among PWID
Definition: Applies to settings where we do not have enough evidence to support a concentrated epidemic, but there is some evidence, usually of lower quality, which suggests that considerable HIV transmission has occurred, or is occurring, among at least some groups of the PWID population.

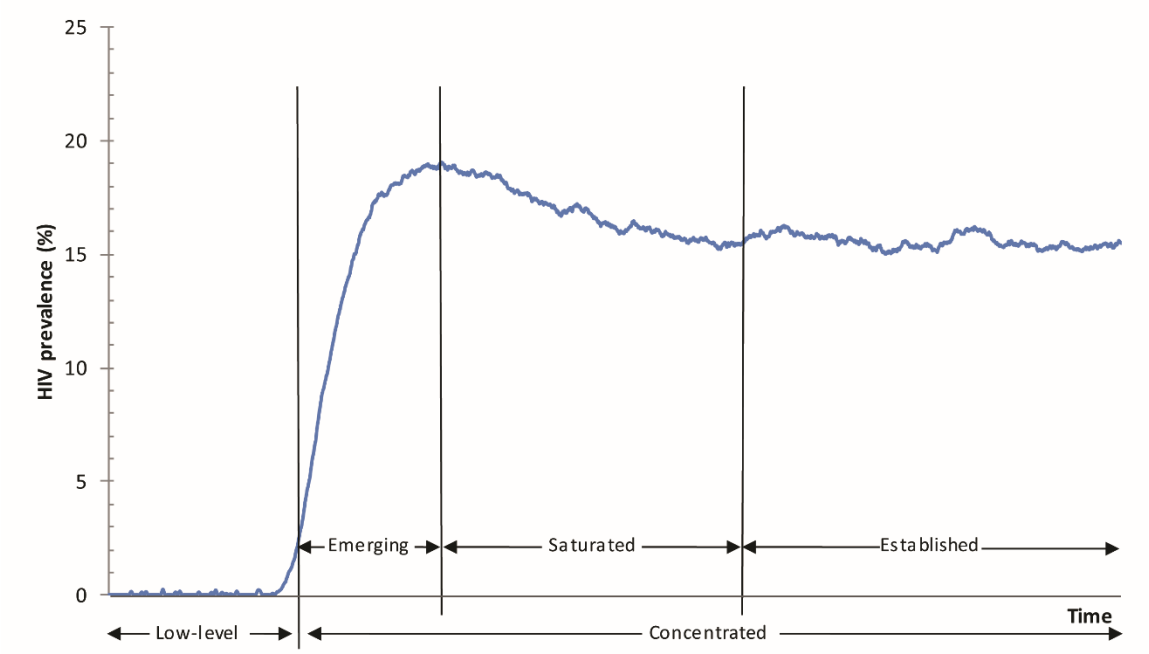

Figure 2.2. HIV epidemic states in a prototype key population at increased risk.
Note: Simulation produced using a stochastic compartmental model [67]

In classifying the HIV epidemics among PWID at country-level in MENA, I followed most recent UNAIDS/WHO guidelines where the proxy threshold defining the different epidemic states (such as the 5% defining a concentrated epidemic) have been discarded [66, 68]. The change was because use of these thresholds caused confusion in interpreting surveillance findings, especially when considered as rigid and conclusive thresholds [66]. Instead, under an updated "know your epidemic" approach, the assessment of the status of the epidemic was based on rigorously grounded epidemiological syntheses and an understanding of transmission dynamics, rather than "arbitrary" prevalence thresholds [68, 69]. This approach takes into consideration that each country has a unique epidemic (or epidemics) and that the epidemic might differ within sub-populations and between geographical areas within a given country [68, 69]. Figure 2.3 describes the triangulation approach used where multiple lines of evidence were synthesized side by side to assess HIV epidemic state among PWID at country-level in MENA.

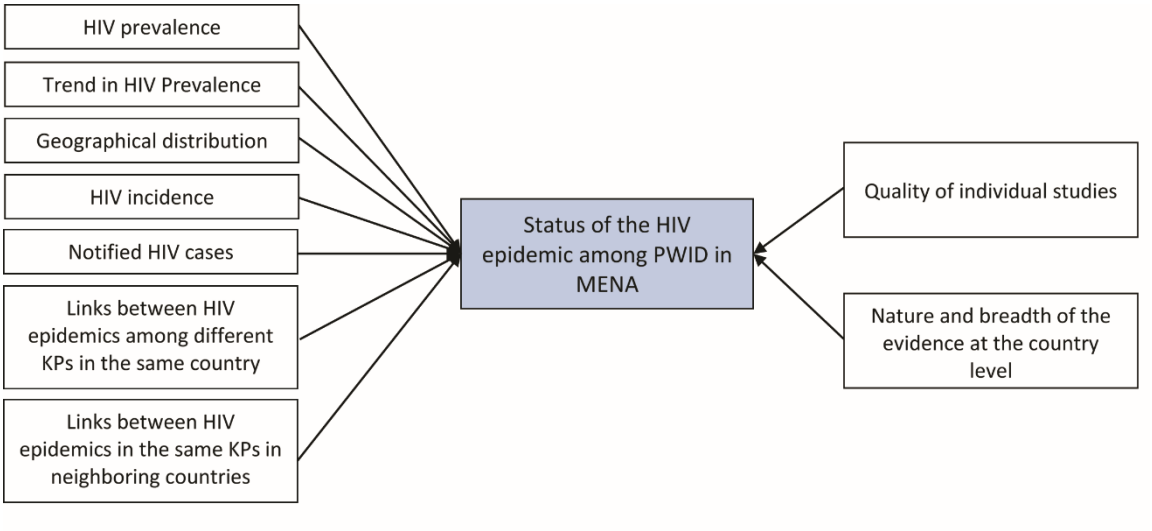

Figure 2.3. Data synthesis of the multiple lines of evidence for characterizing the status of the HIV epidemic among people who inject drugs in the Middle East and North Africa.

2.3. RESEARCH PAPER 1 – SYSTEMATIC REVIEW AND DATA SYNTHESIS

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SECTION A – Student Details

Student	Ghina Mumtaz
Principal Supervisor	Prof. Helen Weiss
Thesis Title	The Epidemiology of HIV Infection Among People Who Inject Drugs in the Middle East and North Africa

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	PLoS Medicine		
When was the work published?	June 17, 2014		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am first and corresponding author on this paper. I co-conceived the study, wrote the protocol of the systematic review, devised the search criteria, conducted database searches, screened all titles and full-texts, extracted data, devised the quality assessment methodology, and analysed the data. I wrote the first draft of the manuscript.

Student Signature: _____  _____ **Date:** January 10, 2017

Supervisor Signature: ____  _____ **Date:** January 10, 2017

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HIV among People Who Inject Drugs in the Middle East and North Africa: Systematic Review and Data Synthesis

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Abstract

Background: It is perceived that little is known about the epidemiology of HIV infection among people who inject drugs (PWID) in the Middle East and North Africa (MENA). The primary objective of this study was to assess the status of the HIV epidemic among PWID in MENA by describing HIV prevalence and incidence. Secondary objectives were to describe the risk behavior environment and the HIV epidemic potential among PWID, and to estimate the prevalence of injecting drug use in MENA.

Methods and Findings: This was a systematic review following the PRISMA guidelines and covering 23 MENA countries. PubMed, Embase, regional and international databases, as well as country-level reports were searched up to December 16, 2013. Primary studies reporting (1) the prevalence/incidence of HIV, other sexually transmitted infections, or hepatitis C virus (HCV) among PWIDs; or (2) the prevalence of injecting or sexual risk behaviors, or HIV knowledge among PWID; or (3) the number/proportion of PWID in MENA countries, were eligible for inclusion. The quality, quantity, and geographic coverage of the data were assessed at country level. Risk of bias in predefined quality domains was described to assess the quality of available HIV prevalence measures. After multiple level screening, 192 eligible reports were included in the review. There were 197 HIV prevalence measures on a total of 58,241 PWID extracted from reports, and an additional 226 HIV prevalence measures extracted from the databases. We estimated that there are 626,000 PWID in MENA (range: 335,000–1,635,000, prevalence of 0.24 per 100 adults). We found evidence of HIV epidemics among PWID in at least one-third of MENA countries, most of which are emerging concentrated epidemics and with HIV prevalence overall in the range of 10%–15%. Some of the epidemics have however already reached considerable levels including some of the highest HIV prevalence among PWID globally (87.1% in Tripoli, Libya). The relatively high prevalence of sharing needles/syringes (18%–28% in the last injection), the low levels of condom use (20%–54% ever condom use), the high levels of having sex with sex workers and of men having sex with men (15%–30% and 2%–10% in the last year, respectively), and of selling sex (5%–29% in the last year), indicate a high injecting and sexual risk environment. The prevalence of HCV (31%–64%) and of sexually transmitted infections suggest high levels of risk behavior indicative of the potential for more and larger HIV epidemics.

Conclusions: Our study identified a large volume of HIV-related biological and behavioral data among PWID in the MENA region. The coverage and quality of the data varied between countries. There is robust evidence for HIV epidemics among PWID in multiple countries, most of which have emerged within the last decade and continue to grow. The lack of sufficient evidence in some MENA countries does not preclude the possibility of hidden epidemics among PWID in these settings. With the HIV epidemic among PWID in overall a relatively early phase, there is a window of opportunity for prevention that should not be missed through the provision of comprehensive programs, including scale-up of harm reduction services and expansion of surveillance systems.

Please see later in the article for the Editors' Summary.

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Competing Interests: The authors have declared that no competing interests exist.

Abbreviations: ART, antiretroviral therapy; HCV, hepatitis C virus; IBBSS, integrated bio-behavioral surveillance surveys; IQR, interquartile range; MENA, Middle East and North Africa; MSM, men who have sex with men; NGO, non-governmental organization; OPT, Occupied Palestinian Territories; PWID, people who inject drugs; pyr, person-years; ROB, risk of bias; STI, sexually transmitted infection; UNAIDS, Joint United Nations Programme on HIV/AIDS; WHO/EMRO, Eastern Mediterranean Regional Office of the World Health Organization.

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Introduction

The Middle East and North Africa (MENA) region has been singled out as the region with little data and where the status of the HIV/AIDS epidemic remained unknown [1–8]. In 2005, the region was characterized as "a real hole in terms of HIV/AIDS epidemiological data" [9]. The MENA region has, however, witnessed a remarkable growth in HIV research over the last decade, with several countries developing surveillance systems to monitor the spread of HIV infection, including among most-at-risk populations [10].

A large fraction of studies conducted in the region has remained unpublished in the scientific literature, and only available in the form of difficult to access country reports. This has meant that data have not been analyzed or synthesized at either country or regional level, and no critical assessment of the quality of available evidence has been conducted. The rationale for this study came from signs of a growing HIV disease burden in the MENA region, which highlighted the urgent need for a critical and comprehensive evaluation of the status of the HIV epidemic and of the quality of evidence among the different population groups to inform HIV policy and programming in the region; this was the mandate of the MENA HIV/AIDS Synthesis Project, the largest HIV study in MENA to date [11].

The present article follows on from a series of studies conducted as part of the Synthesis Project. These studies include a high-level overview of HIV epidemiology in MENA [12], a systematic review of HIV molecular evidence [13], and the first documentation of the emerging HIV epidemic among men who have sex with men (MSM) in MENA [14]. The present study is, to our knowledge, the first systematic review and data synthesis to characterize the status of the HIV epidemic among people who inject drugs (PWID) in MENA. The presented regional analysis takes on an additional importance with the need to capture the volume of bio-behavioral surveillance data that became available within the last few years in MENA, and is yet to be analyzed and synthesized within a country-specific or a regional context [15].

PWID are one of the key populations at high risk of HIV in MENA, a region with several vulnerability factors for injecting drug use. For example, 83% of the global supply of heroin is produced in Afghanistan [16], and over 75% of this is trafficked through Iran and Pakistan. In 2009, Iran bore the highest fraction of the global opium and heroin seizures (89% and 33%, respectively) [16]. Increased availability and purity of heroin at lower prices in MENA appears to have led to a subsequent rise in injecting drug use [17]. In 2010, one gram of heroin in Afghanistan could be purchased for about US$4 compared with up to US$100 in West and Central Europe, US$200 in the United States and Northern Europe, and US$370 in Australia [16]. Most PWID in the region are young adults and marginalized by family members and society; they are stigmatized and lack access to comprehensive and confidential HIV prevention and treatment services [11].

The primary objective of this study was to assess the status of the HIV epidemic among PWID in MENA by describing HIV prevalence and incidence. The secondary objective was to describe the risk behavior environment and the HIV epidemic potential among PWID by describing (1) their injecting and sexual risk behavior and knowledge, and (2) prevalence of proxy biological markers of these behaviors, namely hepatitis C virus (HCV) and sexually transmitted infections (STIs), respectively. The study also estimated the proportion and number of PWID in MENA.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Text S1) [18,19] and Cochrane Collaboration guidelines [20].

Data Sources and Search Strategy

Our review covered the 23 countries included in the MENA definitions of the three international organizations leading the regional HIV response efforts in the region: the Joint United Nations Programme on HIV/AIDS (UNAIDS), the Eastern Mediterranean Regional Office of the World Health Organization (WHO/EMRO), and the World Bank (Figure 1). These countries share specific similarities, whether historical, socio-cultural, or linguistic; and are conventionally included together as part of HIV/AIDS programming for the region.

The following sources of data were searched up to December 16, 2013: (1) Scientific databases (PubMed, Embase, and regional databases [WHO African Index Medicus [21] and WHO Index Medicus for the Eastern Mediterranean Region [22]]), with no publication date or language restrictions. A generic search of "drug use" in MENA was performed in PubMed and Embase using MeSH/Emtree and text terms. The term "HIV" was not included to avoid detection bias. (2) The MENA HIV/AIDS Synthesis Project database of grey and mainly unpublished literature [11,12]. (3) Abstracts of the International AIDS Conference 2002–2012 [23], the International AIDS Society Conference on HIV Pathogenesis and Treatment 2001–2013 [24], and the International Society for Sexually Transmitted Diseases Research Conferences 2003–2013 [25]. (4) International and regional databases of HIV prevalence measures including the US Census Bureau database of HIV/AIDS [26], the WHO/EMRO HIV testing database [27], and the UNAIDS epidemiological fact sheets database [28].

Details of the search criteria are provided in Text S2. Reference lists of all relevant papers and review articles were also searched.

Study Selection

Titles and abstracts of all records identified were screened independently by two authors (GRM and SR), and consensus on potential eligibility reached. Full texts of potentially relevant records were retrieved and assessed for eligibility. Studies satisfying any of the below criteria were eligible: (1) The proportion of PWID in the sample was specified, at least half were PWID, and data on any of the following outcomes were included: Prevalence or incidence of HIV; prevalence of injecting or sexual risk

Figure 1. Map of the Middle East and North Africa region. The defintion adopted in the review includes the following 23 countires: Afghanistan, Algeria, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, OPT, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan (including the newly established Republic of South Sudan), Syria, Tunisia, United Arab Emirates (UAE), and Yemen.
doi:10.1371/journal.pmed.1001663.g001

behaviors, or knowledge; prevalence or incidence of HCV; and prevalence or incidence of other STIs. HCV is transmitted primarily through percutaneous exposures and can be used as a proxy of the risk of parenteral exposure to HIV. Among PWID, a threshold HCV prevalence of about 30% implies sufficient risk behavior to sustain HIV transmission [29,30]. Similarly, the prevalence of STIs is a useful marker of sexual risk behavior and potential for HIV sexual acquisition. (2) Data on population-based prevalence of injecting drug use or PWID population size estimates were reported.

Only studies with primary data were included. The only exception was in relation to national estimates of the number and proportion of PWID in a number of MENA countries where the only available source of data was from two global reviews [4,31] that published data compiled through the Reference Group to the UN on HIV and Injecting Drug Use [32].

We used the term report to refer to the documents (papers, conference abstracts, or public health reports) presenting findings of a study [20]. Reports could contribute to more than one outcome. Findings duplicated in more than one report were included only once (using the more detailed report). Outcomes in more than one population/setting within a report were included separately.

Data Extraction

Data were extracted by one of the authors (GRM) using a pre-piloted data extraction form and entered into a computerized database. Double extraction on about 45% of records was confirmed by another author (LA-R). The few discrepancies were settled by consensus or by contacting authors. Data from articles in English, French, and Arabic were extracted from the full -texts. Data from records in Farsi ($n = 6$) were extracted from the English abstract. There were no records in other languages.

As supporting information, we also analyzed data extracted from countries' reporting on the HIV epidemic to WHO/EMRO in the format of aggregate HIV case notifications.

Scope and Quality of the Evidence

We appraised the status of the evidence on our main outcome, HIV prevalence, at country level by examining the following criteria that take into consideration the quantity, quality, and geographical coverage of available data: (1) the number of HIV prevalence measures and the total sample size they cover, (2) the number of geographic settings with HIV prevalence measures, (3) the number of multi-city studies and the maximum number of cities per study, (4) the number of rounds of integrated

bio-behavioral surveillance surveys (IBBSS), and (5) the quality and precision of individual HIV prevalence measures.

The quality of individual HIV prevalence measures was assessed by describing the risk of bias (ROB). Since the number of prevalence measures among female PWID was very small and often based on small sub-samples, the quality appraisal was restricted to HIV prevalence among predominantly male PWID. Based on the Cochrane approach for assessing ROB [20], we classified each HIV prevalence measure as having a low, high, or unclear ROB for three quality domains: the sampling methodology, the type of HIV ascertainment, and the response rate. Low ROB was considered if (1) sampling was probability-based or preceded by ethnographic mapping, (2) HIV was ascertained with a biological assay, and (3) the response rate was over 80%; or over 80% of the target sample size was reached. HIV prevalence measures extracted from international and regional databases were considered of unknown quality since original reports were not available for assessing their ROB.

A minimum sample size of 100 was considered to produce estimates with good precision. For a median HIV prevalence among PWID in MENA of 8% (see Results), this implies a 95% CI of 4%–15%.

The quality of the evidence in each country was assessed by combining the above factors as described in Text S3. For example, quality was considered better if at least one round of IBBSS was conducted, since these surveys use standard methodology including state of the art sampling techniques of hard-to-reach populations (such as respondent-driven sampling). Countries were categorized as having: (1) No evidence: virtually no data. (2) Poor evidence: The majority of HIV biological measures were of poor quality. (3) Limited evidence: The number of HIV biological measures was small, but of reasonable quality. (4) Good evidence: The number of HIV biological measures was small, but with good quality and informative data. However, the overall volume of data was not sufficient to be conclusive of the status and scale of the epidemic at the national level. (5) Conclusive evidence: There was a sufficient volume of robust evidence to support the conclusion.

Analysis

The low-bound, middle, and high-bound national estimates of the number and prevalence of injecting drug use in MENA countries were extracted from reports. The pooled number and prevalence of PWID for the MENA region were estimated separately using the extracted country-level estimates. The lower (and upper) bound of our pooled regional estimate of the number of PWID in MENA was calculated by adding the lowest (and highest) reported number of PWID in all MENA countries. The middle figure for the number of PWID in MENA is the sum of the middle estimates in each of the MENA countries. When more than one such estimate was available per country, we used the median of the estimates. The pooled numbers of PWID were rounded up to the next thousand.

Middle estimates of the extracted prevalence of PWID were weighted by adult population size to derive the pooled prevalence of injecting drug use in MENA. When more than one such estimate was available per country, we used the median of the estimates. Adult population size was extracted from the United Nations World Population Database [33]. Sub-national estimates of the number and prevalence of injecting drug use were extracted from reports and described separately.

We calculated 95% CI for HIV and HCV prevalence for all reports with available information. The HIV biological data (HIV prevalence from reports and from databases, HIV incidence, and notified HIV cases) were synthesized at country level to assess the status of the HIV epidemic among PWID. Recent WHO/UNAIDS guidelines for classifying HIV epidemics [34,35], which do not recommend use of rigid thresholds [34,36], were adapted to classify the HIV epidemic level in PWID as: (1) Low-level HIV epidemic: HIV has not reached significant levels among PWID. (2) Concentrated HIV epidemic: HIV has reached significant levels and taken root among PWID through transmission chains between members of this population. Concentrated epidemics can be either emerging (HIV has started its initial growth and continues in a trend of increasing HIV prevalence); or established (the epidemic has reached its peak and HIV prevalence is stabilizing towards, or already is at, its endemic level). (3) "At least outbreak-type": Insufficient evidence to support a concentrated epidemic among PWID, but some evidence, usually of lower quality, suggesting that significant HIV transmission has occurred, or is occurring, among at least some PWID groups.

The terms "national" or "at least localized" were assigned to concentrated epidemics to reflect the geographical spread of the epidemic within a given country.

Results

Results of Search Strategy

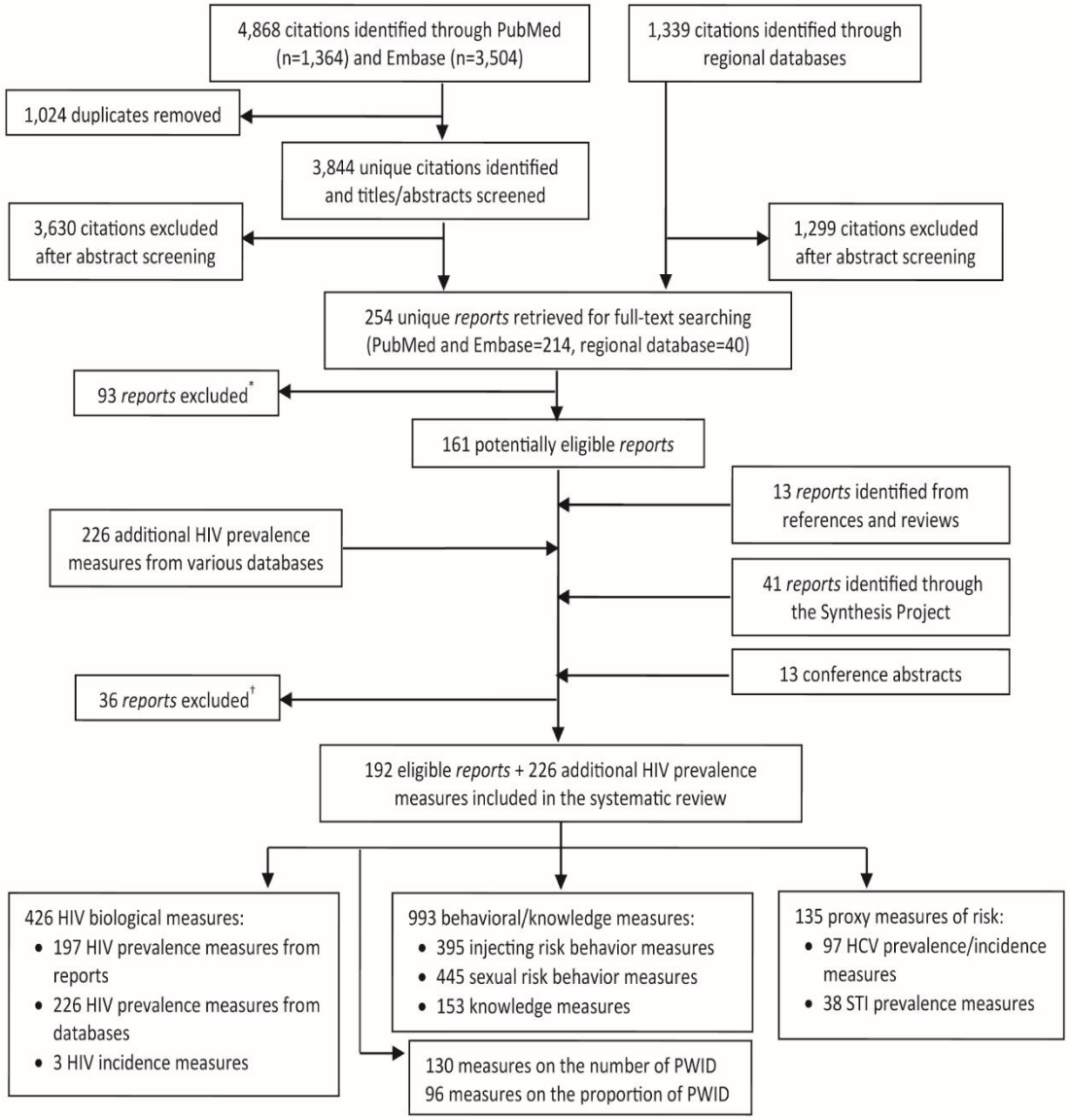
The study selection process is shown in Figure 2. A total of 6,207 citations were retrieved from PubMed, Embase, and the regional databases. After full-text screening and including reports from the other sources, 192 reports were eligible: 121 from PubMed and Embase, 41 from the MENA HIV/AIDS Synthesis Project, 13 from bibliographies of relevant reports and review articles, 13 from the search of scientific conferences, and four from the regional databases. In addition, 226 HIV point-prevalence measures were extracted from the databases of biological markers (Figure 2).

There were 423 HIV prevalence measures, 197 of which were extracted from the eligible reports and 226 from the databases of HIV prevalence; three HIV incidence measures; 93 HCV prevalence measures; four HCV incidence measures; 38 STI prevalence measures; and 993 behavioral and knowledge measures. There were also 130 and 96 measures on the number and proportion of PWID, respectively (Figure 2).

Scope and Quality of the Evidence

The number and quality of HIV prevalence measures varied by country. The largest volume of data was from Pakistan (101 HIV prevalence measures on a total of 24,445 PWID), Iran (99 HIV prevalence measures on a total of 22,181 PWID), and Egypt (39 HIV prevalence measures on a total of 4,480 PWID) (Table 1). A smaller number of HIV prevalence measures but covering a relatively large number of PWID were conducted in Afghanistan (3,277 PWID), Tunisia (1,522 PWID), and Morocco (880 PWID). Multi-city studies have been conducted in several countries including Pakistan, where up to 16 cities were included in one study [37]. IBBSS have been conducted in Afghanistan [38,39], Egypt [40–42], Iran [43,44], Jordan [45], Lebanon [46], Libya [47], Morocco [48], Occupied Palestinian Territories (OPT) [49], Pakistan [37,50–52], and Tunisia (Table 1) [53,54]. Pakistan has the most repeated rounds of IBBSS with four rounds conducted between 2005 and 2011 [37,50–52].

Of 190 HIV prevalence measures extracted from eligible reports and among predominantly male PWID, 98%, 53%, and 34% had low ROB in terms of HIV ascertainment, sampling methodology, and response rate, respectively. Over 60% of the 190 HIV prevalence measures had low ROB in at least two quality domains and 84% had good precision (Tables S1 and S2).



HCV: Hepatitis C virus; PWID: People who inject drugs; STI: Sexually transmitted infections

*Reasons for exclusion:

- Eligibility criteria not met (n=24)
- Full-text did not include data on relevant indicators (n=39)
- Full-text could not be retrieved and abstract does not have data on relevant outcomes (n=3)
- Duplicate (n=27)

†Reasons for exclusion:

- Same dataset as another included relevant publication (n=34)
- Paper presents contradictory/unclear numbers that could not be verified (n=2)

Figure 2. PRISMA flow chart of study selection in the systematic search.

doi:10.1371/journal.pmed.1001663.g002

Table 1. Summary of the HIV biological evidence per country.

Biological Evidence	Afg	Alg	Bah	Dji	Egy	Irn	Irq	Jor	Kuw	Leb	Lib	Mor	Oma	OPT	Pak	Qat	SA	Som	Sud	Syr	Tun	UAE	Yem
Number HIV biological studies[a]	5	—	1	—	7	47	—	1	—	2	1	3	1	1	27	—	—	—	—	1	2	—	—
Number HIV prevalence measures	19	—	23	6	39	99	7	13	17	8	4	21	17	4	101	—	7	—	1	22	10	—	5
From reports (total sample size)	13 (3,277)	—	1 (242)	—	9 (4,480)	78 (22,181)	—	3 (227)	—	2 (121)	1 (328)	5 (880)	3 (135)	1 (199)	77 (24,445)	—	—	—	—	1 (204)	3 (1,522)	—	—
From databases	6	—	22	6	30	21	7	10	17	6	3	16	14	3	*24*	—	7	—	1	21	7	—	5
Number HIV incidence measures[a]	1	—		—	—	1	—	—	—	—	—	—	—		1	—	—	—	—	—	—	—	—
Number cities/ provinces with HIV prevalence measures[a]	6	—	1	—	2	27	—	3	—	1	1	4	1	1	26	—	—	—	—	1	3	—	—
Number multi-city studies (max number cities/ study)[a]	3 (5)	—	—	—	1 (2)	4 (10)	—	1 (4)	—	—	—	2 (2)	—	—	12 (16)	—	—	—	—	—	2 (3)	—	—
Number repeated IBBS[a]	2	—	—	—	2	2	—	1	—	1	1	1	—	1	4	—	—	—	—	—	2	—	—

[a]With reports available.

Afg, Afghanistan; Alg, Algeria; Bah, Bahrain; Dji, Djibouti; Egy, Egypt; Irn, Iran; Irq, Iraq; Jor, Jordan; Kuw, Kuwait; Leb, Lebanon; Lib, Libya; Mor, Morocco; Oma, Oman; Pak, Pakistan; QA, Qatar; SA, Saudi Arabia; Som, Somalia; Sud, Sudan; Syr, Syria; Tun, Tunisia; UAE, United Arab Emirates; Yem, Yemen.

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On the basis of the quality of the evidence assessment, the evidence was determined to be "conclusive" in Iran and Pakistan; "good" in Afghanistan, Egypt, Jordan, Lebanon, Libya, Morocco, OPT, and Tunisia; "limited" in Bahrain and Syria; and "poor" in Djibouti, Iraq, Kuwait, Oman, Saudi Arabia, Sudan, and Yemen. There was "no evidence" in Algeria, Qatar, Somalia, and the United Arab Emirates. A narrative justification for the classification of the scope and quality of evidence is in Text S3.

Although a formal quality assessment was not made for the secondary outcomes in terms of injecting and sexual risk behavior and knowledge, the majority of these data were extracted from the IBBSS studies using standard survey methodology and large samples. Details of these studies (with information on sample size, population characteristics, and/or sampling technique) can be found in the tables summarizing the prevalence of HIV and HCV among PWID (Tables 3 and 6).

Prevalence of Injecting Drug Use

Table 2 describes national estimates of the number and prevalence of PWID. These national estimates were extracted from included reports where they were derived using different methodologies including indirect methods (such as capture-recapture and multiplier methods), population-based surveys, registered number of PWID, and rapid assessments. In two of the sources of data in Table 2 [4,31], some of the country estimates are the collation of several such country-specific estimates using methods described in the original reports [4,31].

Based on available data, the number of PWID in MENA ranges between a low bound of 335,000 and a high bound of 1,635,000, with a middle estimate of 626,000 PWID. Iran, Pakistan, and Egypt have the largest number, with a median of about 185,000, 117,000, and 89,000 PWID, respectively. The weighted mean prevalence of injecting drug use in MENA is 0.24 per 100 adults. It is lowest in Somalia (0.03%) and highest in Iran (0.43%) (Table 2).

Studies of sub-national populations showed geographical heterogeneity (Table S3). For example, in Iran, the prevalence of injecting drug use varied between 0.0% in rural Babol province [55] to 1.0% in Tehran [56]; and in Pakistan it ranged from 0.02% in Rawalpindi to 0.87% and 1.07% in Sargodha and Faisalabad, respectively [57].

Data on the prevalence of female PWID in MENA were scarce. Overall, the mean proportion of females among PWID in included studies was 2.3% (range: 0%–35%). In two studies in Oman and Syria, 25%–58% [58] and 48% [59] of PWID, respectively, reported knowing at least one female PWID.

HIV Prevalence, Incidence, and Mode of Transmission

HIV prevalence measures from reports and databases are summarized in Tables 3 and S4, respectively. Considerable variation in HIV prevalence was seen, with an overall median of 8% (interquartile range [IQR]: 1%–21%) (Table 3). HIV prevalence among PWID in MENA ranged between 0% in some prevalence measures in almost every country up to 7% in Cairo, Egypt in 2010 ($n = 274$) [42]; 18% in Afghanistan in one city near the Iranian borders, Herat, in 2009 ($n = 159$) [38]; 21% in Manama, Bahrain, in the early nineties ($n = 242$) [60]; 27% in Oman among incarcerated PWID ($n = 33$) [58]; 38% in Nador, northern Morocco, in 2008 ($n = 233$) [61]; 52% in the third largest metropolis in Pakistan, Faisalabad, in 2011 ($n = 364$) [37]; 72% in rural Iran in 2004–5 ($n = 61$) [62]; and 87% in Tripoli, Libya in 2010 ($n = 328$) [47] (Table 3). HIV prevalence was consistently low among PWID in Jordan, Lebanon, OPT, Syria, and Tunisia (0%–3.1%). Substantial intra-country variability in HIV prevalence was observed in Afghanistan, Iran, Morocco, and Pakistan (Table 3). In most countries with high HIV prevalence, recent studies report increasing HIV prevalence starting around 2003 (Tables 3 and S4).

Three HIV incidence studies were identified. In Kabul, Afghanistan, HIV incidence among a sample of 479 PWID in 2008 was 2.2/100 person-years (pyr), despite 72% of study participants reporting use of harm reduction services [63]. Among 500 PWID in three cities in Pakistan, HIV incidence was 1.7/100 pyr in 2006 [64]. A very high incidence rate (17.2/100 pyr) was reported in Tehran, Iran, in 2002 among 214 incarcerated PWID [65].

Analysis of notified HIV cases indicated that in 2011, injecting drug use contributed 20% (80/409), 23% (50/216), 38% (6/16), 49% (52/107), and 60% (948/1,588) of all newly notified cases in this year in Egypt, Pakistan, Bahrain, Afghanistan, and Iran, respectively. A smaller contribution was reported in the remaining countries (Table 4).

HIV Epidemic States

The evidence was sufficient to characterize the HIV epidemic state in 13 countries, summarized in Table 5. Details on how the conclusions were reached are in Text S3.

Concentrated HIV epidemics. Concentrated HIV epidemics among PWID were observed in Iran, Pakistan, Afghanistan, Egypt, Morocco, and Libya (Table 5). Iran is the only country with conclusive evidence for an established concentrated epidemic at the national level. The first HIV outbreaks among PWID in Iran were reported around 1996. HIV prevalence then increased considerably in the early 2000s, reaching a peak by the mid-2000s (Figure 3A). HIV prevalence in the 2006 and 2010 multi-city IBBSS was stable at 15% ($n = 2,853$ and $n = 2,479$, respectively) (Figure 4C) [43,44]. The evidence suggests that the HIV epidemic among PWID in Iran is now established at concentrated levels of about 15%.

Emerging concentrated epidemics were seen in Pakistan, Afghanistan, Egypt, and Morocco (Table 5). For example, in Pakistan, after almost two decades of very low HIV prevalence among PWID, a trend of increasing prevalence was observed after 2003 (Figure 3B). This trend is national and ongoing, reaching over 40% in recent studies and with no evidence yet of stabilization (Figure 3B). This trend also manifests itself in the multi-province IBBSS where HIV prevalence among PWID has steadily increased from 10.8% in 2005 ($n = 2,431$) [52], to 15.8% in 2006 ($n = 4,039$) [51], 20.8% in 2008 ($n = 2,969$) [50], and 25.2% in 2011 ($n = 4,593$) [37] (Figure 4A). In view of the high HIV prevalence, the emerging HIV epidemic in Pakistan is considered advanced. Another example is Egypt where HIV prevalence was also very low for about two decades (Tables 3 and S4), including the first round of IBBSS in 2006 [40,41], but increased to 6%–7% in both cities surveyed in the most recent IBBSS in 2010 ($n = 284$ and $n = 274$) (Figure 4B) [42]. Consistently, 19.6% of the 409 newly notified HIV cases in 2010 in Egypt were due to injecting drug use, compared with only 1.6% of the total notified cases up to 2008 (Table 4). In Afghanistan (Figure 4E) and Morocco, the HIV epidemic among PWID appears to be emerging in at least parts of the country, with notably high HIV prevalence in some settings, but still low HIV prevalence in others (Table 3).

The HIV epidemic in Libya is also concentrated, but the trend is unclear. Libya has the highest reported prevalence of HIV among PWID in MENA (87.2%, 95% CI 83.1%–90.6% in the IBBSS in Tripoli [47]). Earlier data, although of unclear quality, also indicate prevalence of up to 59% in 2001 among PWID in

Table 2. National estimates of the number and prevalence of people who inject drugs in the Middle East and North Africa as extracted from included reports.

Country	Population 15–64 Years [33]	Year of Estimate	PWID Estimate (Number)			PWID Prevalence (%)			Source
			Low	Middle	High	Low	Middle	High	
Afghanistan	16,119,000	[a]	22,720	34,080	45,440	0.16	0.24	0.32	[4]
		2005	6,870	6,900	6,930	0.05	0.05	0.05	[31]
		2009	18,000	20,000	23,000				[124]
		2009					0.11		[125]
Algeria	24,246,000	[a]	26,333	40,961	55,590	0.14	0.22	0.29	[4]
Bahrain	983,000	[a]	337	674	1,011	0.08	0.16	0.24	[4]
Djibouti		—	—	—	—	—	—	—	—
Egypt	51,460,000	[a]	56,970	88,618	120,265	0.13	0.21	0.28	[4]
Iran	53,132,000	[a]	70,000	185,000	300,000	0.17	0.46	0.74	[4]
		2004		180,000			0.40		[31]
		2007		250,000					[126]
Iraq	16,967,000	[a]	23,115	34,673	46,230	0.19	0.28	0.37	[4]
Jordan	3,624,000	[a]	3,200	4,850	6,500	0.11	0.16	0.22	[4]
Kuwait	1,937,000	[a]	2,700	4,100	5,500	0.20	0.30	0.41	[4]
Lebanon	2,871,000	[a]	2,200	3,300	4,400	0.09	0.14	0.19	[4]
Libya	4,148,000	[a]	4,633	7,206	9,779	0.15	0.23	0.32	[4]
		2001		1,685			0.05		[31]
Morocco	21,247,000	[a]		18,500			0.10		[4]
Oman	1,956,000	[a]	2,800	4,250	5,700	0.20	0.30	0.40	[4]
OPT	2,212,000	[a]	1,200	1,850	2,500	0.22	0.35	0.47	[4]
Pakistan	104,724,000	[a]	54,000	462,000	870,000	0.07	0.50	1.12	[4]
		2006	125,000	130,460	150,000	0.13	0.14	0.16	[31]
		2006		102,042			0.25		[57]
		2010		99,000					[126]
Qatar	1,503,000	[a]	780	1,190	1,600	0.15	0.22	0.30	[4]
Saudi Arabia	18,306,000	[a]	15,172	23,600	32,028	0.13	0.20	0.27	[4]
		2008		10,000					[126]
Somalia	4,885,000	[a]		1,000			0.03		[4]
Sudan	24,540,000	[a]	24,319	37,828	51,337	0.13	0.20	0.28	[4]
Syria	12,073,000	[a]	4,000	6,000	8,000	0.04	0.07	0.09	[4]
Tunisia	7,294,000	[a]	8,462	13,163	17,864	0.14	0.21	0.29	[4]
		2009		9,000					[126]
UAE	6,200,000	[a]	3,200	4,800	6,400	0.20	0.30	0.40	[4]
Yemen	12,800,000	[a]	12,710	19,770	26,830	0.15	0.23	0.31	[4]

[a]The specific year of the estimate was not mentioned in the original report, but the report covered data from 1998–2005.
UAE, United Arab Emirates.
doi:10.1371/journal.pmed.1001663.t002

Table 3. HIV prevalence among people who inject drugs in the Middle East and North Africa as extracted from reports included in the systematic review.

Country	Citation	Year	City	Study Site	Sampling	Population	Sample Size	HIV Prevalence	
								Percent	95% CI
Afghanistan	MOH, 2012 [39] (Round II)	2012	Herat		RDS	All male	185	13.3[a]	8.9–19.3
			Kabul		RDS	All male	369	2.4[a]	1.1–4.6
			Mazar-i-Sharif		RDS	All male	254	0.3[a]	0.0–2.2
			Jalalabad		RDS	All male	236	1.0[a]	0.1–3.0
			Charikar		RDS	All male	117	0.9[a]	0.0–4.7
	MOH, 2010 [38] (Round I)	2009	Herat		RDS	All male	159	18.2	12.6–25.1
			Kabul		RDS	All male	286	3.2	1.4–5.9
			Mazar-i-Sharif		RDS	All male	102	1.0	0.0–5.3
	Todd, 2011 [69]	2007–2009	Kabul	Harm reduction center & community	CS	All male	483	2.1	1.0–3.8
	Nasir, 2011 [127]	2006–2008	Herat	VCT	CS	99% male	340	3.2	1.6–5.7
			Jalalabad	VCT	CS	99% male	96	0.0	—
			Mazar-i-Sharif	VCT	CS	99% male	187	0.0	—
	Todd, 2007 [128]	2005–2006	Kabul	VCT	CS	All male	463	3.0	1.7–5.0
Bahrain	Al-Haddad, 1994 [60]	1991	Manama	Voluntary drug treatment center	CS	All male	242	21.1	16.1–26.8
Egypt	MOH/FHI, 2010 [42] (Round II)	2010	Alexandria		RDS	All male	284	6.5[a]	3.3–10.3[a]
			Cairo		RDS	All male	274	6.8[a]	3.9–10.8[a]
	Elghamrawy, 2012 [129]	2008–2011	Cairo	Harm reduction center	CS	All male	3,222	1.4	1.0–1.9
	Soliman, 2010 [41] (Round I)	2006	Cairo		RDS	All male	413	0.6[a]	0.1–1.8[a]
	MOH/FHI, 2006 [40] (Round I)	2006	Cairo		RDS	All female	16	0.0	—
	Saleh, 1998 [130]	1994	Alexandria	Voluntary drug treatment center	CS		100	0.0	—
	Attia, 1996 [131]	—	Alexandria	Voluntary drug treatment center	CS		54	0.0	—
	Hasan, 1994 [132]	—			CS		79	7.6	2.8–15.8
	El-Ghazzawi, 1987 [133]	—	Alexandria		CS		38	0.0	—
Iran	Honarvar, 2013 [134]	2012–2013	Shiraz	Voluntary drug treatment center	CS	98% male	233	7.7	4.6–11.9
	Mehrejredi, 2013 [135]	2011	Tehran	VCT and harm reduction center	CS	91% male	209	2.9	1.1–6.1
	MOH, 2010 [44] (Round II)	2010	Fars	VCT, Harm reduction center, voluntary drug treatment center, & community	CS	98% male	250	31.9	26.3–38.2
			Lorestan	Idem	CS	All male	222	26.4	20.9–32.9
			Tehran	Idem	CS	95% male	567	23.9	20.5–27.7
			Sistan & Baluchestan	Idem	CS	99% male	138	18.3	12.1–25.6
			Kermanshah	Idem	CS	99% male	249	16.8	12.4–22.1
			Khouzestan	Idem	CS	99% male	198	9.4	5.9–14.6

Table 3. Cont.

Country	Citation	Year	City	Study Site	Sampling	Population	Sample Size	HIV Prevalence	
								Percent	95% CI
			Mazandaran	Idem	CS	97% male	276	7.0	4.2–10.5
			Kerman	Idem	CS	94% male	213	6.2	3.3–10.2
			Azerbaijan Sharghi	Idem	CS	100% male	118	3.6	0.9–8.5
			Khorasan Razavi	Idem	CS	99% male	248	2.2	0.7–4.6
	Alipour, 2012 [79]	2010	Tehran, Shiraz, & mashhad	Harm reduction center	CS	All male, heterosexually active	226	9.4	5.8–13.9
			Tehran, Shiraz, & mashhad	Harm reduction center	CS	All female, sexual partners of PWID	42	7.7	1.5–19.5
	Ilami, 2010 [136]	2009–2010	Kohgiloyeh & Boyerahmad		CS		158	9.9	5.9–15.9
	Hashemepour, 2013 [137]	2009	North Isfahan	Community	CS		82	1.2	0.0–6.6
			South Isfahan	Community	CS		589	1.0	0.4–2.2
			West Isfahan	Community	CS		479	1.7	0.7–3.3
			East Isfahan	Community	CS		113	3.5	1.0–8.8
			Isfahan city	Community	CS		336	1.5	0.5–3.4
	Dibaj, 2013 [138]	2008–2009	Isfahan	Prison	CS	All male	970	6.4	4.9–8.1
	Javadi, 2013 [139]	2008–2009	Isfahan	Harm reduction center	CS	95% male	539	1.1	0.4–2.4
	Eskandarieh, 2013 [140]	2008	Tehran	Mandatory drug treatment center	CS	97% male	258	18.8	14.4–24.3
	Zamani, 2010 [141]	2008	Isfahan		RDS	98% male	117	0.7[a]	0·6–2.3[a]
	Ghasemian, 2011 [142]	2007–2009	Sari	Clinical setting	CS		88	18.2	10.8–27.8
	Zadeh, 2014 [143]	2007–2008	Tehran	Prison	CS		3,044	3.7	3.1–4.4
	SeyedAlinaghi, 2013 [144]	2007–2008	Tehran	Community	CS	Beggars	658	2.4	1.4–3.9
	Kazerooni, 2010 [67]	2007	Shiraz	Prison	SRS	All male	363	6.6	4.3–9.7
	Aminzadeh, 2007 [145]	2007	Tehran	Clinical setting	CS		70	30.0	19.6–42.1
	Rahimi_Movaghar, 2010 [146]	2006–2007	Tehran	Voluntary drug treatment center & community	CS	All female	38	10.5	2.9–24.8
			Tehran	Voluntary drug treatment center & community	CS	All male	861	10.7	8.7–12.9
	Kheirandish, 2010 [147]	2006	Tehran	Mandatory drug treatment center	CS	All male	459	24.4	20.5–28.6
	MOH, 2008 [43] (Round I)	2006–2007	Azerbaijan Sharghi	Harm reduction center, voluntary drug treatment center, & community	TLS	96% male	294	8.2	5.3–11.9
			Fars	Idem	TLS	92% male	353	24.7	20.2–29.5
			Kerman	Idem	TLS	96% male	162	20.8	15.0–28.1
			Kermanshah	Idem	TLS	99% male	259	30.5	25.0–36.5
			Khorasan Razavi	Idem	TLS	98% male	399	6.5	4.3–9.4
			Khuzestan	Idem	TLS	99% male	168	4.2	1.7–8.4

Table 3. Cont.

Country	Citation	Year	City	Study Site	Sampling	Population	Sample Size	HIV Prevalence	
								Percent	95% CI
			Lorestan	Idem	TLS	97% male	196	35.7	29.0–42.9
			Mazandaran	Idem	TLS	All male	216	11.6	7.6–16.6
			Sistan	Idem	TLS	93% male	142	2.1	0.4–6.0
			Tehran	Idem	TLS	98% male	664	14.4	11.9–17.4
	Malekinejad, 2008 [148]	2006–2007	Tehran		RDS	98% male	548[a]	25.0	18.0–28.3
	Alavi, 2012 [149]	2005–2006	Ahfaz	Voluntary drug treatment center & prison	CS	All male	109	47.7	38.1–57.5
	Ghanbarzadeh, 2006 [150]	2005	Birjand	Prison	CS	All female	10	0.0	—
	Tofigi, 2011 [151]	2004	Tehran	Clinical setting	CS	Cadavers	400	6.3	4.1–9.1
	Imani, 2008 [152]	2004	Shahr-e-Kord	Voluntary drug treatment center	CS	All male	133	0.8	0·0–4·1
	Mojtahedzadeh, 2008 [62]	2004–2005	Rural Northwestern Iran	Voluntary drug treatment center	CS	98% male, rural population	61	72.1	59.2–82.9
	Zamani, 2006 [102]	2004	Tehran	Harm reduction center & community	CS	All female	6	33.3	4.3–77.7
			Tehran	Harm reduction center & community	CS	All male	207	23.2	17.6–29.5
	Shamaei, 2009 [153]	2003–2006	Tehran	Clinical setting	CS	98% male, TB infected PWID	35	45.7	28.8–63.4
	Pourahmad, 2007 [154]	2003	Isfahan, Chaharmahal Bakhtiary, & Lorestan	Prison	CS	All male	401	14.0	10.7–17.7
	Zamani, 2005 [155]	2003–2004	Tehran	Voluntary drug treatment center	CS	All female	5	20.0	0.5–71.6
			Tehran	Voluntary drug treatment center	CS	All male	165	15.2	10.1–21.5
	Farhoudi, 2003 [156]	2003	Karaj	Resident prisoners	CS	All male, resident inmates	371	24.0	19.7–28.7
			Karaj	Newly admitted prisoners	CS	All male, newly 7–admitted inmates	369	22.0	17.8–26.5
	Khodadadizadeh, 2003 [157]	2003	Rafsanjan	Clinical setting	CS	96% male	31	9.7	2.0–25.8
	Alavi, 2010 [158]	2002–2006	Ahfaz	Clinical setting	CS	97% male, hospitalized for ID	333	18.0	14.6–23.2
	Davoodian, 2009 [159]	2002	Hormozgan	Prison	SRS		249	15.1	11.0–20.3
	Behnaz, 2007 [160]	2002–2003	Gorgan	Prison	SRS		22	18.2	5.2–40.3
	Asadi, 2006 [68]	2002–2004	Tehran	Clinical setting	CS	98% male	126	35.7	27.4–44.7
	Alizadeh, 2005 [161]	2002	Hamadan	Prison	SRS	93% male	149	0.7	0.0–3.7
	Mir Nasseri, 2011 [162]	2001–2002	Tehran	Voluntary drug treatment center	CS	97% male	90	7.8	3·7–13·5
			Tehran	Prison	SRS	87% male	371	17.0	13.5–21.2
	Sharif, 2009 [163]	2001–2006	Kashan	Clinical setting	CS	All female, hospitalized for ID	23	0.0	—
			Kashan	Clinical setting	CS	All male, hospitalized for ID	177	1.6	0.4–4.9

Table 3. Cont.

Country	Citation	Year	City	Study Site	Sampling	Population	Sample Size	HIV Prevalence	
								Percent	95% CI
	Alavi, 2009 [164]	2001–2006	Ahfaz	Clinical setting	CS	92% male	142	12.7	7.7–19.3
	Alavi, 2007 [165]	2001–2003	Ahfaz	Clinical setting	CS	All male	154	67.5	59.5–74.8
	Rahbar, 2004 [166]	2001–2002	Mashhad	Voluntary drug treatment center	CS		222	0.0	—
			Mashhad	Prison	CS		101	6.9	2.8–13.8
	Sharifi-Mood, 2006 [167]	2000–2005	Zahedan	Clinical setting	CS	97% male, hospitalized for ID	31	25.8	11.9–44.6
	Mirahmadizadeh, 2004 [168]	1998	Shiraz	Voluntary drug treatment center	CS		464	1.2	0.5–2.8
	Nowroozi, 1998 [169]	1996	Tehran	Prison	SRS	All male	400	0.0	—
	Alavian, 2013 [170]	—	Shiraz	Voluntary drug treatment center	CS	98% male	144	41.7	33.5–50.2
	Azarkar, 2010 [171]	—	Birjand	Prison	SRS		17	0.0	—
	Mirahmadizadeh, 2009 [172]	—	National	National	RCS	96% male	936	20.5	18.0–23.2
	Amini, 2005 [173]	—	Tehran	Voluntary drug treatment center	CS		34	8.8	1.9–23.7
	Alaei, 2002 [174]	—	Kermanshah		CS		429	19.2	15.5–23.2
Jordan	NAP, 2010 [45] (Round I)	2009	Amman		RDS		133	0.0	—
			Aqaba		RDS		78	0.0	—
			Irbid		RDS		16	0.0	—
Lebanon	Mahfoud, 2010 [46] (Round I)	2007–2008	Beirut		RDS	All male	81	0.0	—
	Ramia, 2003 [175]	2000–2002	Beirut	Clinical setting	CS	75% male	40	0.0	—
Libya	Mirzoyan, 2013 [47] (Round I)	2010	Tripoli		RDS		328	87.1[a]	81.5–91.9[a]
Morocco	MOH, 2012 [117] (Round I)	2011–2002	Nador		RDS	99% male	277	25.1[a]	16.1–35.0
	MOH, 2012 [117] (Round I)	2010–2001	Tanger		RDS	98% male	261	0.4	0.0–2.1
	MOH, 2010 [61]	2008	Al Hoceima		RDS			0.0	—
			Nador		RDS		233	37.8	31.5–44.3
	Elmir, 2002 [176]	1991–1999	National		CS		109	33	24–43
Oman	MOH, 2006 [58]	—	Muscat	Voluntary drug treatment center	CS	All male	17	12[b]	2–36
		—	Muscat	Prison	CS	All male	33	27[b]	13–46
		—	Muscat	Community	SBS	All male	85	18[b]	10–27
OPT	MOH, 2010 [177] (Round I)	2010	Al Azaria - East Jerusalem		RDS	98.5% male	199	0.0	—
Pakistan	NAP, 2011 [37] (Round IV)	2011	D G Khan	Community	MSCS	98.4% male	365	49.6	44.3–54.8
			Faisalabad	Community	MSCS	98.4% male	364	52.5	47.2–57.7
			Gurjat	Community	MSCS	98.4% male	208	46.2	39.2–53.2
			Lahore	Community	MSCS	98.4% male	367	30.8	26.1–35.8
			Multan	Community	MSCS	98.4% male	365	24.9	20.6–29.7
			Pakpattan	Community	MSCS	98.4% male	365	3.3	1.7–5.7
			Rahim Yar Khan	Community	MSCS	98.4% male	214	14.9	10.5–20.4

Table 3. Cont.

Country	Citation	Year	City	Study Site	Sampling	Population	Sample Size	HIV Prevalence	
								Percent	95% CI
			Sarghoda	Community	MSCS	98.4% male	365	40.6	35.5–45.8
			Dadu	Community	MSCS	98.4% male	194	16.0	11.1–21.9
			Karachi	Community	MSCS	98.4% male	365	42.2	37.1–47.4
			Larkana	Community	MSCS	98.4% male	365	18.6	14.8–23.0
			Sukkur	Community	MSCS	98.4% male	365	19.2	15.3–23.6
			Haripur	Community	MSCS	98.4% male	65	7.9	2.5–17.0
			Peshawar	Community	MSCS	98.4% male	260	20.0	15.3–25.4
			Quetta	Community	MSCS	98.4% male	365	7.1	4.7–10.3
			Turbat	Community	MSCS	98.4% male	365	21.4	17.3–25.9
	Nai Zindagi, 2009 [66]	2009	Gurjanwala	Community	CS		300	8	5–12
			Mandi Bahauddin	Community	CS		300	52	46–58
			Rawalpindi	Community	CS		300	23	18–28
			Sheikhukupura	Community	CS		300	21	17–26
	Nai Zindagi, 2008 [89]	2008	Faisalabad		CS	All male, married	104	13	8–22
			Lahore		CS	All male, married	103	10	5–17
			Sarghoda		CS	All male, married	252	41	35–47
	NAP, 2008 [50] (Round III)	2008	D G Khan	Community	MSCS	99.8% male	345	18.6	14.6–23.1
			Faisalabad	Community	MSCS	99.8% male	400	12.3	9.2–15.9
			Hyderabad	Community	MSCS	99.8% male	397	30.5	26.0–35.3
			Karachi	Community	MSCS	99.8% male	403	23.1	19.1–27.5
			Lahore	Community	MSCS	99.8% male	401	14.5	11.2–18.3
			Larkana	Community	MSCS	99.8% male	389	28.5	24.1–33.3
			Peshawar	Community	MSCS	99.8% male	231	12.8	8.9–18.0
			Sarghoda	Community	MSCS	99.8% male	403	22.8	18.8–27.2
	Platt, 2009 [178]	2007	Rawalpindi		RDS	98% male	302	2.6	1.2–5.2
			Abotabad		RDS	98% male	102	0.0	—
	NAP, 2006–2007 [51] (Round II)	2006–2007	Bannu	Community	MSCS		72	1.4	0.0–7.5
			Faisalabad	Community	MSCS		400	13.3	10.1–17.0
			Gurjanwala	Community	MSCS		400	1.0	0.3–2.5
			Hyderabad	Community	MSCS		400	29.8	25.3–34.5
			Karachi	Community	MSCS		399	30.1	25.6–34.8
			Lahore	Community	MSCS		400	6.5	4.3–9.4
			Larkana	Community	MSCS		399	16.5	13.0–20.6
			Multan	Community	MSCS		400	0.0	—

Table 3. Cont.

Country	Citation	Year	City	Study Site	Sampling	Population	Sample Size	HIV Prevalence	
								Percent	95% CI
			Peshawar	Community	MSCS		180	2.2	0.6–5.6
			Quetta	Community	MSCS		190	9.5	5.7–14.6
			Sarghoda	Community	MSCS		400	51.3	46.2–56.2
			Sukkur	Community	MSCS		399	5.3	3.3–7.9
	Rahman, 2006 [179]	2005	Lahore		CS	All male		0.0	—
	Nai zindagi, 2005 [180]	2005	Faisalabad		SRS	All male	200	9.5	5.8–14.4
			Lahore		SRS	All male	200	2.5	0.8–5.7
			Sarghoda		SRS	All male	100	12.0	6.4–20.0
			Sialkot		SRS	All male	100	1.0	0.0–5.4
	NAP, 2005 [52] (Round I)	2005	Faisalabad	Community	TLS		400	13.3	10.1–17.0
			Hyderabad	Community	TLS		398	25.3	21.2–30.0
			Lahore	Community	TLS		400	3.8	2.1–6.1
			Multan	Community	TLS		400	0.3	0.0–1.4
			Peshawar	Community	TLS		284	0.4	0.0–1.9
			Quetta	Community	TLS		147	9.5	5.3–15.5
			Sukkur	Community	TLS		402	19.2	15.4–23.3
	Bokhari, 2007 [83]	2004	Karachi	Community	TLS	All male	402	23.1	19.1–27.6
			Lahore	Community	TLS	All male	397	0.5	0.1–1.8
	Achakzai, 2007 [181]	2004	Quetta	Community	CS		50	24.0	13.1–38.2
	Bokhari, 2006 [182] (Pilot)	2004–2005	Karachi		TLS		400	26.0	21.8–30.6
			Rawalpindi		CS		199	0.5	0.0–2.8
	Abbasi, 2005 [183]	2004	Larkana	VCT	CS	All male, homeless	3154	8.3	7.4–9.3
	Abbasi, 2009 [184]	2003	Quetta	Voluntary drug treatment center	CS	All male	300	0.3	0.0–1.8
	Altaf, 2007 [74]	2003	Karachi	Harm reduction center	CS	All male, 80% homeless	161	0.6	0.0–3.4
	Kuo, 2006 [70]	2003	Lahore	Harm reduction center	CS	All male	255	0.0	—
			Quetta	Harm reduction center	CS	98% male	96	0.0	—
	Shah, 2004 [185]	2003	Larkana		CS		175	9.7	5.8–15.1
	Altaf, 2003[75]	2002	Karachi	Harm reduction center	CS	All male, 86% homeless	153	0.0	—
	Hadi, 2005 [64]	2002	Rawalpindi, Swat, & Mardan	Mixed	CS	65% male	500	3.4	2.0–5.4
	Akhtar, 2004 [186]	2002	Faisalabad	Voluntary drug treatment center	CS	All male	74	0.0	—
	Nai Zindagi, 1999 [72]	1999	Lahore	Community	CS	All male	200	0.0	—
	Parviz, 2006 [82]	1996	Karachi	Voluntary drug treatment center & community	CS	All male	231	0.4	0.0–2.4
	Baqi, 1998 [81]	1994	Karachi	Voluntary and mandatory drug treatment center	CS	All male	120	0.0	—

Table 3. Cont.

Country	Citation	Year	City	Study Site	Sampling	Population	Sample Size	HIV Prevalence	
								Percent	95% CI
	Iqbal, 1996 [187]	1987–2004	Lahore	Clinical setting	CS		77	0.0	—
	Khanani, 2010 [188]	—	Karachi	Clinical setting	CS	Afghani refugees	42	19.0	8.6–34.1
	UrRehman, 2002 [189]	—	National				400	0.0	—
Syria	Mental Health Directorate, 2008 [59]	2006	Damascus		SBS	96% male	204	0.5	0.1–2.7
Tunisia	MOH, 2013 [53] (Round II)	2011	Tunis		RDS		506	2.9[a]	1.3–4.4[a]
			Bizerte		RDS		301	0.0	—
	MOH, 2010 [54] (Round I)	2009	Tunis, Bizerte, & Sousse		RDS	91% male	715	3.1	1.9–4.6

[a]Population-adjusted estimate.
[b]Self-report.
CS, convenience sampling; ID, infectious disease; MSCS, multi-stage cluster sampling; RCS, random cluster sampling; RDS, respondent driven sampling; SBS, snow ball sampling; SRS, simple random sampling; TLS, time location sampling; VCT, voluntary counseling and testing.
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Tripoli (Table S4). This indicates a concentrated HIV epidemic among PWID in at least part of Libya. Although the epidemic in Tripoli is most likely to be established, the level of evidence overall is insufficient to characterize whether the national epidemic is emerging, with few outbreaks in the past, or is established with endemic HIV transmission among PWID.

"At least outbreak-type" HIV epidemics. In Bahrain and Oman, data show that there are, or have been, at least some pockets of HIV infection among PWID, with reported prevalence up to 21.1% (Bahrain, $n = 242$) [60] and 27% (Oman, $n = 33$) [58]. However, most available data are from studies with unknown methodology or high ROB; therefore, the quality of evidence is insufficient to indicate whether there is a concentrated epidemic in these two countries, even if localized.

Low-level HIV epidemics. The HIV epidemic among PWID is low-level in Jordan, Lebanon, Tunisia, OPT, and Syria (Table 5). In these countries (except Syria), at least one round of IBBSS has been conducted, in addition to other data; all indicate limited HIV spread among PWID (Figure 4D; Tables 3 and S4). The contribution of injecting drug use to the total notified cases also remains minimal in these countries, further confirming a low-level epidemic (Table 4).

Injecting Risk Behavior

Table S5 summarizes injecting risk behavior measures among PWID in MENA. The key risk behavior that exposes PWID to HIV infection is the use of non-sterile injecting equipment. Available data indicate that the lifetime prevalence of sharing needles/syringes among PWID in MENA was as high as 71% [45], 79% [66], 85% [47], 95% [67], and 97% [58] in Jordan, Pakistan, Libya, Iran, and Oman, respectively. The median prevalence of sharing in the last injection was 23% (IQR: 18%–28%). In Pakistan, most injecting occurs in groups and in public places, and reported use of "street doctors" or professional injectors was common, which is associated with high reuse of injecting equipment (Table S5) [50].

In MENA, PWID inject drugs at median of 2.2 injections per day, with reported rates of 3.3 [68] and 5.7 [69] injections per day among some PWID in Iran and Afghanistan, respectively. The median age at first injection was 26 years (IQR: 24–28 years), and the median duration of injecting drugs was 4.6 years (IQR: 3.8–6.1 years) (Table S5).

Sexual Risk Behavior

The majority of PWID in MENA are sexually active (Table S6). On average, 52% have been ever married (IQR: 35%–56%), 43%–89% report having sex with a regular female partner, 29%–60% reported multiple sexual partnerships, and 18%–42% report sex with non-regular female partners in the last year (Table S6). Reported levels of condom use varied but generally were on the low to intermediate range. Overall, 36% of PWID reported ever using condoms (IQR: 20%–54%) with the lowest prevalence in Afghanistan and Pakistan (10%–38% [70–76]), and the highest in Lebanon (88% [77]). Condom use during last sex was reported by 4%–38% of PWID, reaching 66% only in Libya [47]. Only 12%–25% of PWID reported consistent condom use in the last year (Table S6).

Mixing with Other High-Risk Populations

Risk behaviors of PWID in MENA overlap considerably with other high-risk populations, namely MSM and female sex workers. A median of 18% of male PWID in MENA reported ever having sex with men (IQR: 11%–27%), and a median of

Table 4. Contribution of injecting drug use as a mode of HIV transmission to the total HIV/AIDS cases by country as per various studies/reports and countries' case notification reports [126,190].

Country	2011 Case Notification Report[a]			Cumulative Data since the Start of the Epidemic
	n	*N*	Percent	Percent due to PWID (end year)
Afghanistan	52	107	48.6	44.3% (2011)
Bahrain	6	16	37.5	62.8% (2008)
Egypt	80	409	19.6	1.6% (2008)
Iran	948	1,588	59.7	69.4% (2011)
Iraq	—	—	—	0.0% (2009)
Jordan	0	17	0.0	2.4% (2011)
Kuwait	0	25	0.0	2.2% (2008)
Lebanon	1	51	2.0	6.1% (2009)
Morocco	9	750	1.2	2.7% (2011)
Oman	5	140	3.6	4.3% (2011)
OPT	0	6	0.0	2.8% (2011)
Qatar	0	1	0.0	—
Pakistan	50	216	23.1	33.2% (2008)
Saudi Arabia	46	394	11.7	6.4% (2009)
Syria	0	69	0.0	2.4% (2009)
Tunisia	3	73	4.1	24.4% (2009)
UAE	1	57	1.8	3.6% (2011)
Yemen	1	236	0.4	1.4% (2009)

Only the most recent available report was used.
[a]Except for Bahrain, Egypt, and Iraq (2010 report) and Pakistan (2008 report).
n, number of positive cases that are PWID; *N*, total number of positive cases; Percent, percent of positive cases that are PWID out of the total number of positive cases; UAE, United Arab Emirates.
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7% did so in the last year (IQR: 2%–10%) (Table S6). The highest rates of same-sex sex have been reported in Pakistan. Reported condom use during anal sex was overall very low (Table S6).

PWID in MENA engage in sex work, either through buying or selling sex. A median of 45% reported ever having sex with a sex worker (IQR: 31%–64%), and a median of 23% did so in the last year (IQR: 15%–30%), with generally low levels of condom use (Table S6). Selling sex in the past year was reported by 5%–29% of PWID in Egypt, Iran, Morocco, OPT, and Pakistan (Table S6).

Proxy Biological Markers of Risk Behavior

There was substantial between-and within-country variation in HCV prevalence among PWID, with a median of 44% (IQR: 31%–64%) (Table 6). Very high HCV prevalence was reported such as in Afghanistan (70%, $n = 185$, Herat), Egypt (63%, $n = 100$, Alexandria), Iran (over 80%, $n = 386$ prisoners, Tehran), Libya (94%, $n = 328$, Tripoli), Pakistan (94%, $n = 161$, Karachi), and Saudi Arabia (75%, $n = 1,909$, Jeddah) (Table 6). These figures are consistent with the reported high levels of sharing of injection equipment, such as in Iran, Pakistan, and Libya (Table S5).

Available data on the prevalence of syphilis among PWID in Egypt, Iran, Afghanistan, and Pakistan indicate relatively high prevalence up to 3%, 8%, 17%, and 18%, respectively (Table S6). Considerable herpes simplex virus type 2 prevalence has been reported among PWID in Afghanistan (4%–21%) and Pakistan (6%–19%) (Table S6). Data on the prevalence of gonorrhoea (0%–1.8%) and chlamydia (0%–0.7%) were available only in Pakistan (Table S6).

Knowledge of HIV/AIDS

Levels of basic HIV/AIDS knowledge among PWID in MENA were high overall, with a median of 93% having ever heard of HIV/AIDS (IQR: 72%–99%). Still, there was much variation in the proportion of PWID who correctly identified reuse of non-sterile needles/syringes and unprotected sex as modes of HIV transmission (Table S7). Only a median of 45% (IQR: 30%–63%) of PWID perceived themselves at risk of HIV/AIDS (Table S7). With a few exceptions of high levels of HIV testing such as in Lebanon and Oman, the median prevalence of lifetime testing among PWID ranged between 8% (Egypt) and 45% (Iran) (Table S7).

Discussion

Injecting Drug Use in MENA

We estimate that there are 626,000 PWID in the MENA region. Overall, the mean prevalence of injecting drug use (0.24%) is comparable with global figures which range from 0.06% in South Asia to 1.50% in Eastern Europe [31]. Prevalence of injecting drug use in MENA varied between countries and was higher in the eastern part of the region. Injecting drug use appears to be heavily concentrated among men; but female PWID are one of the hardest-to-reach populations in MENA, thereby limiting our knowledge of this vulnerable group. From limited available data, it appears that injecting drug use among females has a strong

Table 5. Characterization of the state of the HIV epidemic among people who inject drugs in the Middle East and North Africa based on the HIV biological data and quality and scope of the evidence.

Country	Level of HIV Prevalence	Trend in HIV Prevalence	Geographical Distribution	Quality and Scope of Evidence
Iran	Concentrated	Established	National	Conclusive
Pakistan	Concentrated	Emerging	National	Conclusive
Afghanistan	Concentrated	Emerging	At least localized	Good
Egypt	Concentrated	Emerging	At least localized	Good
Morocco	Concentrated	Emerging	At least localized	Good
Libya	Concentrated	Unknown	At least localized	Good
Bahrain	At least outbreak-type	—	—	Limited
Oman	At least outbreak-type	—	—	Poor
Jordan	Low-level	—	—	Good
Lebanon	Low-level	—	—	Good
OPT	Low-level	—	—	Good
Tunisia	Low-level	—	—	Good
Syria	Low-level	—	—	Limited
Djibouti	Unknown	—	—	Poor
Iraq	Unknown	—	—	Poor
Kuwait	Unknown	—	—	Poor
Saudi Arabia	Unknown	—	—	Poor
Sudan	Unknown	—	—	Poor
Yemen	Unknown	—	—	Poor
Algeria	Unknown	—	—	No evidence
Qatar	Unknown	—	—	No evidence
Somalia	Unknown	—	—	No evidence
UAE	Unknown	—	—	No evidence

Countries are sorted by level of HIV prevalence, trend in HIV prevalence, geographical distribution, quality and scope of evidence, then alphabetical order.
UAE, United Arab Emirates.
doi:10.1371/journal.pmed.1001663.t005

association with sex work and having a PWID sexual partner [78,79].

Emerging HIV Epidemics and HIV Epidemic Potential among PWID

After synthesizing a large body of data, we documented HIV epidemics among PWID in one-third of MENA countries. The HIV epidemic is in a concentrated state in about half the countries with available data. Iran is the only country with an established concentrated epidemic, while the most common pattern is that of emerging concentrated epidemics. Most observed epidemics in the region are recent, occurring only in the last decade; around the same time that HIV epidemics among MSM appear to have emerged (2003) [14]. Of note, our classification of epidemic states did not depend only on the size of the epidemic, but also on the trend of HIV prevalence and other biological data. For example in Pakistan, despite high HIV prevalence, the epidemic was classified as emerging since HIV prevalence continues in an increasing trend. HIV prevalence among PWID in MENA countries with concentrated epidemics is overall in the range of 10%–15%, which is in the intermediate range compared to global figures [31]. However, there are settings with very high prevalence, most notably in Tripoli, Libya, which appears to have one of the highest HIV prevalence reported globally (87.1%) [31,47].

In about 20% of MENA countries, the HIV epidemic among PWID was low level, with HIV prevalence consistently low for many years including the most recent IBBSS. In some countries, such as Jordan, Lebanon, and OPT, no HIV infections were found in the IBBSS. The available evidence in countries at low level is restricted to a few cities, and there could be hidden sub-epidemics in other sites. Nevertheless, the low prevalence could be reflective of the intrinsic HIV transmission dynamics, levels of risk behavior, and/or injecting network structure. HIV may not have been introduced to the PWID community, may have been recently introduced, or may have been spreading slowly and inefficiently for some time. The latter may reflect injecting networks with infrequent and few repeated transmission contacts among PWID to sustain HIV dynamics. In Lebanon and Syria for example, it appears that PWID form closed small networks with injecting occurring in private homes and among friends, and not in large groups or at shooting galleries [59,80]. The low prevalence could also be a consequence of stochastic effects where the small number of individuals who introduced HIV to the PWID population happened by chance not to have links that could sustain transmission chains.

Whilst it is conceivable that HIV prevalence may not grow in countries currently at low level, there are settings where HIV prevalence increased considerably in a short period of time. For example in Karachi, Pakistan, after several years of near zero prevalence [74,75,81,82], HIV prevalence in 2004 increased to

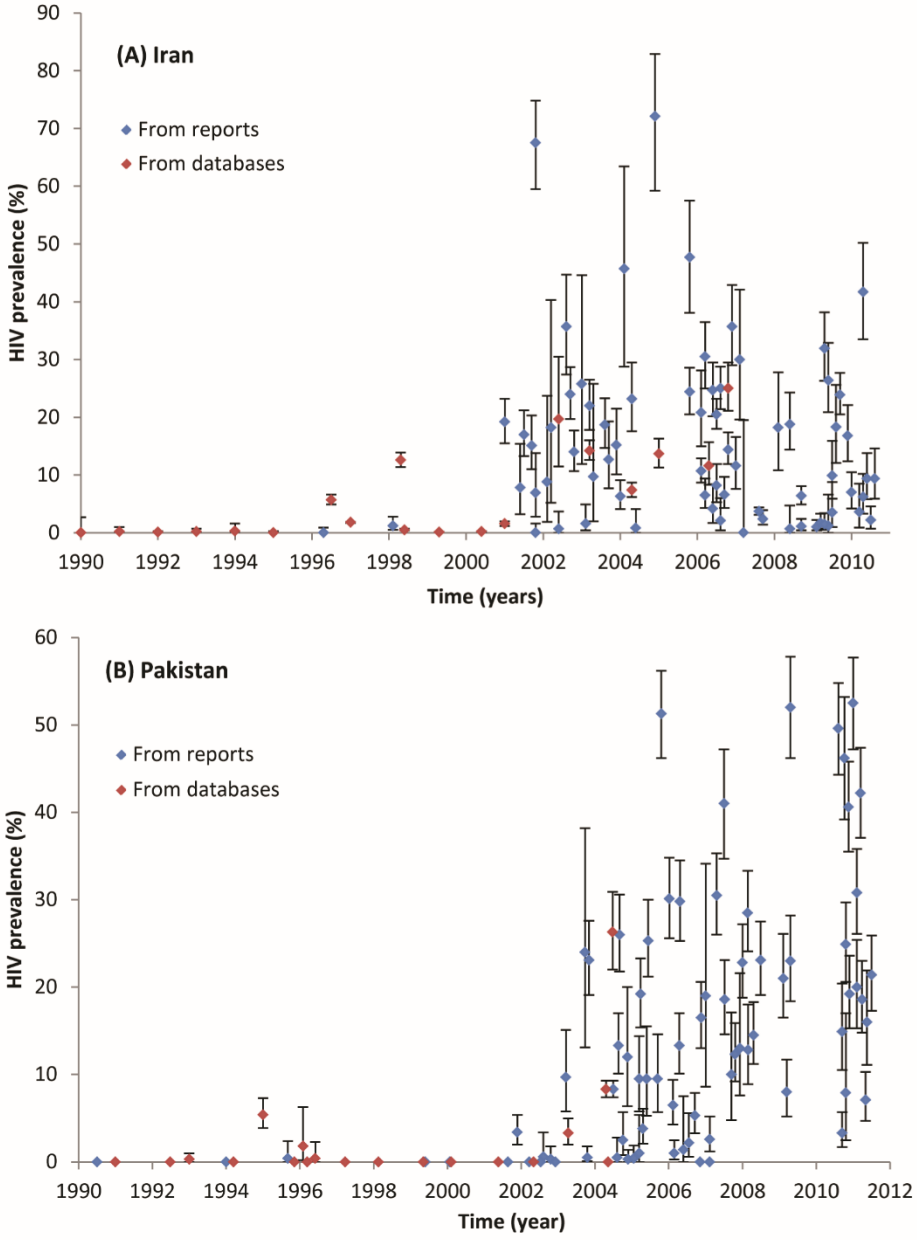

Figure 3. Trend of HIV prevalence among male people who inject drugs in (A) Iran and (B) Pakistan. This graph displays all available HIV prevalence measures for these two countries as extracted from eligible reports (Table 3) and various databases (Table S4). Each dot represents one HIV prevalence measure for the specific year, and the bars around it define the 95% confidence interval. A pattern of established HIV epidemic is observed in Iran (A), while a trend of emerging HIV epidemic is observed in Pakistan (B).
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23% in less than 6 months [83], and reached 42% in 2011 [37]. This pattern is not surprising given the reported risky practices and high HCV prevalence. When HIV prevalence was still very low in Karachi, HCV prevalence was over 85% [74,75], indicating substantial use of non-sterile injecting equipment and suggesting connectivity of injecting networks. In Iran, the substantial HCV prevalence (up to 80%) was predictive of the explosive HIV epidemic that occurred subsequently. In both Iran and Pakistan, injecting networks often seem to be well connected and we found reports of injecting and sharing occurring among persons who are

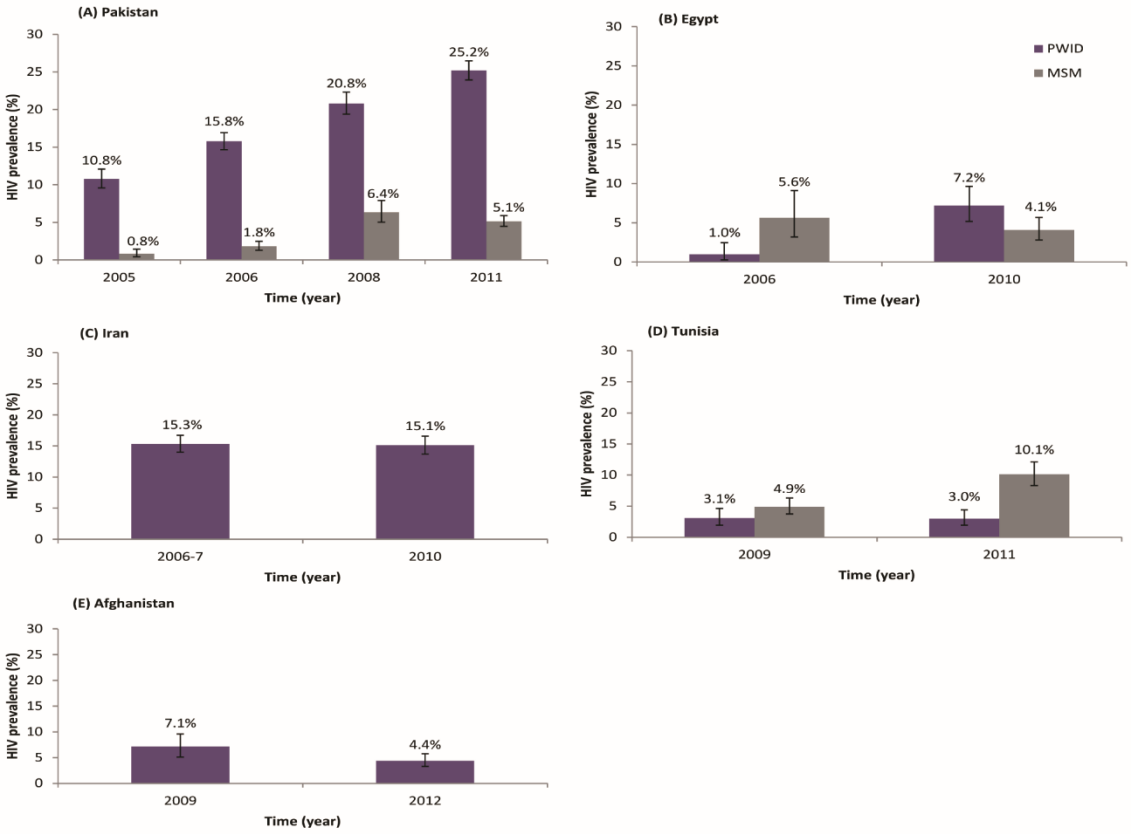

Figure 4. Trend of HIV prevalence among people who inject drugs, and when available men who have sex with men, in repeated rounds of bio-behavioral surveillance surveys. These graphs display the trend of HIV prevalence in repeated rounds of bio-behavioral surveillance surveys using state of the art sampling techniques for hard-to-reach populations including respondent driven sampling and time-location sampling. Country level and aggregate data of multiple cities/provinces are displayed. For consistency between countries and between different rounds within a given country, unadjusted sample estimates are displayed. Three main patterns of HIV epidemics among PWID are depicted. A pattern of emerging concentrated epidemics is observed in Pakistan (A) and Egypt (B); a pattern of established concentrated epidemic is observed in Iran (B); and a pattern of low-level HIV epidemic is observed in Tunisia (D). In Afghanistan (E), there is an emerging epidemic among PWID in apparently only part of the country; the effect of which was diluted in the second round with the inclusion of new cities with still very limited prevalence. The potential overlap of the HIV epidemics among PWID and MSM is depicted in Pakistan and Egypt. In Pakistan, an emerging HIV epidemic among transgender sex workers is observed, but lags the epidemic among PWID (A). In Egypt, the concentrated epidemic among MSM seems to have preceded the epidemic among PWID (B). In Tunisia, the potential link between the MSM and PWID epidemics is not clear because the studies were conducted after the epidemics had already risen.
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not necessarily socially related, e.g. in shooting galleries [84,85]. Data on HCV prevalence among PWID in MENA countries with low-level HIV epidemics are limited. However, HCV prevalence of 40%–61% among some PWID groups such as in Lebanon, OPT, and Syria suggest moderate HIV epidemic potential once the virus is introduced to the PWID community.

Bridging of the HIV Epidemic to Other Population Groups

We found considerable overlap of risk behavior between PWID and other high-risk groups in MENA; this could play a role in emerging HIV epidemics, as it creates opportunities for an infection circulating in one population to be bridged to another one. In Pakistan, the rapidly growing HIV epidemic among PWID was followed closely by an emerging epidemic among transgender sex workers (Figure 4A). Phylogenetic analyses found clustering of subtypes between the two populations, suggesting that the infection might have bridged from PWID to the transgender population [86]. A similar pattern, but in the opposite direction, may have occurred in Egypt where an emerging epidemic among MSM [14] preceded the nascent epidemic among PWID (Figure 4B). While supported by behavioral data [40,42], this needs to be confirmed by phylogenetic analyses.

Our analysis, focused on the HIV disease burden among PWID, still masks the role of these epidemics in driving the onward transmission of HIV to the sexual partners of PWID and further in the population. The majority of PWID are sexually active and about half are married. They often engage in risky sexual behavior as confirmed by the prevalence of STIs. This puts sexual partners

Table 6. Prevalence of hepatitis C virus among people who inject drugs in the Middle East and North Africa.

Country	HCV Prevalence		Year	Sample Size	Population Characteristics	City	Source
	%	95% CI					
Afghanistan	70.0	63.1–76.8	2012	185	Predominantly male	Herat	[39]
	57.9	49.8–65.6	2009	159	Predominantly male	Herat	[38]
	49.1	43.7–54.6	2006–2008	340	Predominantly male	Herat	[127]
	37.1	31.5–42.9	2009	286	Predominantly male	Kabul	[38]
	36.6	32.1–41.1	2006–2008	463	Predominantly male	Kabul	[127]
	36.1	31.7–40.5	2007–2009	483	Predominantly male	Kabul	[69]
	27.6	23.1–32.5	2012	369	Predominantly male	Kabul	[39]
	25.5	17.4–35.1	2009	102	Predominantly male	Mazar-i-Sharif	[38]
	25.0	17.3–33.6	2012	117	Predominantly male	Charikar	[39]
	24.1	18.1–30.8	2006–2008	187	Predominantly male	Mazar-i-Sharif	[127]
	18.8	14.3–24.3	2012	254	Predominantly male	Mazar-i-Sharif	[39]
	12.5	6.6–20.8	2006–2008	96	Predominantly male	Jalalabad	[127]
	9.5	5.9–13.8	2012	236	Predominantly male	Jalalabad	[39]
Egypt	63.0	52.8–72.4	1994	100		Alexandria	[130]
Iran	95.4	77.2–99.9	2002–2003	22	Prisoners	Gorgan	[160]
	88.9	80.0–94.8	2003	81	Predominantly male prisoners	Guilian	[191]
	80.5	76.3–84.4	2001–2002	386	Predominantly male prisoners	Tehran	[162]
	80.1	76.2–83.7	1998	464		Shiraz	[168]
	80.0	76.0–83.5	2006	454	Predominantly male	Tehran	[192]
	76.8	72.4–80.9	2003	401	Predominantly male prisoners	Isfahan, Chaharmahal Bakhtiary, & Lorestan	[154]
	67.4	49.5–82.6	—	34		Tehran	[173]
	65.9	59.8–71.7	2008	258	Predominantly male	Tehran	[140]
	64.8	58.4–70.6	2002	249	Prisoners	Hormozgan	[159]
	63.3	56.2–70.0	2005–2007	199		Hamadan	[193]
	59.4	47.4–68.7	2008	117	Predominantly male	Foulad-Shahr	[141]
	59.4	49.2–69.1	2001–2002	101	Prisoners	Mashhad	[166]
	52.9	35.1–70.2	2007	34	Predominantly male, homeless	Tehran	[194]
	52.1	43.6–60.6	2001–2006	142	Predominantly male	Ahfaz	[164]
	52.0	44.9–59.0	2004	202	Predominantly male	Tehran	[195]
	50.0	11.8–88.2	2008–2009	6	Incarcerated juveniles	Isfahan	[196]
	50.0	21.1–78.9	2006	12		Kermanshah	[197]
	50.0	41.4–58.6	—	138	Predominantly male	Shiraz	[170]
	47.1	42.8–51.4	2008–2009	531	Predominantly male	Isfahan	[198]

Table 6. Cont.

Country	HCV Prevalence		Year	Sample Size	Population Characteristics	City	Source
	%	95% CI					
	45.3	40.3–50.3	1995	402	Predominantly male prisoners	Tehran	[199]
	44.4	27.9–61.9	2006–2007	36	Females	Tehran	[146]
	43.4	40.8–45.9	—	1,485	Predominantly male	Foulad-Shahr	[200]
	43.4	40.2–46.6	—	936	Predominantly male	National	[172]
	42.4	—	2009–2010	—		Kohgiloyeh & Boyerahmad	[201]
	42.0	38.8–45.2	—	951	Prisoners	Foulad-Shahr	[202]
	41.6	38.4–44.8	2008–2009	943	Predominantly male prisoners	Isfahan	[203]
	40.3	34.0–46.9	2012–2013	233	Predominantly male	Shiraz	[134]
	38.6	32.1–45.2	2010	226	Predominantly male	Tehran, Shiraz, & mashhad	[79]
	37.5	20.4–54.9	2007–2009	33		Sari	[142]
	36.6	21.6–52.0	2010	42	Female sexual partners of PWIDs	Tehran, Shiraz, & mashhad	[79]
	36.5	28.2–45.2	2001–2002	132	Predominantly male	Tehran	[162]
	36.0	24.6–48.1	2007	70		Tehran	[145]
	34.1	30.9–37.4	2006–2007	859	Predominantly male	Tehran	[146]
	34.0	31.8–36.3	2008–2009	1,747	Predominantly male	Isfahan	[204]
	31.5	24.2–39.7	2002	149	Predominantly male prisoners	Hamadan	[161]
	30.9	26.0–36.2	2002–2006	333	Predominantly males, hospitalized for infectious disease	Ahfaz	[158]
	22.8	9.6–41.1	2000–2005	31	Hospitalized for infectious disease	Zahedan	[167]
	16.1	5.5–33.7	2003	31		Rafsanjan	[157]
	13.0	2.8–33.6	2001–2006	23	Females, hospitalized for infectious disease	Kashan	[163]
	12.9	2.8–33.6	2006	23		Tehran & Hormozgan	[56]
	11.9	7.5–17.6	2001–2006	177	Predominantly males, hospitalized for infectious disease	Kashan	[163]
	11.3	6.5–17.9	2004	133	Predominantly male	Shahr-e-Kord	[152]
	26.8[a]	20.9–33.3	2011	209	Predominantly male	Tehran	[135]
Lebanon	51.0	33–74	2007–2008	43		Beirut	[46]
	5.0	0.6–16.9	2000–2002	40	25% female	Beirut	[175]
Libya	94.2	90.8–96.7	2010	328	Predominantly male	Tripoli	[47]
Morocco	79.2	72.1–85.7	2011–2012	274	Predominantly male	Nador	[117]
	45.6	35.5–56.6	2010–2011	261	Predominantly male	Tanger	[117]
Oman	36.0[a]	12.8–64.9	—	14	Predominantly male	Muscat	[58]
	11.0[a]	0.3–48.2	—	9	Predominantly male prisoners	Muscat	[58]
	53.0[a]	40.0–66.3	—	60	Predominantly male	Muscat	[58]

Table 6. Cont.

Country	HCV Prevalence		Year	Sample Size	Population Characteristics	City	Source
	%	95% CI					
OPT	40.3	29.2–52.2	2010	192	Predominantly male	East Jerusalem	[177]
Pakistan	94.3	89.7–97.4	2003	161		Karachi	[74]
	92.9	89.1–95.8	2003	255	Predominantly male	Lahore	[70]
	91.8	88.6–94.4	2004	380	Predominantly male	Lahore	[205]
	89.0	83.8–93.0	1999	200	Predominantly male	Lahore	[72]
	89.0	85.5–91.9	—	400		National	[189]
	87.0	83.3–90.1	2004	399	Predominantly male	Karachi	[205]
	86.9	80.5–91.8	2002	153	Homeless	Karachi	[75]
	76.0	—	2005	—	Predominantly male	Lahore	[179]
	75.0	65.1–83.3	2003	96	Predominantly male	Quetta	[70]
	62.5	24.5–91.5	2007–2009	8	Remote rural population	Kech	[206]
	60.0	45.2–73.6	2004	50		Quetta	[181]
	46.4	34.5–57.9	—	76	Predominantly male prisoners	Kabul	[207]
	45.2	29.8–61.3	—	42	Afghani refugees	Karachi	[188]
	44.7	39.0–50.5	2003	300	Predominantly male	Quetta	[184]
	42.0	37.6–46.5	2002	500	35% female	mix of cities	[64]
	31.5	25.1–38.4	—	200	Predominantly male	Khyber pakhtunkhwa	[208]
	17.3	13.1–22.0	2007	302	Predominantly male	Rawalpindi	[178]
	14.3	5.4–28.5	—	42		Khyber pakhtunkhwa	[209]
	8.0	3.4–14.9	2007	102	Predominantly male	Abotabad	[178]
Saudi Arabia	74.6	72.6–76.5	1995–1996	1909	Predominantly male	Jeddah	[210]
	69.0	64.7–72.9	1995–1996	505			[211]
	38.1	32.9–43.4	—	344			[212]
Syria	60.5	43.4–76.0	2006	38	Predominantly male	Damascus	[213]
	21.0[a]	11.4–33.9	2006	57	Predominantly male	Damascus	[59]
Tunisia	35.8	29.1–42.5	2011	506	Predominantly male	Tunis	[53]
	29.1	25.8–32.6	2009	701	Predominantly male	Tunis, Bizerte, & Sousse	[54]
	2.4	0.6–4.1	2011	301	Predominantly male	Bizerte	[53]

The table is sorted by country then by descending order of HCV prevalence.
[a]Self report.
doi:10.1371/journal.pmed.1001663.t006

of PWID at risk of HIV. A substantial number of infections in MENA have been documented in women who acquired HIV from their PWID husbands; and in some countries, the majority of HIV infections among women were acquired from a PWID sexual partner [79,87–89]. This highlights the vulnerability of sexual partners of PWID, who are often female spouses. An illustration of the role of the HIV epidemics among PWID in driving the onward transmission of HIV emerges from recent mode of transmission (MoT) modeling studies in the region [90–92]. For example, in Iran, PWID directly contributed 56% of the total HIV Incidence; and indirectly, only through infections to their current sexual partners, an additional 12% of the total incidence [92]. More onward HIV transmissions would arise if the sexual partners of PWID transmitted the infection to their other sexual partners.

Study Limitations

One limitation of our study is that the quantity and quality of data varied by countries. There were virtually no HIV data in four countries, and the data quality in six others was insufficient to assess the status of the epidemic. Longitudinal repeated IBBSS data were available in only five countries. Six countries have recently conducted their first round of IBBSS; and in most of these, subsequent rounds are either planned or being implemented. The quality of data was "good" or "conclusive" in ten out of the 23 countries.

While most of the data were from cross sectional surveys, there was a substantial improvement in the quality of data over time. Many studies were conducted with state of the art research methodologies in HIV research. These consist of IBBSS studies using innovative sampling methodologies for hard-to-reach populations such as respondent-driven sampling and time-location sampling. Most of these studies benefited from large sample sizes and some from broad geographical coverage at the national level.

Of note that in several countries there were no recent national estimates of the number and proportion of PWID. The only national data available for these countries were extracted from earlier global reviews of injecting drug use [4,31]. The reviews were based mainly on estimates by the Reference Group to the UN on HIV and Injecting Drug Use, which systematically collects and analyses global data on injecting drug use and HIV [32]. The Reference Group is considered the main reference for PWID estimates globally, providing the estimates to the United Nations Office on Drugs and Crime (UNODC), WHO, and UNAIDS secretariats. We complemented the Reference Group data with PWID national risk-group size estimation studies that were conducted in the last few years in five countries namely Afghanistan, Iran, Pakistan, Saudi Arabia, and Tunisia. Since we partly relied on secondary sources of data and since the data that we used came from studies using different methodologies, our pooled estimates of the number and prevalence of PWID in MENA should be considered as approximate figures.

In assessing the status of the epidemic at the country-level, we did not limit our analysis to one line of evidence, but synthesized and corroborated findings from different data sources and types such as HIV prevalence and incidence, notified HIV cases, injecting and sexual risk behavior, and other related and contextual data. Thus we could make a comprehensive assessment of the epidemic status and address potential limitations in any one line of evidence [93]. We did a rigorous appraisal of the scope and quality of the evidence within each country by assessing the amount and geographical coverage of available data, as well as the ROB and precision of individual point estimates. A qualifier for the scope and quality of the evidence at the country level was integrated with each HIV epidemic state assigned. Our search criteria were expansive, covering different literature sources. Before the present submitted work, the status of the epidemic across MENA country was poorly understood. On the basis of our integrated data synthesis and using rigorous methodology and data quality assessment, we were able to concretely qualify the epidemic status in 13 countries (over half of MENA countries), and to document the overall trend of emerging epidemics. The lack of evidence in several MENA countries does not preclude the possibility of hidden epidemics among PWID in these settings.

HIV Response among PWID in MENA

Not only does the region overall lag behind in responding to the emerging HIV epidemics among PWID; in occasions misguided policy has contributed to these epidemics. Most notably in Libya, the large HIV epidemic among PWID appears to have been exacerbated by restrictions imposed on the sale of needles and syringes at pharmacies in the late 1990s [11,94]. Overall, harm reduction programs still remain limited in MENA, and there is a need to integrate such programs within the socio-cultural framework of the region [95]. Several countries though have made significant strides in initiating such programs in recent years [11,96]. Needle/syringe exchange programs are currently implemented in nine countries, and opioid substitution therapy in five [96]. Iran remains the leader in the provision of harm reduction services to PWID with the highest coverage of needle/syringe exchange programs in the region [12,96]. It appears also to be the only country in MENA to provide such services in prisons [96,97] and to provide female-operated harm reduction services targeted at female drug users [96].

Iran has also initiated triangular clinics that integrate services for treatment and prevention of injecting drug use, HIV/AIDS, and other STIs; and these clinics have received international recognition as best practice [98–100]. Among other interventions implemented in Iran are drop-in centers, integration of substance use treatment and HIV prevention into the rural primary health care system, and community education centers [62,101–105]. These efforts appear to have been successful in reducing sharing of injecting equipment [106–108], though the coverage of harm reduction continues to be lower than adequate [104].

Other countries in the region have also made progress in revising their policies, adopting harm reduction programs, and integrating such programs in their national strategic plans such as Afghanistan, Egypt, Lebanon, Morocco, Pakistan, and Tunisia [11,109]. Access to antiretroviral therapy (ART) has also expanded in MENA in recent years, and treatment outcomes reported by country ART programs are comparable to globally reported outcomes [110,111]. Good adherence to ART has been also observed, such as in Morocco [112], though some non-adherence and treatment interruptions, among other obstacles, have been also reported in several countries [112–114].

Non-governmental organizations (NGOs) have been instrumental to the success in harm reduction in MENA. It can be noted that in countries where NGOs are strong, HIV response has been also strong [11,109]. The Iranian NGO Persepolis, for example, played an important role in the transformation to effective policies in Iran [115]. Building on the growing role of NGOs, a regional civil society network was established in 2007 covering 20 countries in MENA; the Middle East and North Africa Harm Reduction Association (MENAHRA) [116]. MENAHRA has the objective of building the capacity of civil society organizations in harm reduction efforts through training, sharing of information, networking and providing direct support to NGOs to initiate or scale-up harm reduction services. The network is a collaborative initiative by regional and international organizations with funding

from international donors, and has been influential in promoting harm reduction.

Despite the recent progress in harm reduction, HIV prevention efforts among PWID in MENA remain impeded by generic and routine planning, competing priorities, limited human capital, and lack of monitoring and evaluation [7]. National policies remain inadequate and not sufficiently reflecting evidence-informed approaches [7]. The scope and coverage of prevention services remain patchy across and within countries [11,96,109]. An indicator of the low effective coverage is that only a minority of PWID report ever being tested, and a smaller proportion report being tested within the last year [11]. In Morocco and Pakistan, two countries with a strong HIV response, only 32.5% [117], 47.8% [117], 6.1% [51], and 20.7% [50] of PWID in different surveys reported ever being tested. Even where services are available, PWID may not be aware of them, and when aware of them, they may not utilize them. In Pakistan for example, 37% of PWID in one study were aware of HIV prevention programs in their city, but only 19% ever used them [52]. There is an urgent need to expand the provision, scope, and coverage of HIV interventions among PWID in MENA to be ahead of the growing HIV epidemics.

Conclusion

Our study identified a large volume of HIV-related biological and behavioral data among PWID in the MENA region, including quality data that appear in the scientific literature for the first time. The in-depth analyses, the quality assessment of evidence, and the comprehensive synthesis of data facilitated, for the first time to our knowledge, a rigorous characterization of the state of the epidemic among PWID across different countries in this region.

We found robust evidence for HIV epidemics among PWID in multiple countries, most of which have emerged only recently and continue to grow. The high risk and vulnerability context suggest potential for further HIV spread. HIV surveillance among PWID must be expanded to detect and monitor these budding and growing HIV epidemics, and to inform effective HIV policy and programming. This mainly includes conducting IBBSS studies among PWID in countries where such surveys have not been conducted yet, and implementing subsequent rounds, for the provision of longitudinal data, in countries that are already developing their surveillance base. Population size estimations and mapping and ethnographic studies are also needed for a better understanding of the profile and injecting and sexual networks of PWID in MENA.

The window of opportunity to control the emerging epidemics should not be missed. HIV prevention among PWID must be made a priority for HIV/AIDS strategies in MENA; and obstacles must be addressed for the provision of comprehensive services and enabling environments for PWID [118]. There is need to review current HIV programs among PWID in light of the emerging epidemics, and to develop service delivery models with embedded links between community-based prevention (needle/syringe exchange programs and condom provision), HIV testing, and treatment (opioid substitution and ART). Such comprehensive approach has already proven its utility in preventing HIV transmission among PWID [119–121], but would require better resource allocation and sufficient services in priority areas for PWID.

Prevention efforts need to prioritize those most likely to be reluctant to approach facility-based services, and those with multiple and overlapping risks. Outreach and peer education can provide a means to reach those most at risk with information and services. Access to ART should be expanded in such a region with one of the lowest ART coverage globally [122]. Such expansion must address the low diagnosis rate among people living with HIV [110]. Reaching the at-risk populations even in discreet unpublicized ways would contribute positively to HIV prevention [14,123]. Improving HIV programming among PWID in MENA is essential not only to confront the growing HIV problem in this population group, but also to prevent the onward transmission of HIV, and the bridging of the infection to other groups as has already occurred in parts of the region.

Supporting Information

Table S1 Precision and risk of bias of individual HIV prevalence measures among people who inject drugs in the Middle East and North Africa as extracted from eligible reports.
(DOCX)

Table S2 Summary of precision and risk of bias of HIV prevalence measures as extracted from eligible reports.
(DOCX)

Table S3 Subnational estimates of the number and prevalence of people who inject drugs in the Middle East and North Africa.
(DOCX)

Table S4 HIV point-prevalence measures among people who inject drugs as extracted from various databases including the US Census Bureau database, the WHO/EMRO testing database, the UNAIDS epidemiological fact sheets databases, and other sources of data with unidentified reports.
(DOCX)

Table S5 Measures of injecting risk behavior among people who inject drugs in the Middle East and North Africa.
(DOCX)

Table S6 Measures of sexual risk behavior and sexually transmitted infections prevalence among people who inject drugs in the Middle East and North Africa.
(DOCX)

Table S7 HIV/AIDS knowledge, perception of risk, and HIV testing among people who inject drugs in the Middle East and North Africa.
(DOCX)

Text S1 PRISMA checklist.
(DOCX)

Text S2 Search criteria.
(DOCX)

Text S3 Narrative justification for quality of the evidence and status of the epidemic at the country level.
(DOCX)

Author Contributions

Conceived and designed the experiments: GRM LJA HAW SLT. Performed the experiments: GRM SR LJA. Analyzed the data: GRM LJA HAW. Contributed reagents/materials/analysis tools: HS GR FAA IS OT DW. Wrote the first draft of the manuscript: GRM. Contributed to the writing of the manuscript: GRM HAW ST SR HS GR FAA IS OT DW LJA. ICMJE criteria for authorship read and met: GRM HAW ST SR HS GR FAA IS OT DW LJA. Agree with manuscript results and conclusions: GRM HAW ST SR HS GR FAA IS OT DW LJA.

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Editors' Summary

Background. About 35 million people worldwide are currently infected with HIV, the virus that causes AIDS, and around 2.3 million people become newly infected every year. HIV is mainly transmitted through unprotected sex with an infected partner. However, people who inject drugs (PWID) have a particularly high risk of HIV infection because blood transfer through needle and syringe sharing can transmit the virus. Worldwide, 5%–10% of all HIV-positive people are PWID but in some regions of the world the fraction of all HIV-positive people that are PWID is even higher. To meet the global health challenge of the high HIV prevalence (the proportion of a population that has a specific disease) among PWID, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and other international bodies endorse harm reduction strategies to prevent risky injection behaviors among PWID. These strategies include education and the provision of clean needles, syringes, and opioid substitution therapy.

Why Was This Study Done? To maximize the effect of these harm-reduction strategies in specific regions, it is important to understand the status of the HIV epidemic among PWID. Although surveillance systems provide the information on HIV infection needed to track the progress of HIV epidemics among PWID in many regions, little is known about the HIV epidemic among PWID in the Middle East and North Africa (MENA, a geographical region that encompasses countries that share historical, socio-cultural, linguistic, and religious characteristics). Several factors contribute to the likelihood of individuals injecting drugs in MENA. For example, Afghanistan (a MENA country) produces most of the world's supply of heroin, which is largely trafficked through Iran and Pakistan (also MENA countries). In this systematic review and data synthesis, the researchers use predefined criteria to identify all the published and unpublished data on HIV prevalence and incidence (the number of new cases of a disease in a population in a given time) among PWID in MENA and combine (synthesize) these data to assess the status of the HIV epidemic in this key population for HIV transmission in MENA.

What Did the Researchers Do and Find? The researchers identified 192 reports that reported the prevalence/incidence of HIV, other sexually transmitted infections and infection with hepatitis C virus (HCV, another virus transmitted through drug injection) among PWID, the prevalence of injecting or sexual risk behaviors among PWID, or the number/proportion of PWID in MENA. From these data, the researchers estimated that there are about 600,000 PWID in MENA (a prevalence of 0.24 per 100 adults, which is comparable with figures from other regions). The data provided evidence for HIV epidemics among PWID in at least a third of MENA countries, mainly emerging concentrated epidemics (epidemics that are still growing but in which HIV infection and transmission are already considerable). HIV prevalence among PWID in MENA varied considerably, reaching an extremely high prevalence of 87.1% in Tripoli, Libya. The data also revealed a high injecting and sexual risk environment among PWID in MENA (for example, on average, about a quarter of PWID shared a needle or syringe in their most recent injection and only a third reported ever using condoms) that, together with a high prevalence of HCV and sexually transmitted infections among PWID, indicates the potential for more and larger HIV epidemics.

What Do These Findings Mean? These findings indicate that substantial amounts of HIV-related data have been collected from PWID in MENA but that the coverage and quality of these data vary widely between countries. They provide robust evidence for growing HIV epidemics, most of which have emerged within the past decade, among PWID in several MENA countries, but do not preclude the possibility of hidden epidemics among PWID in additional MENA countries. Overall, these findings suggest that the HIV epidemic among PWID in MENA is at a relatively early stage. This window of opportunity to control the emerging epidemics should not be missed, warn the researchers. HIV surveillance among PWID in MENA must be expanded to detect and monitor emerging and growing HIV epidemics, they suggest, and to inform effective HIV policy and programming. Improvements in HIV prevention and treatment among PWID in MENA are essential, they conclude, to confront the growing HIV problem in this population and, to prevent the onward transmission of HIV from PWID to other population groups.

Additional Information. Please access these websites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1001663.

- A 2010 report produced by the World Bank, UNAIDS, and WHO provides information on the status of the HIV epidemic in the Middle East and North Africa; the UNAIDS Middle East and North Africa Regional Report on AIDS 2011 provides further information
- The 2013 UNAIDS World AIDS Day Report provides up-to-date information about the AIDS epidemic and efforts to halt it
- The Middle East and North Africa Harm Reduction Association (MENAHRA) provides information about harm reduction efforts, services, and programs in the Middle East and North Africa; Harm Reduction International provides information about harm reduction concepts, strategies, programs, and publications globally
- Information is available from the US National Institute of Allergy and Infectious Diseases on HIV infection and AIDS
- NAM/aidsmap provides basic information about HIV/AIDS, and summaries of recent research findings on HIV care and treatment
- Information is available from Avert, an international AIDS charity, on many aspects of HIV/AIDS, including information on people who inject drugs and HIV/AIDS and on harm reduction and HIV prevention (in English and Spanish)
- The US National Institute on Drug Abuse also provides information about drug abuse and HIV/AIDS (in English and Spanish)
- Personal stories about living with HIV/AIDS are available through Avert, Nam/aidsmap, and Healthtalkonline

2.4. SUPPLEMENTARY ONLINE MATERIAL OUTLINE

The following is the outline of the supplementary online material as cited in Research paper 1. The corresponding files are found in Appendix A.

Text S1.	PRISMA checklist
Text S2.	Search criteria
Text S3.	Narrative justification for quality of the evidence and status of the epidemic at the country level
Table S1.	Precision and risk of bias of individual HIV prevalence measures among people who inject drugs in the Middle East and North Africa as extracted from eligible reports
Table S2.	Summary of precision and risk of bias of HIV prevalence measures as extracted from eligible reports
Table S3.	Subnational estimates of the number and prevalence of people who inject drugs in the Middle East and North Africa
Table S4.	HIV point-prevalence measures among people who inject drugs as extracted from various databases including the US Census Bureau database, the WHO/EMRO testing database, the UNAIDS epidemiological fact sheets databases, and other sources of data with unidentified reports
Table S5.	Measures of injecting risk behaviour among people who inject drugs in the Middle East and North Africa
Table S6.	Measures of sexual risk behaviour and sexually transmitted infections prevalence among people who inject drugs in the Middle East and North Africa
Table S7.	HIV/AIDS knowledge, perception of risk, and HIV testing among people who inject drugs in the Middle East and North Africa

2.5. SUMMARY OF FINDINGS

This study identified a large volume of HIV-related biological and behavioural data among PWID, including quality IBBSS in multiple countries. The population proportion of injecting drug use in MENA was found to be comparable to global figures. There is evidence for HIV epidemics among PWID in one third of countries, most of which are concentrated emerging HIV epidemics that emerged in the last decade. Iran is the only country where there is conclusive evidence for an established HIV epidemic at a national level. The status of the HIV epidemics is unknown in about half of countries, and the lack of sufficient evidence does not preclude the possibility of hidden epidemics among PWID in these settings. The high injecting and sexual risk behaviour environment suggests potential for further HIV spread among PWID. There is also overlap of risk behaviour between PWID and the other KPs which facilitates bridging of the HIV epidemic from one KP to the other, as has happened in Pakistan and possibly in Egypt. Since most HIV epidemics among PWID in MENA are nascent, there is a window of opportunity for prevention.

3. HCV AS A PREDCITOR OF HIV EPIDEMIC POTENTIAL AMONG PWID: THEORETICAL UNDERPINNINGS

3.1. INTRODUCTION

Chapter 2 documented a pattern of nascent HIV epidemics and a high risk environment among PWID in several MENA countries. Considerable overlap of risk behaviour with other KPs, such as MSM, who may be experiencing HIV epidemics was also documented. All these findings suggest that there could be further HIV spread in these settings. Also, in many countries with insufficient data to characterize HIV epidemic state, there could be undetected HIV transmission and similar epidemic patterns. Sharp increases in HIV prevalence among PWID over short periods of time have been observed in the region, such as in Pakistan [70], testifying to the prevailing high risk environment and high HIV epidemic potential.

These findings highlighted the necessity to identify settings in the region that are at high risk of future HIV spread and potentially large HIV epidemics among their PWID populations. Most MENA countries, however, have limited resources for conducting repeated surveys to track the course of the HIV epidemic. Also, in a context of emerging, and at times rapidly growing, epidemics, time is an important factor for consideration. For example, in Egypt, the first round of IBBSS was conducted in 2006 and found very little HIV transmission among PWID (1% prevalence) [71, 72]. It was only until 2010 that the second round was implemented, by which time HIV prevalence among PWID had reached over 7% [73]. Relying on existing sources of data to predict the future spread of HIV is a cost-effective and practical way to prioritize PWID populations for HIV prevention and treatment, and to inform policy and resource allocation. One of these existing sources of data is HCV prevalence data. HCV infection is transmitted among PWID along the same parenteral route, and could be used as a proxy biomarker of injecting risk behaviour and, hence, of future HIV spread.

In this chapter, mathematical modelling is used to theoretically explore the association between HCV and HIV infections among PWID and to demonstrate whether HCV could be used as a predictor of future HIV epidemic spread. This chapter lays the theoretical foundation for the application of this concept among PWID in MENA (Chapter 4).

3.2. RESEARCH PAPER 2 - MATHEMATICAL MODELLING STUDY

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Ghina Mumtaz
Principal Supervisor	Prof. Helen Weiss
Thesis Title	The Epidemiology of HIV Infection Among People Who Inject Drugs in the Middle East and North Africa

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	BMC Public Health		
When was the work published?	December 3, 2016		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am co-first author and corresponding author. I co-conceived the plan of analysis, contributed to the conduct of analyses, lead the interpretation of findings, and wrote the first draft of the manuscript.

Student Signature:  **Date:** January 10, 2017

Supervisor Signature: ____  ____ **Date:** January 10, 2017

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RESEARCH ARTICLE Open Access

HCV prevalence can predict HIV epidemic potential among people who inject drugs: mathematical modeling analysis

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Abstract

Background: Hepatitis C virus (HCV) and HIV are both transmitted through percutaneous exposures among people who inject drugs (PWID). Ecological analyses on global epidemiological data have identified a positive association between HCV and HIV prevalence among PWID. Our objective was to demonstrate how HCV prevalence can be used to predict HIV epidemic potential among PWID.

Methods: Two population-level models were constructed to simulate the evolution of HCV and HIV epidemics among PWID. The models described HCV and HIV parenteral transmission, and were solved both deterministically and stochastically.

Results: The modeling results provided a good fit to the epidemiological data describing the ecological HCV and HIV association among PWID. HCV was estimated to be eight times more transmissible per shared injection than HIV. A threshold HCV prevalence of 29.0% (95% uncertainty interval (UI): 20.7-39.8) and 46.5% (95% UI: 37.6-56.6) were identified for a sustainable HIV epidemic (HIV prevalence >1%) and concentrated HIV epidemic (HIV prevalence >5%), respectively. The association between HCV and HIV was further described with six dynamical regimes depicting the overlapping epidemiology of the two infections, and was quantified using defined and estimated measures of association. Modeling predictions across a wide range of HCV prevalence indicated overall acceptable precision in predicting HIV prevalence at endemic equilibrium. Modeling predictions were found to be robust with respect to stochasticity and behavioral and biological parameter uncertainty. In an illustrative application of the methodology, the modeling predictions of endemic HIV prevalence in Iran agreed with the scale and time course of the HIV epidemic in this country.

Conclusions: Our results show that HCV prevalence can be used as a proxy biomarker of HIV epidemic potential among PWID, and that the scale and evolution of HIV epidemic expansion can be predicted with sufficient precision to inform HIV policy, programming, and resource allocation.

Keywords: HIV, Hepatitis C virus, People who inject drugs, Mathematical modeling, Prediction

Background

Prioritization of populations and settings for HIV prevention interventions is critical to increase the cost-effectiveness of programs [1]. This is particularly the case in resource-limited settings such as most of the Middle East and North Africa (MENA) where HIV surveillance among most-at-risk populations, including people who inject drugs (PWID), remains deficient [2]. In this region, emerging and sometimes rapidly rising HIV epidemics have been recently documented among PWID [3]. Identification of settings with high HIV epidemic potential among PWID would help in prioritization and resource allocation for prevention interventions before HIV prevalence reaches high endemic levels. In this work, we provide the theoretical foundation, and describe an application in MENA, for an innovative approach to identify PWID populations at high

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risk of future HIV epidemic expansion. The concept is to use prevalence data on hepatitis C virus (HCV) to predict HIV epidemic potential.

Both HCV and HIV are transmitted through percutaneous exposures, and among PWID, sharing of non-sterile injecting equipment is the main mode of transmission [4]. However, HCV is more transmissible than HIV [5], has a higher prevalence, and is hyperendemic in most PWID populations [6, 7]. Globally, 63% of PWID are HCV infected [6, 7] while only 19% are HIV infected [6]. A recent meta-analysis identified that 82% of HIV-infected PWID are co-infected with HCV [8]. At the individual level, with HCV being most often transmitted before HIV along the same route of transmission, it could be used as a marker of the risk of exposure to HIV.

Few studies have investigated the association between HCV and HIV among PWID [9–13]. Ecological analyses on global [10] and MENA [9] epidemiological data have identified a positive association between the two infections. The association was found to be most robust when both infections are at endemic equilibrium [9], and is characterized by a threshold effect whereby HIV prevalence is likely to be negligible below a certain HCV prevalence of about 30% [10]. Two mathematical modeling studies reproduced the epidemiological epidemic dynamics [11, 13]. They projected the presence of an HCV threshold effect for a sustainable HIV epidemic; but the value of this HCV threshold was found to be highly sensitive to a number of behavioral parameters such as heterogeneity in risk, level of mixing, and duration of injecting [11, 13]. The models were also able to reproduce, above the threshold, the diversity of HCV and HIV epidemics occurring in different settings [11, 13]. These models however, with the uncertainty in behavioral parameters, questioned the utility of HCV prevalence in predicting HIV epidemic scale.

In this study, we re-examine the HCV-HIV association among PWID using a modeling approach that accommodates stochasticity and a complex injecting contact structure. We estimate the HCV thresholds for HIV epidemic expansion, and assess the extent to which this threshold is affected by variations in behavioral and HCV/HIV biological parameters. We also examine new aspects in the HCV-HIV association that include 1) estimating the HCV to HIV infectiousness ratio, 2) identifying the different dynamical regimes in the overlapping HCV-HIV epidemiology, and 3) developing and estimating summary measures that quantify the association between the two infections and that can be used, beyond modeling, for predictions of HIV epidemic potential among PWID. We further quantify the margins in HCV predictability of HIV epidemic scale across a wide range of HCV prevalence, through the conduct of uncertainty analyses. Finally, an application is provided for one MENA country where the HCV-HIV association is used to predict the scale and evolution of the HIV epidemic.

Methods

HCV and HIV models structure

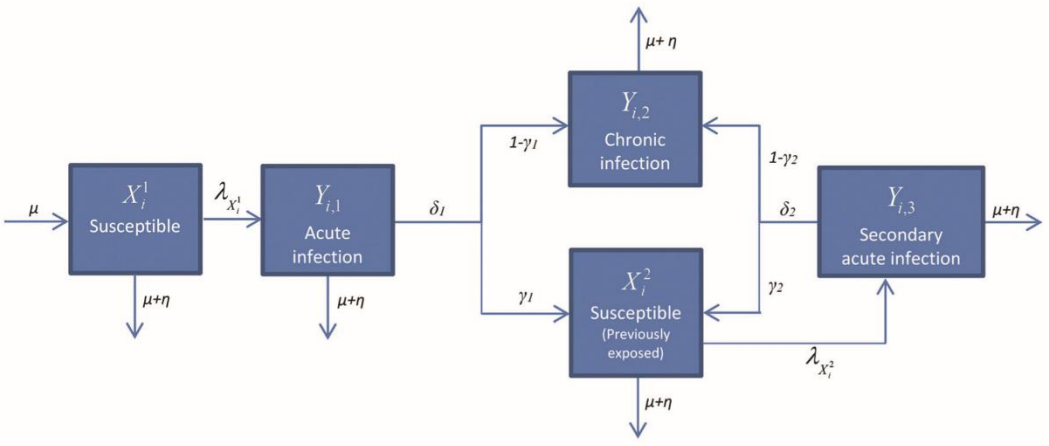
Two population-level compartmental models were constructed to simulate the evolution of HCV and HIV epidemics among PWID (Figs. 1 and 2, and Additional file 1). The models describe HCV/HIV parenteral transmission through sharing of non-sterile needles/syringes, and were solved both deterministically and stochastically. The deterministic versions of the models were expressed each through a system of coupled nonlinear differential equations, and stratified the PWID population into compartments according to HCV/HIV status, stage of HCV/HIV infection, and level of injecting risk behavior. The stochastic versions used the same transition rates in the deterministic systems to generate the stochastic processes. HIV progression in the HIV model was divided into three stages: acute, latent, and advanced; while progression in the HCV model was divided into stages of acute (primary infection), chronic, and secondary acute. The latter denotes the acute phase following HCV re-infection, in the event the primary infection was cleared.

Both the HCV and HIV models used the same injecting behavior structure and parameter values. To accommodate heterogeneity in injecting risk behavior, we stratified the PWID population into seven risk groups with increasing level of injecting risk behavior. We assumed that individuals become PWID at a constant rate and remain in the same risk group until the end of their injecting career or death. We also assumed that the distribution of the PWID population across the seven risk groups follows a gamma distribution, as motivated by previous theoretical and applied mathematical modeling work [14–19] (Eq. 1 and Additional file 1).

$$p(i) = \frac{1}{b^a \Gamma(a)} i^{a-1} e^{\frac{-i}{b}} \quad (1)$$

Here a is the shape parameter and b is the scale parameter in the gamma distribution. With such a distribution, the majority of the PWID population belongs to relatively lower risk groups while a small fraction belongs to the higher risk groups. PWID of different risk groups interact according to a mixing matrix with a continuous spectrum between assortative (choosing injecting partners from within their risk group) and proportionate (choosing partners with no preferential bias based on the type of risk group) mixing.

The level of risk behavior was modeled by the effective partnership change rate. While expressed in units of injecting partners per year, the effective partnership



$$\frac{dX_i^1}{dt} = \mu N_{0,i} - (\mu+\eta)X_i^1 - \lambda_{X_i^1} X_i^1$$

$$\frac{dY_{i,1}}{dt} = \lambda_{X_i^1} X_i^1 - (\mu+\eta)Y_{i,1} - \delta_1 Y_{i,1}$$

$$\frac{dY_{i,2}}{dt} = \delta_1(1-\gamma_1)Y_{i,1} + \delta_2(1-\gamma_2)Y_{i,3} - (\mu+\eta)Y_{i,2}$$

$$\frac{dX_i^2}{dt} = \delta_1\gamma_1 Y_{i,1} + \delta_2\gamma_2 Y_{i,3} - (\mu+\eta)X_i^2 - \lambda_{X_i^2} X_i^2$$

$$\frac{dY_{i,3}}{dt} = \lambda_{X_i^2} X_i^2 - (\mu+\eta)Y_{i,3} - \delta_2 Y_{i,3}$$

Symbol	Parameter
i	Injecting risk group (i =1, 2, ..., 7)
X_i^1	HCV susceptible population in the i -risk group
$Y_{i,\beta}$	HCV infected population in the i -risk group and β -stage
β	Stage of HCV pathogenesis (β =1,2,3)
X_i^2	Previously exposed HCV susceptible population in the i -risk group
$N_{0,i}$	Initial population size in each i -risk group
μ	Natural mortality rate
η	Leaving injecting career rate
δ_1 , δ_2	Rate of progression from one HCV stage to the next
γ_1	Percentage of primary HCV infections that clear
γ_2	Percentage of secondary HCV infections that clear
$\lambda_{X_i^1}$	HCV force of infection experienced by the X_i^1 population
$\lambda_{X_i^2}$	HCV force of infection experienced by the X_i^2 population

Fig. 1 HCV mathematical model description, equations, and parameter definitions. The details pertaining to the force of infection can be found in Additional file 1

change rate is a complex summary measure of the overall risk of exposure to HCV/HIV infections. It captures effectively different factors that reflect the nature of injecting risk behavior and networks, but are difficult to quantify, such as clustering within networks, concurrency, and variability in risk behavior [20–24]. Accordingly, the effective partnership change rate reflects the distribution and strength of the risk of exposure to HCV/HIV infection. Motivated by previous mathematical modeling work [25–29], the distribution of the level of injecting risk behavior, that is of the effective partnership change rate, across the seven risk groups was defined through the following power law function where the level of risk behavior grows larger and larger with the risk group number (Eq. 2 and Additional file 1):

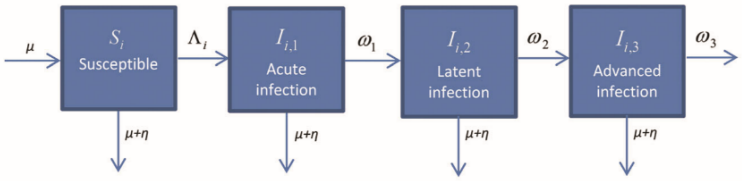
$$\rho_{P_i} = Ci^{\alpha} \quad (2)$$

where α is the exponent in the power-law function and C is an overall constant. The different HCV/HIV epidemic scales were generated by changing the value of the average effective partnership change rate in the PWID population. Further details on model structure can be found in Additional file 1.

Data sources and model fitting

The model parameters were derived using recent empirical HCV/HIV natural history and epidemiology data, as well as through model fitting for some of the parameters. All HCV/HIV biological and behavioral parameter values and their references are summarized in Additional file 2. Further justification for the parameter values are provided in Additional file 1, Section 4.

HCV and HIV model predictions were fitted to global epidemiological HCV and HIV prevalence data among PWID [10]. These data were identified in an earlier systematic review of literature and included 863 paired HCV-HIV data points among PWID from 343 different geographical areas in 61 countries [10]. The paired



$$\frac{dS_i}{dt} = \mu N_{0,i} - (\mu+\eta)S_i - \Lambda_i S_i$$
$$\frac{dI_{i,1}}{dt} = \Lambda_i S_i - (\mu+\eta)I_{i,1} - \omega_1 I_{i,1}$$
$$\frac{dI_{i,2}}{dt} = \omega_1 I_{i,1} - (\mu+\eta)I_{i,2} - \omega_2 I_{i,2}$$
$$\frac{dI_{i,3}}{dt} = \omega_2 I_{i,2} - (\mu+\eta)I_{i,3} - \omega_3 I_{i,3}$$

Symbol	Parameter
i	Injecting risk group (i =1, 2, ..., 7)
S_i	HIV susceptible population in the i -risk group
$I_{i,\beta}$	HIV infected population in the i -risk group and β -stage
β	Stage of HIV pathogenesis (β =1,2,3)
$N_{0,i}$	Initial population size in each i -risk group
μ	Natural mortality rate
η	Leaving injecting career rate
ω_1, ω_2	Rate of progression from one HIV stage to the next
ω_3	Rate of HIV/AIDS disease progression
Λ_i	HIV force of infection

Fig. 2 HIV mathematical model description, equations, and parameter definitions. The details pertaining to the force of infection can be found in Additional file 1

HCV-HIV prevalence data were then fitted to a statistical segmented linear regression model, indicating a positive ecological association between HCV and HIV prevalence [10]. Our modeling predictions of endemic HCV and HIV prevalence at various levels of injecting risk behavior were fitted to this ecological statistical association describing the epidemiological global HCV-HIV data [10]. The main purpose of the fitting was to determine the best-fit value for the HCV/HIV infectiousness ratio (that is the ratio of the HCV transmission probability per shared injection to that of HIV), a biological parameter and not a population-specific parameter. This fitting insured that our modeling predictions describe the actual HCV-HIV association observed empirically among PWID. The fitting was made in the range of HCV prevalence of 40–60%, where there is the highest volume of epidemiological data [10]. We used a nonlinear least-square fitting method incorporating the Nelder-Mead simplex algorithm as described in Lagarias et al. to find the best fit [30]. The method, as well as most of our modeling analyses, were implemented in MATLAB [31, 32].

In addition to the infectiousness ratio of HCV to HIV, three other measures were derived through the optimum fit to the global epidemiological data: The scale and shape parameters of the gamma distribution of the population across injecting risk groups, and the exponent parameter of the power law distribution of the level of injecting risk behavior across risk groups.

Plan of analysis

HCV thresholds for HIV epidemic expansion

Derivation After fitting to global epidemiological data, we used the best-fit parameters in applying the HCV and HIV models. As a first step, we examined the association between the prevalence of the two infections in broad epidemic scales by plotting, at endemic equilibrium, HIV prevalence as a function of HCV prevalence. This was done by varying the average injecting risk behavior parameter (effective partnership change rate) and generating endemic HCV and HIV prevalence for each value of average injecting risk behavior, using the deterministic versions of the models. The endemic HCV prevalence at which the corresponding endemic HIV prevalence became greater than 1% was identified as the HCV threshold for sustainable HIV epidemic, and the endemic HCV prevalence that corresponded to an endemic HIV prevalence of 5% was identified as the threshold for concentrated HIV epidemic.

Sensitivity analysis We conducted extensive univariate sensitivity analyses to explore the HCV-HIV association at broad ranges of changes in each model parameter, including not only plausible but also extreme values that are not even seen empirically. We examined the sensitivity of our modeling predictions of the HCV thresholds, for both sustainable and concentrated HIV epidemics, to variations in 1) the infectiousness ratio of HCV to HIV, 2) several injecting risk behavior parameters including: the degree of assortative mixing, the scale and shape parameters of the gamma distribution of the population across injecting risk groups, the exponent parameter of the power law distribution of the level of injecting risk behavior, and the duration of injecting and 3) scale-up of antiretroviral therapy (ART) among those eligible for treatment. We assumed that all infected

PWID in the advanced HIV stage and half of those in the latent HIV stage would be eligible for ART treatment, which corresponds roughly to a CD4 cell count criterion for treatment of 500 cells/μl [33]. We assumed that the efficacy of ART in reducing HIV transmission among PWID is 100%, based on a clinical trial of treatment for prevention and other observational data [34, 35]. We also assumed that, by slowing disease progression, 100% coverage among those eligible for ART would double the average duration from onset of infection to death among the total HIV infected population. Wide ranges of values for the parameters of the sensitivity analyses were chosen to produce a broad range of epidemics.

Uncertainty analyses

Two separate multivariate uncertainty analyses were conducted to specify ranges of uncertainty in the predicted HCV thresholds, for both sustainable and concentrated HIV epidemics, with respect to 1) biological parameters and 2) behavioral parameters. The biological parameters that were varied included: the probabilities of HCV and HIV transmission per shared injection in each infection stage, the duration of each HCV and HIV stage, and the proportions of virus clearance for HCV primary infection and HCV reinfection. The behavioral parameters that were varied included: the duration of injecting, the degree of assortative mixing, the scale and shape parameters of the gamma distribution of the population across risk groups, the exponent parameter of the power law distribution of the level of risk behavior, and the frequency of sharing acts per partnership. These were the same set of parameters that were varied in all subsequent behavioral uncertainty analyses (as discussed below).

The parameters of the uncertainty analyses were varied within 20% of their point estimates (Additional file 2). We implemented 5,000 runs of the deterministic HCV and HIV models using Monte Carlo sampling from uniform probability distributions for the uncertainty in these parameters. Estimates for the mean values and associated 95% uncertainty intervals (UI) for the predicted HCV thresholds were determined by fitting a log-normal distribution to the range of values as described elsewhere [36].

Overlapping epidemiology of HCV and HIV infections

We quantified the epidemiological association between HCV and HIV among PWID using the risk ratio ($RR_{HCV/HIV}$) and odds ratio ($OR_{HCV/HIV}$) of HCV prevalence to HIV prevalence. The two measures were defined as follows:

$$RR_{HCV/HIV} = \frac{P_{HCV} - P_{threshold}}{P_{HIV}} \tag{3}$$

$$OR_{HCV/HIV} = \left(\frac{P_{HCV} - P_{threshold}}{1-(P_{HCV} - P_{threshold})}\right) / \left(\frac{P_{HIV}}{1-P_{HIV}}\right) \tag{4}$$

where P_{HCV} is HCV prevalence, $P_{threshold}$ is the minimum HCV prevalence for a sustainable HIV epidemic, and P_{HIV} is HIV prevalence.

HCV and HIV prevalence at endemic equilibrium, $RR_{HCV/HIV}$, and $OR_{HCV/HIV}$ were examined as a function of the average injecting risk behavior, that is the effective partnership change rate, to qualitatively and quantitatively describe the overlapping dynamics of the two infections at variable epidemic scales.

Effect of behavioral uncertainty on HCV-based predictions of HIV epidemic scale

Our overarching aim is to use the above observed association between HCV and HIV infections to predict the future size of HIV epidemics using HCV prevalence. We assessed the precision of HCV prevalence in predicting HIV prevalence at endemic equilibrium by quantifying, across the whole spectrum of HCV prevalence, the effect of behavioral uncertainty on our modeling prediction of HIV prevalence. For each value of HCV prevalence, increasing in increments of 4%, we implemented 50 runs of the deterministic model using the uncertainty analysis methods described above. The new set of parameter values was used to refit the model to the specific HCV prevalence. We then compared, at each HCV prevalence level, the difference between the baseline prediction of HIV prevalence and the 50 predictions of HIV prevalence including the behavioral uncertainty.

Application to Iran

HIV epidemic size prediction We applied the concept of using HCV prevalence to predict HIV epidemic scale in Iran as an illustrative example. We applied the deterministic version of the HCV model, and varied the average injecting risk behavior until the model generated the observed HCV prevalence in Iran. This specific value of the average injecting risk behavior was then used in applying the stochastic HIV model and predicting the time course of the HIV epidemic in this country.

The predicted time course of the HIV epidemic was compared to the observed HIV prevalence levels in the two conducted nationally-representative surveillance surveys among PWID in Iran [37, 38]. In addition to these two quality national data points, there are close to 100 HIV point prevalence measures over time among PWID in Iran [3]. These data show a clear trend for the

HIV PWID epidemic which started its emergence in the late 1990s, reached a peak around the year 2005, then stabilized over the last decade or so at a national prevalence of about 15% [3] (Additional file 3). This large volume of HIV prevalence data was used to inform the fitting in Iran by ensuring that it generates a result that is in line with the trend described by the epidemiological data. In the absence of nationally-representative HCV prevalence data among PWID, we used the median, 25th percentile, and 75th percentile of all available HCV prevalence data in Iran, as identified in a recent systematic review of PWID in MENA [3], and therefore produced three predicted HIV epidemic time courses.

HIV prevalence at endemic equilibrium in Iran was also predicted directly, by subtracting the HCV threshold for sustainable HIV epidemic from each of the three HCV prevalence levels (25th, 50th, or 75th percentile), then dividing by the deterministically model-estimated $RR_{HCV/HIV}$ corresponding to each HCV prevalence level—that is using Eq. 3.

Effect of stochasticity Since epidemic stochasticity could affect our modeling predictions by generating different HIV epidemic scales for the same HCV prevalence level, we examined the effect of stochasticity on our predictions of HIV prevalence at endemic equilibrium and also on $RR_{HCV/HIV}$ and $OR_{HCV/HIV}$ in Iran. We used the behavioral parameter values which correspond to the HCV prevalence level (25th, 50th, or 75th percentile) that agrees most with the observed HIV prevalence data in Iran. We generated 5,000 stochastic epidemic simulations and calculated the mean value and 95% UI for the predicted HIV prevalence, $RR_{HCV/HIV}$, and $OR_{HCV/HIV}$ by fitting a log-normal distribution to the range of values.

Uncertainty analyses We also examined the precision of our predictions of the HIV epidemic course in Iran. We conducted two separate multivariate biological and behavioral uncertainty analyses, using the methods described above, to specify the range of uncertainty in the predicted HIV prevalence, $RR_{HCV/HIV}$, and $OR_{HCV/HIV}$ that correspond to the HCV prevalence level that agrees most with the observed HIV prevalence data in Iran. At each run, the model was refit to this specific HCV prevalence.

Results

HCV to HIV infectiousness ratio

The HCV and HIV model projections provided a good fit to the global epidemiological data describing the ecological association between HCV and HIV among PWID (Fig. 3). The optimum fitting value of the infectiousness ratio of HCV to HIV was found to be 7.8 (Additional file 2), suggesting that HCV is about eight times more transmissible per shared injection than HIV.

Epidemiologic association and threshold effect

The fitted models were used to generate a broad spectrum of HCV and HIV prevalence and their epidemiological overlap (Fig. 3). As shown in Fig. 3, the predictions indicate a positive association between HCV and HIV prevalence at endemic equilibrium, with a threshold HCV prevalence of 27.9% for a sustainable HIV epidemic (>1%) and 45.2% for a concentrated HIV epidemic (>5%).

Based on results of the sensitivity analyses (Figs. 4 and 5), changes in the HCV/HIV infectiousness ratio and in injecting risk behavior parameters within the specified wide ranges had a rather small effect on the existence or values of the HCV thresholds for sustainable and concentrated HIV epidemics. More specifically, there was a large reduction in the HCV thresholds only when the HCV/HIV infectiousness ratio was <7, while the effect of higher values of this ratio on the HCV thresholds was limited (Figs. 4 and 5 (a)). The HCV thresholds were mildly sensitive to changes in the degree of assortative mixing, except near the extremes of fully proportionate

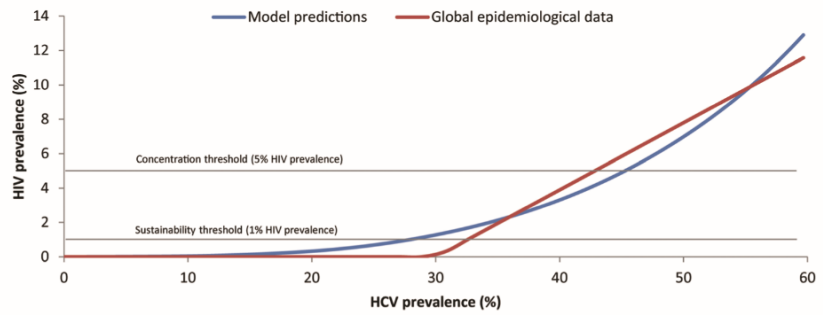


Fig. 3 Relationship between HCV and HIV prevalence at endemic equilibrium among people who inject drugs, and model fitting to the segmented linear regression statistical model that summarizes the global epidemiological data as derived by Vickerman et al. [10]

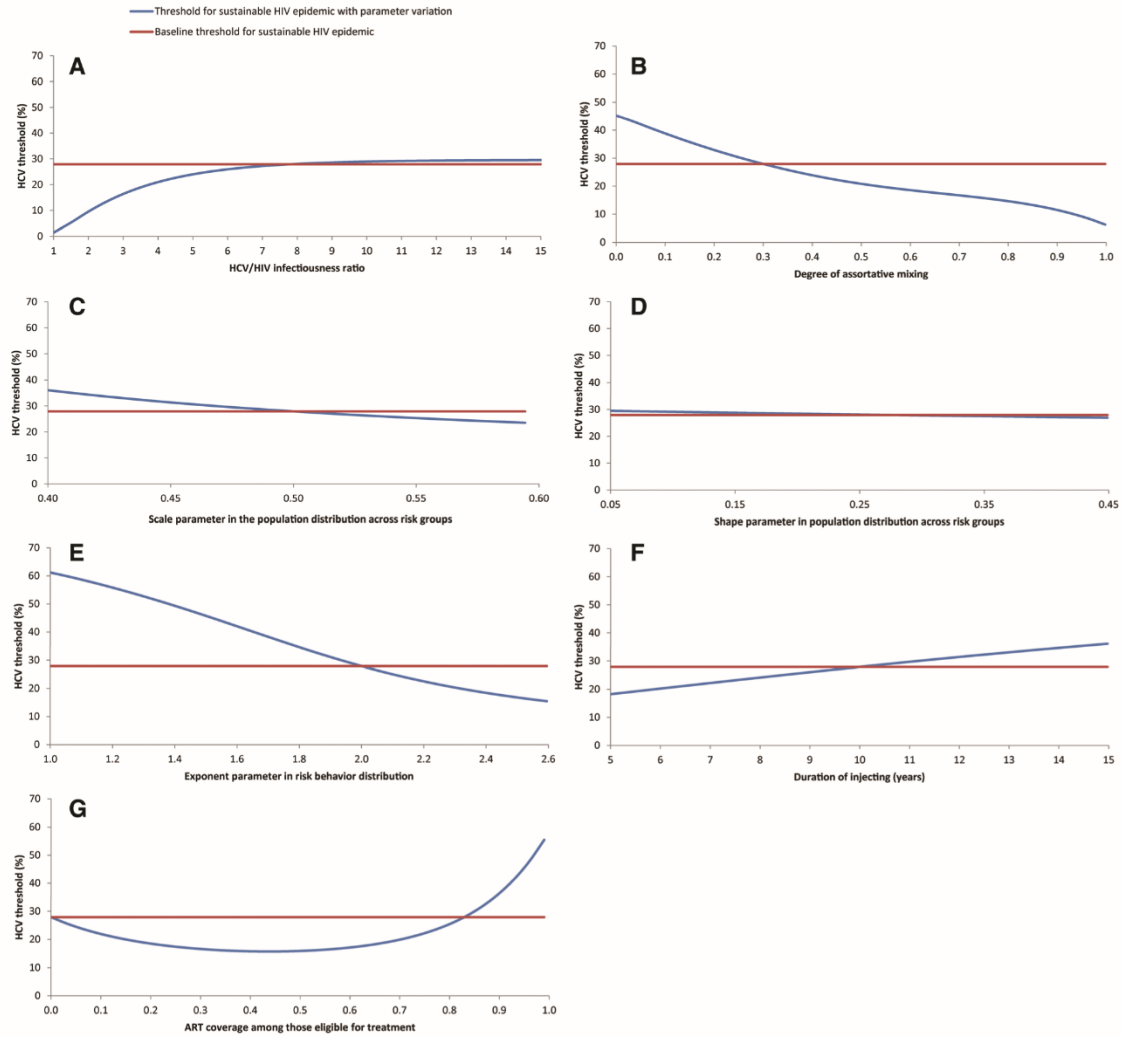


Fig. 4 Sensitivity analyses on the HCV threshold for sustainable HIV epidemic (HIV prevalence >1%). These graphs illustrate the effect, on the HCV threshold for sustainable HIV epidemic, of the HCV/HIV infectiousness ratio (**a**), the degree of assortative mixing (**b**), the scale (**c**) and shape (**d**) parameters of the gamma distribution of the population across risk groups, the exponent parameter of the power law distribution of risk behavior (**e**), duration of injecting (**f**), and anti-retroviral therapy (ART) coverage (**g**). For each set of parameter values in these graphs, the average injecting risk behavior was varied; endemic HCV and HIV prevalence for each value of average injecting risk behavior were generated; and the HCV threshold for sustainable HIV epidemic was identified and plotted

or fully assortative mixing (Figs. 4 and 5 (b)). Similarly, the HCV thresholds showed somewhat mild dependence to variation in the exponent parameter of the power law distribution of risk behavior, with a more pronounced effect when the exponent was closer to one (Figs. 4 and 5 (e)). There were small and limited effects, respectively, of the scale and shape parameters of the gamma distribution of the population across risk groups (Figs. 4 and 5 (c and d)). The duration of injecting and ART scale up had likewise a rather small effect on both thresholds. The effect of ART was most pronounced at very high coverage of above 90% (Figs. 4 and 5 (f and g)).

Figure 6 shows our prediction and 95% UI of the HCV thresholds per the uncertainty analysis including all behavioral parameters. Results indicate a mean HCV threshold for sustainable and concentrated HIV epidemics of 29.0% (95% UI: 20.7-39.8) and 46.5% (95% UI: 37.6-56.6), respectively. The effect of the biological uncertainly on the HCV thresholds was smaller with a

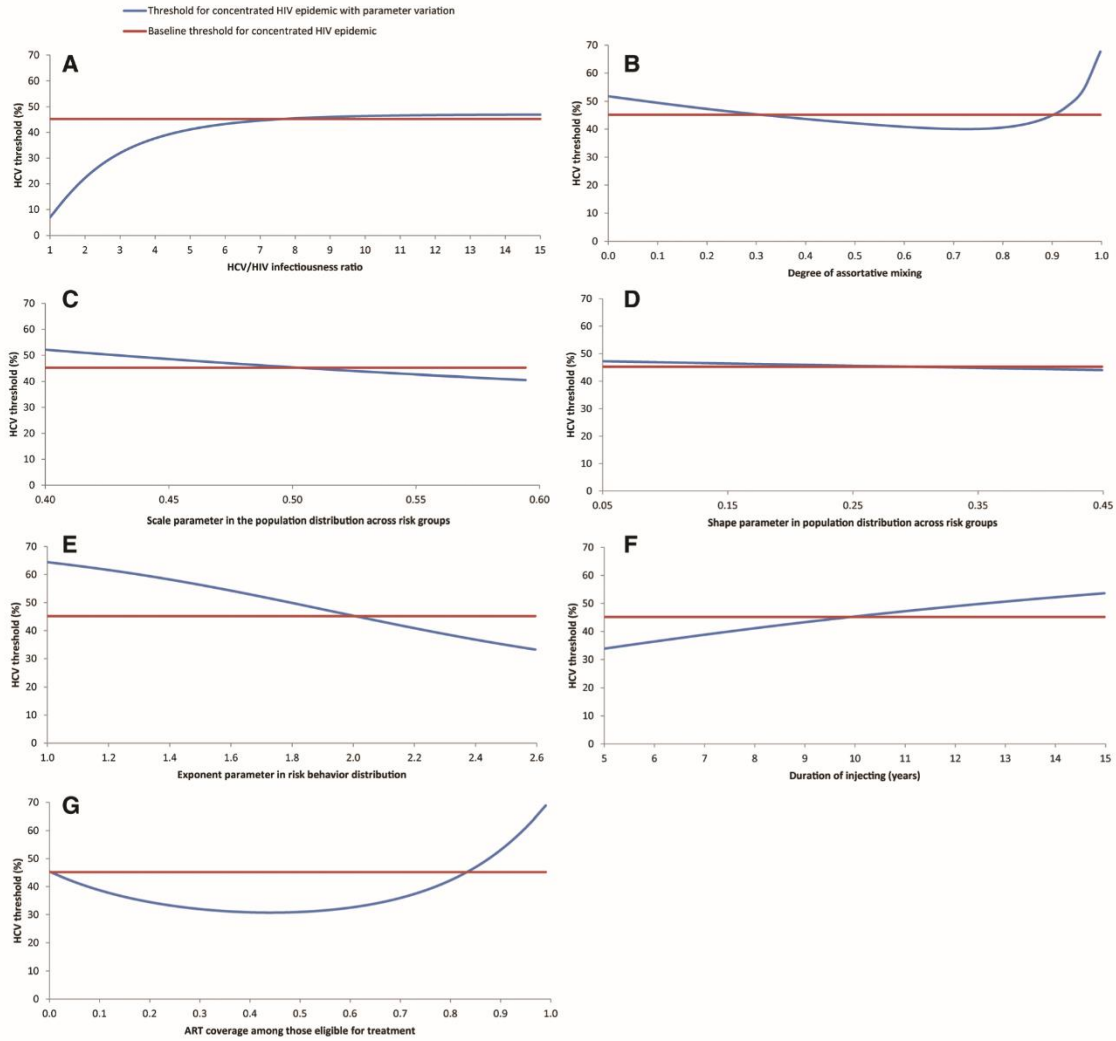


Fig. 5 Sensitivity analyses on the HCV threshold for concentrated HIV epidemic (HIV prevalence >5%). These graphs illustrate the effect, on the HCV threshold for concentrated HIV epidemic, of the HCV/HIV infectiousness ratio (**a**), the degree of assortative mixing (**b**), the scale (**c**) and shape (**d**) parameters of the gamma distribution of the population across risk groups, the exponent parameter of the power law distribution of risk behavior (**e**), duration of injecting (**f**), and anti-retroviral therapy (ART) coverage (**g**). For each set of parameter values in these graphs, the average injecting risk behavior was varied; endemic HCV and HIV prevalence for each value of average injecting risk behavior were generated; and the HCV threshold for concentrated HIV epidemic was identified and plotted

mean HCV prevalence of 27.5% (95% UI: 23.2-31.9) and of 44.7% (95% CI: 39.8-49.4) for sustainable and concentrated HIV epidemics, respectively.

Overlapping epidemiology of HCV and HIV infections

The epidemiological overlap between HCV and HIV infections among PWID is illustrated in Fig. 7. Six dynamical epidemiological regimes were discerned based on the qualitative behavior of the prevalence of both infections, the $RR_{HCV/HIV}$, and the $OR_{HCV/HIV}$ (Fig. 7). The regimes are summarized in Table 1.

In regime I, both HCV and HIV infections are below epidemic sustainability. In regime II, there is sustainable HCV transmission but HCV prevalence is low scale (below 30%); HIV is still below epidemic sustainability. In regime III, HCV prevalence is in the range of 28–45%. At this stage, HIV passed into epidemic sustainability but is below 5%, the threshold defining a concentrated HIV epidemic. In regime IV, HIV is in a

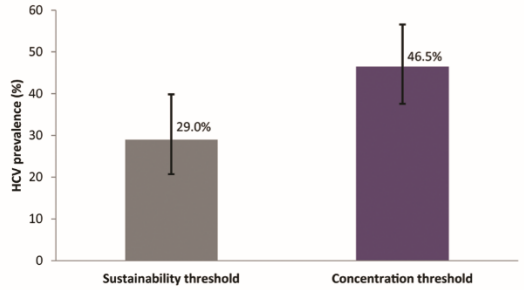


Fig. 6 Estimated HCV thresholds for sustainable and concentrated HIV epidemic among PWID. The error bars represent the upper and lower bounds of the 95% uncertainty interval around the predicted HCV prevalence

concentrated state (prevalence 5–24%) since HCV prevalence is already above the threshold for a concentrated HIV epidemic (HCV prevalence >45%). In regime V, HCV prevalence is between 70 and 80%, and HIV prevalence is large scale, in the range of 25–42%. In regime VI where HCV prevalence is approaching maximum possible prevalence (100%), the HIV epidemic is very large scale and eventually also approaches maximum possible prevalence (100%) (Fig. 7, Table 1).

These six epidemiological regimes are also reflected in the trend and range of $RR_{HCV/HIV}$ and $OR_{HCV/HIV}$. These two measures of association become expressed only in regimes III-VI where both infections are above epidemic sustainability (Fig. 7, Table 1). In regime III, HCV epidemic expansion is substantially faster than that of HIV, resulting in $RR_{HCV/HIV}$ and $OR_{HCV/HIV}$ of 3.7-3.5 and 4.1-4.0, respectively. However, in subsequent regimes, HIV epidemic expansion gradually catches up with HCV

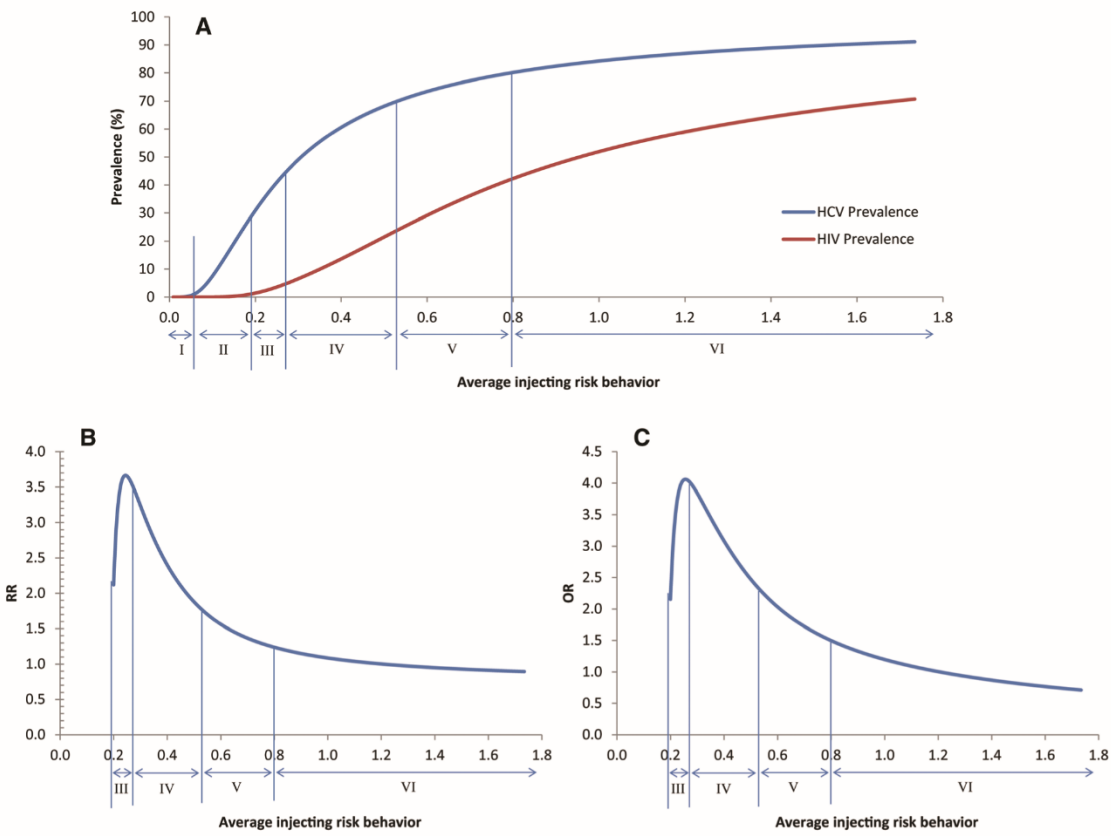


Fig. 7 Epidemiological overlap between HCV and HIV infections among people who inject drugs. These graphs describe the epidemiological relationship between HCV and HIV infections by plotting endemic HCV and HIV prevalence (**a**), the risk ratio of endemic HCV to HIV prevalence ($RR_{HCV/HIV}$) (**b**), and the odds ratio of endemic HCV to HIV prevalence ($OR_{HCV/HIV}$) (**c**), as a function of the average injecting risk behavior (effective partnership change rate). Six epidemiological regimes linking HIV prevalence and HCV prevalence are discerned (**a**). The $RR_{HCV/HIV}$ (**b**) and $OR_{HCV/HIV}$ (**c**) are displayed for regimes III-VI with sustainable epidemics for both infections

Table 1 Description of the dynamical regimes of the overlapping epidemiology of HCV and HIV infections among people who inject drugs

	HCV prevalence		HIV prevalence		$RR^{ab}_{HCV/HIV}$	$OR^{ab}_{HCV/HIV}$
	Range	Description	Range	Description	Range	Range
Regime I	<1%	Below sustainability	<1%	Below sustainability	..	..
Regime II	1–28%	Above sustainability - low scale HCV epidemic	<1%	Below sustainability	..	..
Regime III	28–45%	Large scale HCV epidemic	1–5%	Above sustainability threshold for HIV epidemic expansion and below concentration threshold	3.7-3.5	4.1-4.0
Regime IV	45–70%	Large scale HCV epidemic	5–24%	Concentrated HIV epidemic	3.5-1.8	4.0-2.3
Regime V	70–80%	Very large scale HCV epidemic	24–42%	Large scale HIV epidemic	1.8-1.2	2.3-1.5
Regime VI	>80%	Approaching maximum prevalence	>42%	Very large scale HIV epidemic and approaching maximum prevalence	<1.2	<1.5

[a] We are reporting the range of *RR* and *OR* excluding those corresponding to the immediate vicinity of the HCV threshold for HIV sustainable transmission
[b] The $RR_{HCV/HIV}$ and $OR_{HCV/HIV}$ are reported in descending order to reflect the decreasing trend in the ratios as a function of injecting risk behavior as per Fig. 7

epidemic expansion. This is reflected in the decreasing trend in $RR_{HCV/HIV}$ and $OR_{HCV/HIV}$ which reach 1.8 and 2.3 by the end of regime IV, respectively; and 1.2 and 1.5 by the end of regime V, respectively. In regime VI where both infections eventually reach maximum prevalence, the $RR_{HCV/HIV}$ and $OR_{HCV/HIV}$ ultimately reach their final asymptotic values (Fig. 7, Table 1).

Predicting HIV epidemic scale using HCV prevalence: Effect of behavioral uncertainty

The effect of behavioral uncertainty on the prediction of HIV epidemic scale (HIV prevalence) across a wide range of HCV prevalence settings is shown in Fig. 8 and summarized by HCV/HIV dynamical regime in Table 2. Overall, 20% uncertainty in behavioral parameters resulted in a median of <1% and a maximum of <10% absolute HIV prevalence difference with the baseline prediction for HIV prevalence. The effect of behavioral uncertainty was negligible in regimes I & II and increased with higher regimes, until it reached a maximum in regimes IV and V with a median HIV prevalence difference of 1.9% (IQR: 0.9–3.4% and 0.9–3.8%, respectively) between the baseline prediction of HIV prevalence and the prediction including behavioral uncertainty (Fig. 8, Table 2).

Case study: Iran

Predicting the time course of the HIV epidemic

Based on available studies among PWID in Iran, the median HCV prevalence is 43.4% (interquartile range (IQR) 35.1–59.4%) [3]. The predicted time course of the HIV

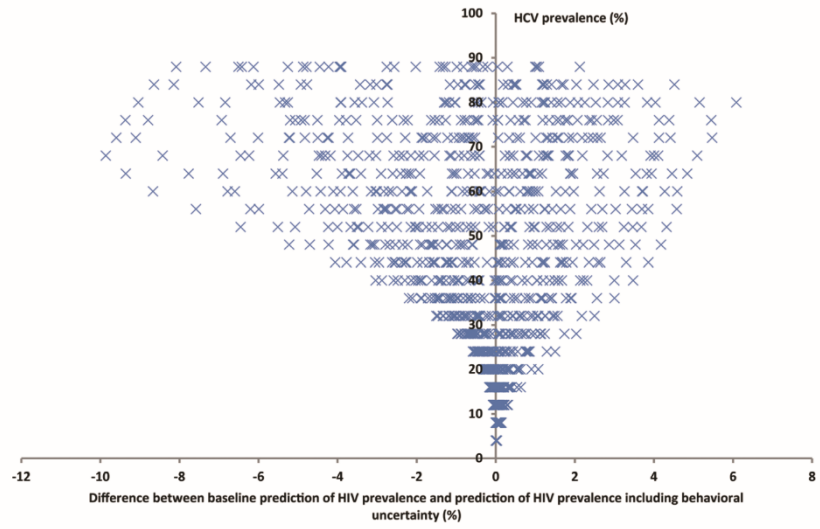


Fig. 8 Effect of behavioral uncertainty on the HCV predictability of HIV epidemic expansion. The graph displays, for each HCV prevalence level, the difference between the baseline prediction of HIV prevalence and 50 random predictions of HIV prevalence, at this specific HCV prevalence level, that accommodate behavioral uncertainty

Table 2 Effect of behavioral uncertainty on HCV predictions of HIV epidemic scale by HCV/HIV epidemiological regime

	HCV prevalence (%)	Predicted HIV prevalence (%)	HIV prevalence prediction difference (%)[a]	
	Range	Range	Median	IQR
Regime I	<1	<1	N/A	N/A
Regime II	1–28	<1	0.1	0.0-0.3
Regime III	28–45	1–5	1.1	0.6-1.7
Regime IV	45–70	5–24	1.9	0.9-3.4
Regime V	70–80	24–42	1.9	0.9-3.8
Regime VI	>80	>42	1.7	0.8-3.9
All regimes			0.9	0.2-2.2

IQR interquartile range
[a] Difference between baseline prediction of HIV prevalence and prediction of HIV prevalence including behavioral uncertainty

epidemic corresponding to each of these HCV prevalence levels is shown in Fig. 9 for three representative stochastic model runs. The predicted scale and time evolution of the HIV epidemic corresponding to the 75th percentile of HCV prevalence agreed best with the actual time course of the HIV epidemic observed in Iran, whereby two rounds of nationally-representative surveillance surveys reported an HIV prevalence of 15.3% in 2006–7 [37] and 15.1% in 2010 [38]. An HIV prevalence at endemic equilibrium of 14.5% was predicted by the indicated stochastic run corresponding to 59.4% HCV prevalence (Fig. 9). The HIV stochastic predictions at the 25th percentile and median HCV prevalence levels could not generate the observed HIV prevalence in Iran as they are below or just at the threshold for concentrated HIV epidemic, respectively.

To illustrate a simpler method for predicting HIV endemic prevalence using HCV prevalence, HIV prevalence at endemic equilibrium in Iran was also predicted using Eq. 3 involving the $RR_{HCV/HIV}$ as derived from the deterministic modeling results presented above. As per Fig. 7, we predicted a $RR_{HCV/HIV}$ of 2.5 for an observed HCV prevalence of 59% in Iran, resulting in predicted HIV prevalence of 13%. This value is comparable with the 15% HIV prevalence currently observed among PWID in this country [37, 38] and also with the value predicted above in a representative stochastic run (Fig. 9). Identical results were also obtained, as expected, when we used Eq. 4 in terms of the $OR_{HCV/HIV}$ and its predicted value of 3.2 for HCV prevalence of 59% (Fig. 7).

Effect of stochasticity and behavioral and biological uncertainty on the predicted epidemic time course

The effect of stochasticity and of behavioral and biological uncertainty on our modeling predictions of endemic HIV prevalence, $RR_{HCV/HIV}$, and $OR_{HCV/HIV}$ in Iran corresponding to an HCV prevalence of 59.4% are shown in Additional file 4. Stochasticity generated a normal distribution of the natural log of HIV prevalence, $RR_{HCV/HIV}$, and $OR_{HCV/HIV}$, with a mean of 14.3% (95% UI: 13.0-15.5), 2.4 (95% UI: 2.2-2.6), and 3.1 (95% UI: 2.8-3.5), respectively. Uncertainty in behavioral parameters generated a skewed distribution of the natural log of HIV prevalence, $RR_{HCV/HIV}$, and $OR_{HCV/HIV}$, with a mean of 12.1% (95% UI: 5.4-21.1), 2.6 (95% UI: 1.5-5.8), and 3.3 (95% UI: 1.7-8.0), respectively. Uncertainty in

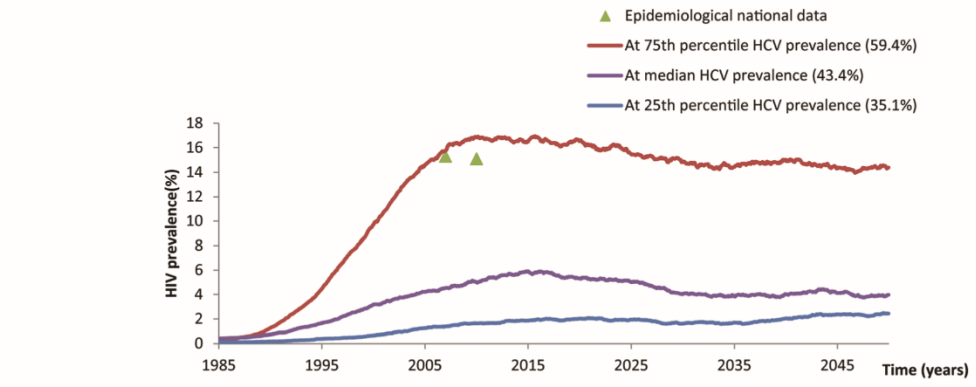


Fig. 9 Representative stochastic simulations of HIV epidemic expansion at different HCV endemic prevalence levels among people who inject drugs in Iran, and comparison with epidemiological data

biological parameters generated a normal distribution of the natural log of HIV prevalence, $RR_{HCV|HIV}$, and $OR_{HCV|HIV}$, with a mean of 13.5% (95% UI: 10.5–17.4%), 2.3 (95% UI: 1.8-3.0), and 2.9 (95% UI: 2.2-3.9), respectively.

Discussion

Our mathematical modeling approach reproduced the epidemiologically-observed ecological association between HCV prevalence and HIV prevalence among PWID [10]. We estimated that HCV infection is 7.8 times more infectious per shared injection than HIV, and confirmed the existence of an HCV threshold for a sustainable HIV epidemic, which we estimated at 29.0%. We further estimated an HCV threshold of 46.5% for a concentrated HIV epidemic. These thresholds were independent of the uncertainty in biological parameters, and largely insensitive to the details of injecting risk behavior, except near extreme values of mixing pattern and variation in risk behavior among the different risk groups in a PWID population. The association between HCV and HIV was further described with six distinct dynamical regimes depicting the overlapping epidemiology of the two infections, and was quantified using defined and estimated measures of association.

Our main aim was to use this association between HCV and HIV to predict HIV epidemic potential using HCV prevalence. We showed, across a wide range of HCV prevalence settings, that behavioral uncertainty, arising from our limited knowledge of the details of the risk behavior environment in PWID, resulted in acceptable difference compared with our modeling predictions of HIV epidemic scale. This was demonstrated for data from Iran, where our modeling predictions reproduced the actual time course of the HIV epidemic, even in context of epidemic stochasticity and biological and behavioral uncertainty. All of these findings support our hypothesis that HCV prevalence can be used to make at least broad predictions of the future size of the HIV epidemic among PWID; and that these predictions can be further refined by applying mathematical models at specific HCV prevalence levels and potentially also for specific risk behavior environments.

HCV is known to be more infectious per percutaneous exposure than HIV, but the infectiousness ratio of the two infections via the parenteral route has not been estimated precisely. Evidence from needle-stick injury studies suggests that HCV is 4–10 times more transmissible per percutaneous injection than HIV [39–42]. By fitting our modeling approach to global epidemiological data for HCV and HIV prevalence, we provided, using a very different methodology, an independent estimate of the HCV to HIV infectiousness ratio among PWID at 7.8, which is in line with the above range.

The natural dynamics of our modeling approach generated a threshold behavior in the HCV-HIV association and estimated, in agreement with epidemiological data [10], a minimum HCV prevalence of about 30% below which HIV prevalence would be negligible. Earlier modeling work indicated that this threshold is dependent on the risk environment and thus likely to vary by setting, potentially explaining why some settings with similar HCV prevalence may have varying HIV prevalence levels [11, 13]. Because it is constrained by fitting to the epidemiologically-observed HCV-HIV association, our modeling did not lead to as wide variation in the value of the threshold. Despite accounting for uncertainty in biological and behavioral parameters, the HCV threshold was estimated within a reasonable range that is sufficient to inform policy and programming. Our modeling predicted that the HCV threshold of about 30% for a sustainable HIV epidemic is likely to apply in most global settings, except in unusual injecting settings where some risk behavior features are not typical of the common patterns of injecting networks.

One possible explanation for the diversity in HCV/HIV epidemics observed above the sustainability threshold could be that a number of the HIV epidemics globally may not have reached endemic equilibrium. Analysis of HCV-HIV epidemiological data among PWID has shown that the association between the two infections is strongest in settings of established HIV epidemics where HIV has reached an endemic level [9]. In MENA, for example, most HIV epidemics among PWID are emerging and have not reached endemic equilibrium [3]; this could be the case in other regions/settings where HIV prevalence levels are not typical of HCV-based predictions. Another possible explanation could be established harm reduction programs that are differentially effective in preventing HIV. This could be either due to the higher biological transmissibility of HCV compared to HIV, or because these programs were introduced after HCV reached endemic equilibrium but before HIV started its epidemic expansion. One such example is possibly Australia, a country with well-established needle-syringe exchange programs and where HIV prevalence has been low at about 1% despite HCV prevalence of 50–70% [43, 44].

Prioritization of affected populations for prevention interventions is tied to the potential for concentrated HIV epidemics (HIV prevalence >5%). We therefore derived the threshold HCV prevalence necessary for a concentrated HIV epidemic, which we estimated at about 45%. The effect of this threshold is manifested in settings of low intensity HIV epidemics where there is some HIV transmission among PWID, but the level of injecting risk behavior, as reflected by HCV prevalence of <45%, is not high enough to sustain concentrated HIV epidemics.

The diverse HIV epidemic dynamics within Afghanistan provides an example of this threshold phenomenon (Table 3). HCV prevalence among PWID in Jalalabad and Mazar-i-Sharif (10–26%) is below the predicted sustainability threshold for HIV, and indeed HIV prevalence in these two cities has not exceeded 1% [45–47]. In Kabul however, where HCV prevalence at 28–37% is over the predicted sustainability threshold for HIV, but below the predicted concentration threshold for HIV, HIV prevalence, as expected, is in the range of 2–3% [45–47]. In Herat nonetheless, the high HCV prevalence of 49–70% is predicted to sustain a large concentrated HIV epidemic, and as expected, HIV prevalence has increased from 3% in 2007 to 13–18% in subsequent surveys [45, 46] (Table 3).

Six epidemiological regimes incorporating the HCV thresholds were discerned in describing the overlapping epidemiology of HCV and HIV infections among PWID (Figs. 7 and 8). In the first regime, the level of injecting risk behavior is extremely low and does not sustain an HCV nor HIV epidemic. In the second regime, the level of injecting risk behavior is relatively low, but enough to sustain a low scale HCV epidemic. With HIV being eight times less transmissible than HCV, an injecting risk network in this regime cannot sustain an HIV epidemic; HIV spreads slowly and inefficiently at very low level and is sensitive to stochastic fluctuations. In the third regime, the level of risk behavior is above the threshold needed to maintain a sustainable HIV epidemic, but is still not high enough to maintain an HIV prevalence larger than 5%. In the fourth and apparently most common regime globally [10], the level of risk behavior is substantial, as reflected by an HCV prevalence of 45–70%, and this level of risk behavior is large enough to maintain concentrated HIV epidemics reaching up to about 25% in HIV prevalence. In the fifth regime, HCV prevalence increases very slowly with risk behavior as it has already attained extreme values reflecting infection transmission saturation (>70%). However, HIV prevalence increases substantially even with very small increments in HCV prevalence, resulting in large scale HIV epidemics. In the last regime, HCV continues its very slow growth with risk behavior, while HIV is still growing noticeably, though at slower pace compared with the fourth regime. In this last regime, both infections eventually reach maximum possible prevalence.

In sum, HIV epidemic behavior in a PWID population can be broadly predicted based on the regime HCV prevalence belongs to. Any public health intervention aiming at reducing injecting risk behavior among PWID (such as education and awareness programs) may, if successful, shift endemic HCV and HIV prevalence levels to a new regime where HCV will still be predictive of HIV but according to the HCV-HIV association characterized by the new regime (Fig. 7).

The boundaries of each of these six epidemiological regimes were further described in our study by the $RR_{HCV|HIV}$ and $OR_{HCV|HIV}$, which were defined and estimated to quantify the association between HCV and HIV infections. The ranges of $RR_{HCV|HIV}$ and $OR_{HCV|HIV}$ in each regime were found to be relatively narrow. For example, in the fourth regime where a large fraction of the HIV PWID epidemics worldwide belongs [10], the $RR_{HCV|HIV}$ and $OR_{HCV|HIV}$ are relatively stable and hover around a value of 3 (Fig. 7b and c, Table 1). This indicates that when HCV prevalence is in the range of 45–70%, HIV prevalence will be about three times smaller than the observed HCV prevalence minus 27.9%, the threshold HCV prevalence for a sustainable HIV epidemic (Eq. 3). We found that behavioral uncertainty, and to a lesser extent biological uncertainty and stochasticity, could affect the predicted values of the $RR_{HCV|HIV}$ and $OR_{HCV|HIV}$, but overall in a predictable way that does not undermine their potential programmatic use to

Table 3 Illustration of the threshold effects in Afghanistan

	Year	HCV prevalence (%)	Status	HIV prevalence (%)	Study
Jalalabad	2007	12.5	Below sustainability threshold	0.0	[47]
	2012	9.5		1.0	[46]
Mazar-i-Sharif	2007	24.1	Below sustainability threshold	0.0	[47]
	2009	25.5		1.0	[45]
	2012	18.8		0.3	[46]
Kabul	2005-6	36.6	Above sustainability threshold & below concentration threshold	3.0	[56]
	2008	36.1		2.1	[57]
	2009	37.1		3.2	[45]
	2012	27.6		2.4	[46]
Herat	2007	49.1	Above concentration threshold	3.2	[47]
	2009	57.9		18.2	[45]
	2012	70.0		13.3	[46]

characterize HCV-HIV overlapping epidemiology and to make predictions of future HIV epidemic scale.

Our findings provide a rationale for using HCV prevalence as a predictor of future HIV epidemic scale in PWID. This approach provides also several specific prediction methods with different levels of precision. First, the derived HCV thresholds can be used in conjunction with observed HCV prevalence to predict, in a broad term, whether a PWID population is likely or not to experience a sustainable or concentrated HIV epidemic (such as in the example of Table 3). Second, linking a PWID population with its epidemiological regime based on HCV prevalence, that is one of the six epidemiological regimes in Table 1, can provide a range for the predicted future HIV prevalence. For example, a PWID population with an HCV prevalence of 50% belongs to regime IV and is therefore likely to experience an HIV epidemic with an HIV prevalence in the range of 5–24%. Third, a more precise HIV prevalence range can be estimated using the derived $RR_{HCV|HIV}$ (or $OR_{HCV|HIV}$) range for each specific epidemiological regime and Eq. 3 (or Eq. 4). For example, the $RR_{HCV|HIV}$ in regime IV ranges between 1.8 and 3.5. For a PWID population at 50% HCV prevalence, this $RR_{HCV|HIV}$ range translates, through Eq. 3, into a predicted HIV prevalence range of 6–12%. Finally, the most precise estimation of HIV epidemic scale can be obtained by applying the mathematical models directly at a specific HCV prevalence. For a 50% HCV prevalence, modeling predicts an HIV prevalence of 7%. Uncertainty analyses can be also conducted on the later estimate, using also the models, to provide an uncertainty interval for this estimate, as was done for Iran above.

There were several limitations in our study. Although we used an elaborate mathematical model structure, we may not have captured some of the complexities of injecting risk networks and of HCV/HIV dynamics. For example, we did not allow movement of PWID between different risk groups, and did not incorporate the effect of HCV-HIV co-infection and its potential effect on HCV transmission and spontaneous clearance. We also did not consider the sexual transmission of HIV since its relative importance among PWID is small except among specific sub-populations of PWID who are also men who have sex with men or female sex workers [3, 10, 39, 48]. In most of MENA settings where our applications are aimed at, the HIV epidemics are characterized by limited sexual HIV transmission not only among PWID, but even among populations at high risk of HIV sexual transmission such as men who have sex with men and female sex workers and their clients [49–52]. It is therefore unlikely that sexual transmission of HIV would affect our results and their applications in MENA. Our model could be extended in future research to include sexual HIV transmission where it would be of value to estimate the relative contribution of sexual versus parenteral HIV transmission. This would be especially relevant for applications of the methodology to settings other than MENA where sexual transmission may be more prominent.

The HIV model did not include scale-up of ART, but ART coverage was included in a sensitivity analysis where it had overall a minor effect on the HCV thresholds except near extreme values of coverage (>90%). Currently MENA has the lowest ART coverage of all regions globally at 17% [30], with unpublished data suggesting even lower coverage among PWID (World Health Organization, unpublished). Similarly, and with the very low coverage among PWID [53], the model did not include the effect of HCV treatment. However, with the newly available direct-acting antivirals to treat HCV, scale-up of HCV treatment among PWID is expected to increase, thus possibly influencing HCV transmission dynamics and complicating the relationship between HIV and HCV. In this case, our models would need to be extended to capture HCV treatment scale up and coverage, in addition to uneven healthcare services among PWID, to adjust the modeling predictions of future HIV prevalence based on existing HCV prevalence levels.

Our modeling predictions can be also constrained by limitations in the data input of our models. Nevertheless, a wide range was attached to the biological and behavioural parameters to capture the uncertainty in our knowledge of these parameters. We also fitted our modeling predictions to available global epidemiological data [10] to derive key parameters that are not precisely measured, mainly the HCV/HIV infectiousness ratio. While admittedly the epidemics in different global settings could be in different stages, and not all epidemics of substantial HCV and HIV prevalence are at equilibrium, we fitted to all global data rather than to the temporal trend of the epidemic in a specific setting, since the main purpose was to derive this biological and not setting-specific parameter. Also, fitting our dynamical model to the actual epidemiological data and their time series would have been superior to fitting to the regression line that summarizes these data [10]. Finally, predictions of HIV epidemic scale using the methodology we propose will depend on the quality and representativeness of HCV prevalence data, in the same way any other prediction method is dependent on the quality of input data. This highlights the importance of collecting quality and representative HCV prevalence data among PWID.

Despite these limitations, we structured our models through a parsimonious approach to ensure that the models complexity is constrained by the available data,

and predictions are robust even with broad ranges in parameter values. Biological parameters in our model are generally obtained from primary and most recent empirical data, similar to comparable mathematical modeling studies in the literature. Admittedly, behavioral parameters have more uncertainty but the extensive sensitivity and uncertainty analyses we conducted indicated overall a minor effect on our model's predictions of HCV thresholds and endemic HIV prevalence. Our model further fitted well the global epidemiological data and was able to reproduce a number of the findings of previous ecological and modeling work [9–11, 13].

Our findings, and the concept we present, have important policy, programming, and resource allocation implications. We demonstrated that HCV can be used to predict future HIV epidemics and their scale. Because of stochasticity and biological and behavioural uncertainty, predictions may not be very precise in terms of the exact HIV prevalence foreseen. However even with coarse predictions, such an approach can be effective in pinpointing settings that are likely to experience substantial HIV epidemics in the future, and accordingly need to be prioritized for prevention interventions. In this sense, HCV acts as a *temperature scale* of the level of risk behavior in an injecting network, and can be used as an index to measure the risk and severity of potential HIV epidemics among PWID. This is, in essence, a population-based diagnostic test or a screening approach, similar to other individual-based diagnostic tests or public health screening programs, such as for heart disease or breast cancer. While such diagnostics or screening programs may not have perfect sensitivity or specificity for the disease of interest, they have an important public health impact by averting or controlling disease through early detection. Moreover, studies have shown that identifying and targeting most-at-risk populations significantly improve the cost-effectiveness of interventions [1]. For example, a recent study has indicated that by dividing the population into two groups of high and low risk behavior, targeting those at higher risk of acquiring HIV would increase the effectiveness of an intervention (voluntary medical male circumcision) ten-fold [54, 55]. By dividing the population into six risk groups, the intervention becomes 80 times more effective if the highest risk group is targeted compared to targeting the lowest risk group [54, 55].

Conclusions

We investigated and characterized the poorly-understood association between HCV and HIV infections among PWID. The overlapping epidemiology of the two infections was described using distinct dynamical regimes and quantified with devised measures of association. Despite the complexity of the models and of the HCV-HIV association, these measures offered a simple applied tool for policy makers and program officers to predict HIV epidemic potential in PWID populations. We also proposed several methods with varying levels of precision for predicting HIV epidemic scale, and this concept was demonstrated in a specific country, Iran. The methodology proposed in the present study has a practical relevance which can be disseminated directly at the level of national stakeholders or in consultation with the international organizations leading the HIV/HCV response in the region, namely the World Health Organization, Joint United Nations Programme on HIV/AIDS, and the World Bank.

By identifying and targeting settings where HIV prevalence among PWID is currently at low level, but where the level of risk behavior as reflected by HCV prevalence is indicative of substantial future HIV epidemics, the proposed methodology not only helps in prioritization of PWID populations with high HIV epidemic potential, but also will lead to higher cost-effectiveness of HCV/HIV interventions. This is particularly critical in resource-limited settings, such as MENA and other regions in the world.

Additional files

Additional file 1: Mathematical models description. (DOCX 302 kb)

Additional file 2: Models assumptions in terms of parameter values. (DOCX 95 kb)

Additional file 3: Trend of HIV prevalence among PWID in Iran as described by available HIV point-prevalence measures 1990–2013. (TIF 1115 kb)

Additional file 4: Effect of stochasticity (purple) and of behavioral (blue) and biological (red) uncertainty on the modeling predictions of the endemic HIV prevalence, $RR_{HCV/HIV}$ and $OR_{HCV/HIV}$ at 59.4% HCV prevalence in Iran. (TIF 3208 kb)

Abbreviations

ART: Antiretroviral therapy; HCV: Hepatitis C virus; IQR: Interquartile range; MENA: Middle East and North Africa; $OR_{HCV/HIV}$: Odds ratio of HCV prevalence to HIV prevalence; PWID: People who inject drugs; $RR_{HCV/HIV}$: Risk ratio of HCV prevalence to HIV prevalence; UI: Uncertainty interval

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Availability of data and materials

There are no primary data in this study. All relevant data supporting the conclusions of this article are within the article and its additional files.

Authors' contributions

VA coded the models, generated simulations, and conducted analyses. GRM contributed to the conception of the study, conducted analyses, and wrote

the first draft of the manuscript. SFA contributed to the coding and simulations. HAW contributed to the conception and design of the study. LJA conceived the study and simulations, and contributed to the analyses. All authors have read and agreed with the final version of the manuscript.

Competing interests
The authors declare that they have no competing interests.

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Not applicable.

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Not applicable.

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3.3. SUPPLEMENTARY ONLINE MATERIAL OUTLINE

The following is the outline of the supplementary online material as cited in Research paper 2. The corresponding files are found in Appendix B.

Additional file 1.	Mathematical models description
Additional file 2.	Models assumptions in terms of parameter values
Additional file 3.	Trend of HIV prevalence among PWID in Iran as described by available HIV point-prevalence measures 1990-2013
Additional file 4.	Effect of stochasticity (purple) and of behavioural (blue) and biological (red) uncertainty on the modeling predictions of the endemic HIV prevalence, $RR_{HCV/HIV}$ and $OR_{HCV/HIV}$ at 59.4% HCV prevalence in Iran

3.4. SUMMARY OF FINDINGS

This study characterized the poorly-understood association between HCV and HIV infections among PWID. HCV was found to be eight times more transmissible per shared injection than HIV. There is a threshold HCV prevalence of 29% below which HIV is not sustainable in a PWID population (HIV prevalence <1%). There is also a threshold HCV prevalence of 47% needed to sustain a concentrated HIV epidemic among PWID (HIV prevalence >5%). Both HCV thresholds for sustainable and concentrated HIV epidemics are largely insensitive to the details of injecting risk behaviour, except near extreme values of some behavioural attributes.

The association between HCV and HIV prevalence at endemic equilibrium is characterized with six dynamical regimes which define the nature and magnitude of the association between HCV and HIV prevalence. Existing HCV prevalence levels in a PWID population can predict future endemic HIV prevalence, and HIV predictions across a wide range of HCV prevalence are overall robust with respect to behavioural uncertainty. HCV acts like a temperature scale of the level of risk behaviour in an injecting network and can be used as an index to measure the risk and severity of potential HIV epidemics among PWID.

This study offers a simple applied tool for policy makers and program officers to make predictions for HIV epidemic potential in PWID populations using existing HCV prevalence levels. Although the priority for public health programs should be settings already at high HIV prevalence, this method helps in prioritizing PWID populations that are likely to experience such HIV infection spread before it actually happens.

4. HCV AS A PREDCITOR OF HIV EPIDEMIC POTENTIAL AMONG PWID: APPLIED ECOLOGICAL ANALYSIS IN MENA

4.1. INTRODUCTION

After the concept of using HCV prevalence as a predictor of future endemic HIV prevalence was theoretically demonstrated in Chapter 3, Chapter 4 follows with an epidemiological application of this concept in MENA. In this study, the paired HCV-HIV epidemiological data (that is HCV and HIV prevalence on the same PWID population) extracted from Chapter 2 systematic review are used to analyse and quantify the association between HCV and HIV prevalence at endemic equilibrium. This association is then used to make predictions of HIV epidemic potential among PWID at country-level, based on existing HCV prevalence levels.

Chapter 2 documented relatively high levels of sharing needles/syringes among PWID in MENA which suggest that there could be room for further HIV spread, especially that the observed HIV epidemics are for the most part probably in their early phase. However, measures of injecting risk behaviour could be subject to reporting bias, whether under-reporting or over-reporting. Also injecting risk behaviour is a complex phenomenon that encompasses factors that are beyond simple measures of needles sharing, such as patterns of partnership formation and heterogeneity in levels of risk and mixing. The levels of these risks are in large part dictated by network structure [74-77], which is not easy to capture, measure, or quantify. For these reasons, the behavioural data need to be complemented by other more objective biological measures, such as HCV infection, which reflect levels of injecting risk behaviour, and also can be used as summary proxy measures to indicate HIV epidemic potential.

In this chapter, we complement our epidemiological understanding of the injecting risk behaviour environment in MENA, by using measured levels of HCV prevalence to make quantitative (estimate HIV prevalence at endemic equilibrium) and qualitative (classify HIV epidemic growth relative to current levels) estimations of HIV epidemic potential among PWID at country-level in MENA.

4.2. RESEARCH PAPER 3 – ECOLOGICAL ANALYSIS

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Ghina Mumtaz
Principal Supervisor	Prof. Helen Weiss
Thesis Title	The Epidemiology of HIV Infection Among People Who Inject Drugs in the Middle East and North Africa

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	AIDS		
When was the work published?	August 24, 2015		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am first and corresponding author on this paper. I designed the study, conducted all statistical analyses, interpreted the findings, and wrote the first draft of the manuscript.

Student Signature: _____ _____ **Date:** January 10, 2017

Supervisor Signature: ___  _____ **Date:** January 10, 2017

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OPEN

Using hepatitis C prevalence to estimate HIV epidemic potential among people who inject drugs in the Middle East and North Africa

Ghina R. Mumtaz[a,b], Helen A. Weiss[b], Peter Vickerman[c], Natasha Larke[b] and Laith J. Abu-Raddad[a,d,e]

Objectives: The objective of this study is to understand the association between HIV and hepatitis C virus (HCV) among people who inject drugs (PWIDs) in the Middle East and North Africa (MENA), and to estimate HIV epidemic potential among PWIDs using HCV prevalence.

Design/methods: Using data from a systematic review of HIV and HCV among PWID in MENA, we conducted two analyses, stratified by HIV epidemic state: a meta-analysis of the risk ratio of HCV to HIV prevalence ($RR_{HCV/HIV}$) using DerSimonian-Laird random-effects models, and multivariable linear regression predicting log HIV prevalence. The HCV-HIV association from both analyses was used to estimate HIV prevalence at endemic equilibrium. We compared predicted with current HIV prevalence to classify HIV epidemic potential at country-level as low, medium or high, using predefined criteria.

Results: The review identified 88 HCV prevalence measures among PWID in MENA, of which 54 had a paired HIV prevalence measure. The pooled $RR_{HCV/HIV}$ were 16, 4 and 3 in low-level, emerging and established HIV epidemics, respectively. There was a significant linear relationship between HCV and HIV at endemic equilibrium ($P = 0.002$). The predicted endemic HIV prevalence ranged between 8% (Tunisia) and 22% (Pakistan). Of the nine countries with data, five have high and three medium HIV epidemic potential. Only one country, Pakistan, appears to have reached saturation.

Conclusion: HCV prevalence could be a predictor of future endemic HIV prevalence. In MENA, we predict that there will be further HIV epidemic growth among PWID. The proposed methodology can identify PWID populations that should be prioritized for HIV prevention interventions.

AIDS 2015, **29**:1701–1710

Keywords: epidemic, hepatitis C virus, HIV, Middle East and North Africa, people who inject drugs, prediction

Introduction

People who inject drugs (PWID) are a key population at risk for HIV infection in the Middle East and North Africa (MENA) [1]. A recent systematic review documented emerging HIV epidemics among PWID in at least one-third of MENA countries [2]. Most epidemics are recent and suggest potential for further

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growth [2]. Our research question is to estimate the HIV epidemic potential among PWID, that is to estimate the predicted growth in HIV prevalence to the time it reaches endemic equilibrium, in order to inform policy and intervention programmes.

Although HIV and, in rare instances [3], hepatitis C virus (HCV) can be transmitted sexually, sharing of needles/syringes is their main transmission mode among PWID [4]. HCV is about 10 times more infectious than HIV through percutaneous exposure [5–7], partially explaining why HCV is hyperendemic among PWID globally, but HIV is not [8,9]. As HCV is transmitted more rapidly than HIV along the same transmission route, it could be used as a marker of HIV potential spread among PWID. Ecological studies and mathematical modelling have found a positive association between HCV and HIV among PWID globally, with a threshold HCV prevalence of about 30% to sustain HIV transmission [6,7,10]. The relationship between the two infections is however complex, dependent on the setting and risk environment, and overall remains poorly understood [7].

The use of HCV as a population-level marker of injecting risk behaviour and, consequently, HIV risk and epidemic potential is appealing with the constrained resources for HIV research and programming. In MENA, wherein surveillance is rather limited and difficult to implement, using existing data to make inferences about future size of HIV epidemics is a potentially efficient strategy.

The aims of this study are to understand analytically the epidemiological links and association between HCV and HIV infections among PWID, and to estimate HIV epidemic potential in this population across MENA countries, using data compiled through the systematic review of HIV and HCV among PWID in MENA [2].

Materials and methods

Conceptual framework and hypotheses

We hypothesize that endemic HCV prevalence predicts HIV prevalence among PWID, as both infections result from injecting risk behaviour. We further hypothesize that the relationship between HCV and HIV prevalence is dependent on the HIV epidemic state among PWID, whether low-level (HIV has not reached significant levels), emerging (HIV prevalence has started its initial growth and is increasing) or established/saturated (the epidemic has reached its peak and HIV prevalence is approaching, or already is at, its endemic level) [2]. We hypothesize that the association between HCV and HIV in established HIV epidemics can be used to predict HIV epidemic potential among PWID in other settings, even where the HIV epidemic is still at low level or emerging.

Our hypothesis is motivated by theoretical mathematical modelling work on the joint epidemiology of HCV and HIV. A stochastic compartmental model was built to simulate HCV and HIV epidemic trajectories among a prototype PWID population (V. Akbarzadeh, G.R. Mumtaz, L.J. Abu-Raddad, in preparation). Figure 1a depicts a case scenario wherein HIV is introduced into a PWID population originally naive to HIV and where HCV is endemic at high prevalence indicating substantial injecting risk behaviour. When the HIV epidemic is still at low level, HCV prevalence is not predictive of the level of HIV prevalence (Fig. 1a). When the HIV epidemic emerges, HCV prevalence becomes associated with HIV prevalence; however, the magnitude of this association varies with time, as HIV prevalence is still increasing (Fig. 1a). It is only when the HIV epidemic becomes established, that the association between HCV and HIV prevalence becomes stable and simply quantified, as both infections have reached endemicity (Fig. 1a). This pattern is reflected in the risk ratio of HCV to HIV prevalence ($RR_{HCV/HIV}$) (Fig. 1b). As the HIV epidemic emerges, the $RR_{HCV/HIV}$ decreases until it reaches a plateau, with a stable $RR_{HCV/HIV}$, when the HIV epidemic reaches equilibrium (established HIV epidemic, Fig. 1b). Endemic HCV prevalence can accordingly be used to predict the future size (at endemic equilibrium) of the HIV epidemic among PWID. Varying levels of endemic HCV prevalence entail varying levels of endemic HIV prevalence.

On the basis of the above analytical framework, we will stratify our analyses by HIV epidemic state to explore the differential association between HCV and HIV in the three epidemic states. Results of the analyses in settings of established HIV epidemics will be used to predict HIV epidemic potential among PWID.

Sources of data

This study used data extracted from a recent systematic review whose main objective was to assess the status of the HIV epidemic among PWID in 23 MENA countries that are part of the MENA definition of the Joint United Nations Programme on HIV/AIDS (UNAIDS), WHO and World Bank [2]. In brief, the review followed PRISMA guidelines and included all studies on PWID, published in PubMed, Embase and regional databases, and unpublished in the form of country reports, until 16 December 2013 [2].

In the present study, we started with 197 HIV and 93 HCV prevalence measures among PWID (Fig. 2) [2]. After excluding four HIV and five HCV self-reported prevalence measures, there were 71 paired biological HCV-HIV data points, that is HCV and HIV prevalence on the same PWID population. As we are studying the relationship between the two infections, the analysis was restricted to settings wherein HIV has already been introduced, and thus, 16 HCV-HIV data points with zero

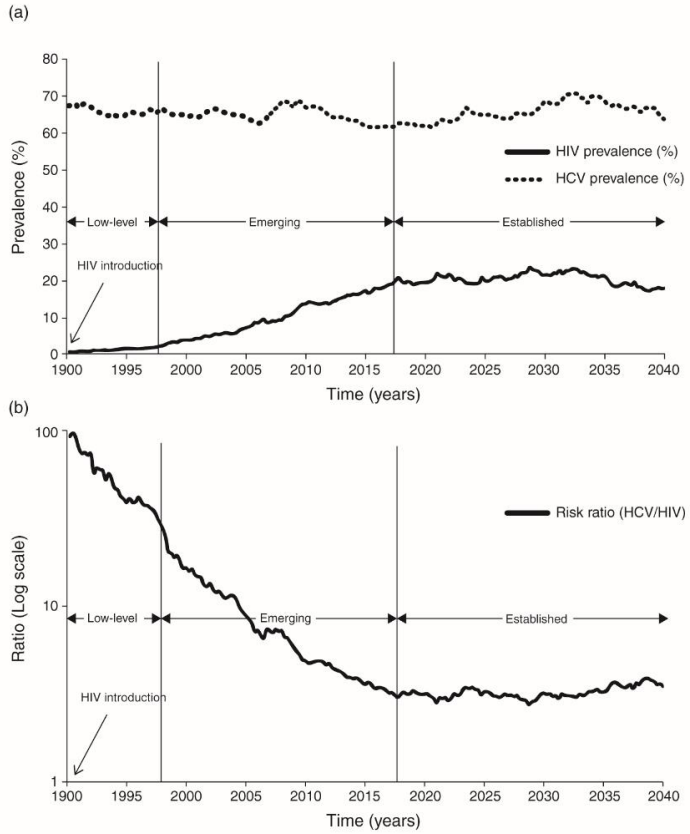

Fig. 1. Mathematical modelling simulation of an HIV epidemic expansion among a prototype PWID population. (a) A case scenario for an HIV epidemic expansion in a PWID population wherein HCV is endemic at a prevalence level of about 75% indicating high injecting risk behaviour. HIV is introduced in 1990, starts emerging with increasing prevalence about two decades later in the late 1990s, and saturates near the year 2020 at a prevalence of about 20%. The corresponding three HIV epidemic states – low level, emerging and established – are shown on the graph. (b) The risk ratio of HCV to HIV prevalence ($RR_{HCV/HIV}$) among this PWID population.

HIV prevalence were excluded. One outlier (89% HIV prevalence in Libya [11]) was further excluded, leaving 54 paired HCV-HIV prevalence measures in the statistical analysis (Fig. 2).

Classification by HIV epidemic state

Country-specific criteria were devised to classify the data into one of three HIV epidemic states: low-level, emerging or established [2]. This classification was a main aim of the MENA PWID systematic review, wherein a comprehensive analysis of available HIV biological data was performed using rigorous methodology to characterize HIV epidemic state at country-level [2]. HCV biological data were not part of the criteria to characterize HIV epidemic states. Details of the methods, classification criteria and findings that led to these epidemic states can be found in the corresponding publication [2]. The epidemic states for countries in the present study are summarized in Table S1. This baseline classification was adjusted in specific cases to accommodate for geographic heterogeneity in HIV epidemic dynamics within a single country [2]. For example, in Iran, all data points after 2006 were classified as 'established', except for one province, Isfahan, where HIV prevalence among PWID has been consistently negligible [2].

Data analysis

Analyses were performed in STATA/SE 13.0 (Stata Corp., College Station, Texas, USA). Two types of analyses were conducted to understand the association between the two infections: a meta-analysis of the

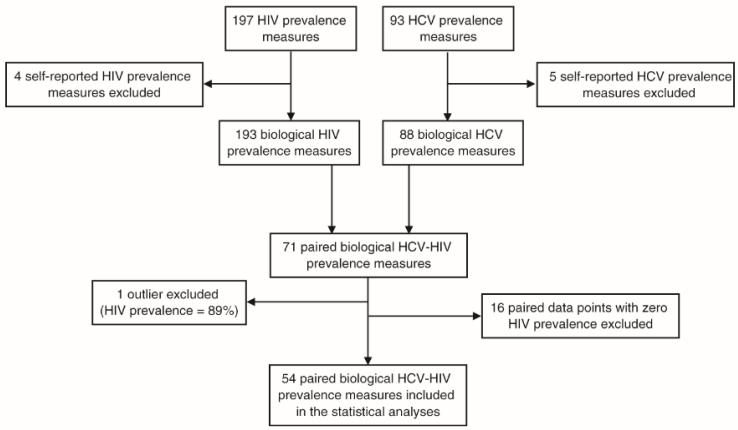

Fig. 2. Sample selection process.

$RR_{HCV/HIV}$ and linear regression to quantify the extent to which any change in HIV prevalence is related to change in HCV prevalence. Results of these analyses were used to predict future HIV prevalence at endemic equilibrium among PWID at country-level.

Meta-analysis

Three meta-analyses of the $RR_{HCV/HIV}$ in each of the three HIV epidemic states were applied. The $RR_{HCV/HIV}$ is an 'ecological' risk ratio defined as the ratio of the prevalence ('risk') of HCV to that of HIV in the same population. The objective of using this measure was to quantify the association between the two infections at the population level.

The 54 $RR_{HCV/HIV}$ were pooled using DerSimonian–Laird random-effects models with inverse variance weighting using the *metan* command [12]. The I^2 statistic was calculated as a measure of heterogeneity in effect size, which is the proportion of overall between-study variation in $RR_{HCV/HIV}$ that is due to differences between studies in effect size and not chance [12].

Linear regression

Three multivariable linear regression models, one in each HIV epidemic state, were fitted to the data. Log HIV prevalence was the dependent variable. Explanatory variables included HCV – our main predictor of interest – country and study characteristics including sampling technique (probability versus nonprobability-based), sample size (<100 or ≥ 100) and study site (community, facility-based or prison). The regression analyses used robust standard errors to adjust for heteroscedasticity. Each data point was weighed by its sample size. As a first step, all explanatory variables were included in the model and only variables significant at P value less than 0.1 (in addition to HCV) were kept in the final model.

HIV epidemic potential prediction

The final regression model predicting HIV prevalence in settings of established HIV epidemics was used to estimate the prevalence and 95% confidence intervals of HIV at endemic equilibrium among PWID, using the *margins* command. On the basis of predictions of the fitted model, *margins* calculate HIV prevalence for specific values of covariates in the model. The predictions were made using the mean HCV prevalence among PWID per country using all available biological HCV prevalence measures (including where HIV is zero) [11,13–78]. The prevalence of HIV at endemic equilibrium was also estimated using results of the meta-analysis by dividing the mean HCV prevalence by the pooled $RR_{HCV/HIV}$. Results of the two methods of prediction were compared.

We devised criteria to classify HIV epidemic potential. They depend on comparing the predicted HIV prevalence with the most recent representative HIV prevalence as extracted from surveillance studies [2]. HIV epidemic potential was classified as high, moderate or low. High epidemic potential was considered if the estimated HIV prevalence at endemic equilibrium was at least 10 absolute percentage points higher than current HIV prevalence and at least twice as high as current HIV prevalence (estimated/current HIV prevalence >2). Low epidemic potential was considered if the estimated HIV prevalence at endemic equilibrium was less than five absolute percentage points higher than current HIV prevalence and less than 20% higher than current HIV prevalence (estimated/current HIV prevalence <1.2). Moderate epidemic potential was considered in remaining scenarios.

Results

The 54 paired HCV-HIV prevalence measures among PWID were from five countries: Iran ($n=31$), Afghanistan ($n=11$), Pakistan ($n=8$), Morocco ($n=2$) and

Tunisia ($n=2$). There were 20 paired HCV-HIV measures in low-level, 22 in emerging, and 12 in established HIV epidemic settings. Iran was the only country in the established epidemic strata. The data are summarized in Table S2.

The meta-analyses showed that the $RR_{HCV/HIV}$ is highest in low-level HIV epidemics at 16.3 [95% confidence interval (95% CI) 11.5–23.1], followed by that in emerging HIV epidemics at 3.8 (95% CI 3.1–4.7), while the lowest $RR_{HCV/HIV}$ was observed in established HIV epidemics at 2.8 (95% CI 2.1–3.6) (Table 1). The corresponding forest plots are in Figures S1–S3. These results suggest that HIV prevalence at endemic equilibrium is about one-third of the endemic HCV prevalence, assuming no major confounding effect by other predictors. There was evidence of heterogeneity between studies in the three epidemic states with an I^2 of 80–87% ($P<0.001$), indicating that the variation in $RR_{HCV/HIV}$ between studies is due to differences in effect size, and not chance.

Table 2 summarizes the final multivariable regression models predicting log HIV prevalence. HCV prevalence was not associated with HIV in low-level HIV epidemics (ß = −1.3, 95% CI −3.4 to 0.9). In these settings, country and study site were the significant predictors of HIV. HCV was a significant predictor of HIV prevalence in sites wherein the HIV epidemic is emerging or established. In emerging epidemics, HCV was significantly associated with the highest increase in log HIV prevalence compared with the other epidemic states (ß = 5.4, 95% CI 2.7–8.2). Country and study site were also significant predictors of HIV in emerging epidemic states. In established epidemics, HCV prevalence was the only predictor of HIV (ß = 1.7, 95% CI 0.8–2.7) (Table 2).

Table 3 displays the predicted HIV prevalence at endemic equilibrium among PWID in MENA using results of both regression analysis and meta-analysis. The two methods predicted similar endemic HIV prevalence, with a median difference of 10% between the two methods. The median estimated HIV prevalence across countries was 17% [interquartile range (IQR): 13–20%] and 19% (IQR: 13–22%) as predicted by the regression and meta-analysis models, respectively. The highest estimated endemic HIV prevalence was 20–22% in Egypt, Morocco, Pakistan, Saudi Arabia and Syria. The lowest was 8% in Tunisia (Table 3).

HIV epidemic potential was found to be high among PWID in Egypt, Lebanon, Palestine, Saudi Arabia and Syria, and moderate in Afghanistan, Morocco and Tunisia. Apart from Iran that was used to derive the predictive relationship, Pakistan was the only country with low epidemic potential and where the HIV epidemic among PWID is predicted to have reached or is close to saturation (Table 3).

Discussion

This study illustrates our hypothesis that HCV prevalence can be used to predict HIV epidemic potential among PWID. With HCV being hyperendemic among PWID globally, its prevalence is indicative of the level of injecting risk behaviour and therefore could possibly predict future HIV prevalence. Our analyses in MENA suggest that HIV prevalence will reach, at endemic equilibrium, about one-third of HCV prevalence in a given PWID population wherein HIV is introduced.

The association between HCV and HIV among PWID is complex and varied depending on HIV epidemic state, as postulated in our hypothesis and motivated by the modelling simulations. When the HIV epidemic was at low level, HCV was not predictive of HIV prevalence. HIV may have been recently introduced, or may have been spreading for some time but slowly and inefficiently due to stochastic effects. In these settings, HIV prevalence is not a reflection of the level of injecting risk behaviour. In an emerging HIV epidemic, the intensity of HIV prevalence growth depends on the level of injecting risk behaviour, and this is confirmed by the observed association between HCV and HIV prevalence. However, there are also other predictors of epidemic expansion intensity including time since epidemic emergence, and other factors such as setting of injection and country, both of which were significant predictive proxies for the risk environment (Table 2). In established HIV epidemics, and confirming our hypothesis (Fig. 2), HCV was the only significant predictor of HIV prevalence. This highlights how HCV is a proxy of injecting risk behaviour in PWID

Table 1. Pooled risk ratio of hepatitis C virus to HIV prevalence ($RR_{HCV/HIV}$) among people who inject drug in Middle East and North Africa.

Epidemic state	No datasets	Total un-weighted HCV prevalence	Total un-weighted HIV prevalence	Studies $RR_{HCV/HIV}$ Median (IQR)	Pooled $RR_{HCV/HIV}$ % (95% CI)	I^2	P
Low level	20	3264/7699 (42.4%)	217/7730 (2.8%)	13.8 (9.6–56.9)	16.3 (11.5–23.1)	80.2%	0.000
Emerging	22	2200/3749 (58.7%)	554/3698 (15.0%)	4.4 (3.1–5.6)	3.8 (3.1–4.7)	79.5%	0.000
Established	12	1635/3498 (51.1%)	605/3508 (23.2%)	3.3 (2.1–4.2)	2.8 (2.1–3.6)	87.2%	0.000

CI, confidence interval; HCV, hepatitis C virus; IQR, interquartile range.

Table 2. Multivariable linear regression models[a] predicting log of HIV among people who inject drug in Middle East and North Africa, stratified by HIV epidemic state among people who inject drug.

HIV epidemic state	Variables	β	95% CI	*P*	R^2
Low level ($n=16$)	HCV prevalence[b]	−1.3	−3.4 to 0.9	0.216	0.754
	Country			0.000	
	Afghanistan	ref			
	Iran	−0.3	−1.6 to 1.0		
	Morocco	−1.8	−3 to −0.6		
	Pakistan	−0.6	−2.4 to 1.1		
	Tunisia	0.3	−1.0 to 1.6		
	Study site			0.025	
	Community	ref			
	Prison	1.3	−0.3 to 3.0		
	Facility-based	−0.1	−1.7 to 1.5		
	Mixed	0.4	−1.3 to 2.1		
Emerging ($n=21$)	HCV prevalence[b]	5.4	2.7–8.2	0.001	0.724
	Country			0.001	
	Afghanistan	ref			
	Iran	−2.2	−3.1 to −1.4		
	Morocco	−0.6	−1.1 to −0.2		
	Pakistan	−1.3	−2.2 to −0.3		
	Study site			0.000	
	Community	ref			
	Prison	1.0	0.1–2.0		
	Facility-based	2.8	1.3–4.2		
	Mixed	2.8	2.0–3.7		
Established ($n=12$)	HCV prevalence[b]	1.7	0.8–2.7	0.002	0.340

CI, confidence interval.
[a]Weighting for sample size and using robust methods to adjust for heteroscedasticity. The displayed final models include only statistically significant covariates.
[b]Proportion.

and can be used to generate inferences on the size of HIV epidemics, regardless of current HIV epidemic state. HCV prevalence 'summarizes' collectively the risk environment and acts as a 'temperature scale' of the level of risk behaviour and HIV epidemic potential in a PWID population.

We estimated HIV epidemic potential in nine countries where HCV prevalence data were available. Both the regression analysis and meta-analysis produced similar results, not a surprising outcome, as HCV was the only significant predictor of HIV in the regression analysis of established HIV epidemics. In most countries, we found room for further HIV growth, with five of these having high and three moderate HIV epidemic potential, highlighting the emerging and growing nature of the HIV epidemic among PWID in MENA, as suggested recently [1,2]. Although HIV prevalence in Pakistan showed an increasing trend from 10.8% in 2005 to 25.2% in 2011 [79–82], our predictions suggest that the HIV epidemic could be reaching saturation with limited potential for further growth. Still, HIV incidence remains considerable in such settings of high HIV prevalence, and the limited epidemic potential should not be interpreted as low priority for prevention interventions.

Our findings have important policy implications, as they provide a simple tool to identify PWID populations at a high risk of future HIV epidemic expansion. In half of MENA countries with considerable epidemic potential, the HIV epidemic is still at low level, and therefore, there is significant benefit in preventing the infection from taking root in this population. In countries where epidemic status is unknown, using HCV prevalence data could help identify hidden HIV epidemics before they grow substantially. One example is Saudi Arabia where the high HCV prevalence suggests the potential for substantial, though undetected, HIV transmission. Recent case notification data also hint at this conclusion [1]. Although the top priority for public health programmes should be settings already at known high HIV incidence, such country-specific predictions highlight the need to also implement intervention packages and conduct surveillance studies in settings with high HIV epidemic potential and where there could be complacency in view of the current low HIV prevalence.

There were several limitations in our study. The analysis used a relatively simple approach to a probably complex association. We assumed a linear association between HCV and HIV, which fitted well our data. However, the effect size can be affected by heterogeneity in risk and nonlinearity in this association, as suggested by the observed high I^2 values, earlier modelling work [7,10] and an ecological analysis [6]. The latter also suggests a threshold effect where HIV prevalence would remain negligible in countries with low HCV prevalence [6], such as Tunisia. The HCV-HIV association can also be affected by interventions, if they affect each infection differentially, such as antiretroviral therapy (ART) that

Table 3. Estimated HIV prevalence at endemic equilibrium among people who inject drug in Middle East and North Africa.

	No datasets	Mean HCV prevalence	HIV epidemic state among PWID[a] [2]	Most recent representative HIV prevalence [2]	Estimated endemic HIV prevalence using regression		Estimated endemic HIV prevalence using meta-analysis		HIV epidemic potential
					%	95% CI	%	95% CI	
Afghanistan	13	34.2%	Emerging	4.4%	12.5	8.7–18.0	12.3	9.6–15.9	Medium
Egypt	1	63.0%	Emerging	7.2%	20.7	16.1–26.6	22.7	17.6–29.3	High
Iran	42	47.1%	Established	15.1%	15.7	11.8–20.9	17.0	13.2–21.9	Low
Lebanon	2	29.0%	Low-level	0.0%	11.4	7.7–17.1	10.5	8.1–13.5	High
Morocco	2	57.6%	Emerging	13.0%	18.9	14.6–24.3	20.8	16.1–26.8	Medium
Palestine	1	43.8%	Low-level	0.0%	14.8	10.9–20.0	15.8	12.2–20.4	High
Pakistan	19	60.7%	Emerging	25.2%	19.9	15.5–25.6	21.9	17.0–28.3	Low
Saudi Arabia	3	60.5%	Unknown	0.6%	19.8	15.4–25.5	21.8	16.9–28.2	High
Syria	1	60.5%	Low-level	0.5%	19.8	15.4–25.5	21.8	16.9–28.2	High
Tunisia	3	22.6%	Low-level	3.0%	10.2	6.5–16.0	8.2	6.3–10.5	Medium

CI, confidence interval; HCV, hepatitis C virus.
[a]Overall current HIV epidemic state among PWID at country-level.

affects survival with HIV and infection transmission. In MENA, ART coverage is low across countries, with a median of 16% (IQR: 6–17%) [83]. If ART coverage increases substantially in the coming years, our current predictions may underestimate endemic HIV prevalence with the longer survival effect. ART can affect the quantitative HCV-HIV association, but not its existence nor the principle behind it. When applied to settings with substantial ART coverage, a more generic association could be derived by including ART coverage as one additional covariate in the regression models.

We assumed that HCV and HIV among PWID are transmitted through sharing of needles/syringes and that there is limited sexual transmission of these infections in this population. We also assumed a negligible effect of background HCV prevalence due to iatrogenic transmission, as HCV prevalence in the population at large is generally much smaller than HCV prevalence among PWID [2,84,85]. We further assumed that HCV is at endemic equilibrium. All of these assumptions are only approximately valid.

The small sample size of paired HCV-HIV measures limited the range of mathematical complexity that could be explored and number of potential confounders to control for and prevented us from conducting meta-regressions to account for heterogeneity in effect size. Iran was also the only country providing data in the established HIV epidemic state, but this could introduce bias if the data from other countries are not representative of the same generic HCV-HIV epidemiological association. The predictions of HIV epidemic potential also depend on the quality of HCV prevalence data. For some countries, there were few measures and these may not be representative of the PWID population at large. Our predictions were also made at the national level, but there could be geographic heterogeneity in risk environment, leading to geographically clustered HCV prevalence and predicted HIV epidemic size. For example in Pakistan, HCV prevalence of over 90% was observed in Karachi and Lahore [2], while the mean prevalence at the country-level was only 61%. Finally, our methodology provides only the scale and not the timeframe of predicted epidemic growth. It is expected, however, based on generic mathematical modelling results [11,86], that the pace of an epidemic should correlate with its HIV epidemic potential, as estimated here.

Despite these limitations, our study provides important insights into a poorly understood and barely investigated association [6,7]. Using a mechanistic and analytical methodology, our study confirms that the HCV-HIV association is robust and characterized differentially by HIV epidemic state. The association can also be described, at least grossly, using a simple methodology that can be easily and widely applied to assess HIV epidemic potential. Even if some of the input data used to generate the

predictions may prove unrepresentative with further empirical data, the value of this work remains in delineating a powerful concept of using data on one infection, HCV, to estimate the scale of epidemics of another infection, HIV. This concept exploits the epidemiological links that underpin the dynamics of two infections sharing the same mode of transmission and propagating on the same network structure. With further data over the coming years, and use of global data on PWID beyond MENA, the value of this approach can be enhanced for a wider applicability across countries and contexts, including fine-grained predictions at small geographic scales. Moreover, if combined with appropriate dynamic mathematical modelling, our results could be used to generate predictions for the time evolution of epidemics.

In conclusion, we described a concept that has a pragmatic and useful application, to predict future HIV epidemics and their scales using HCV prevalence. The proof of concept was manifested by modelling the HCV-HIV association in few countries, and then generating predictions for more countries with limited HIV data. In addition to informing our theoretical understanding of the overlapping epidemiology of these two infections, this approach optimizes the use of available data and informs resources allocation and planning of interventions and research studies. Findings from this proposed methodology can complement those of other methods of measurement and estimation such as prospective incidence studies, and indirect estimations of HIV incidence using the innovative HIV incidence assays and mathematical models [87,88]. Triangulation of complimentary approaches will allow the corroboration of findings across different methods, the adjustment of potential limitations in each one of them and is essential for the formulation of an optimal HIV response.

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Conflicts of interest

There are no conflicts of interest.

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4.3. SUPPLEMENTARY ONLINE MATERIAL OUTLINE

The following is the outline of the supplementary online material as cited in Research paper 3. The corresponding files are found in Appendix C.

Table S1.	HIV epidemic states among people who inject drugs in select Middle East and North Africa countries with sufficient data to explore the HCV-HIV association
Table S2.	Summary of the 54 paired HCV-HIV prevalence data among people who inject drugs in the Middle East and North Africa
Figure S1.	Forest plot for the meta-analysis of the risk ratio of HCV to HIV prevalence among people who inject drugs in Middle East and North Africa settings of low-level HIV epidemics
Figure S2.	Forest plot for the meta-analysis of the risk ratio of HCV to HIV prevalence among people who inject drugs in Middle East and North Africa settings of emerging HIV epidemics
Figure S1.	Forest plot for the meta-analysis of the risk ratio of HCV to HIV prevalence among people who inject drugs in Middle East and North Africa settings of established HIV epidemics

4.4. SUMMARY OF FINDINGS

This ecological analysis in MENA supports the theoretical findings of Chapter 3, whereby HCV prevalence was a significant predictor of HIV prevalence in settings where the HIV epidemic is established and therefore where both HCV and HIV infections are at endemic equilibrium. Our analyses in MENA suggest that HIV prevalence will reach, at endemic equilibrium, about one third of HCV prevalence in a given PWID population where HIV is introduced. Using this association, it is predicted that there will be further HIV epidemic growth among PWID in several MENA countries, based on existing HCV prevalence levels. Out of nine MENA countries with HCV prevalence data among PWID, five have high HIV epidemic potential, three have medium HIV epidemic potential, and one has low HIV epidemic potential. Settings with limited current HIV transmission among PWID, but where further HIV epidemic expansion is predicted, should be prioritized for HIV/drug use prevention interventions, alongside settings with already large HIV PWID epidemics.

5. HIV INCIDENCE AMONG PWID IN MENA

5.1. INTRODUCTION

Chapter 2 documented emerging HIV epidemics among PWID in several MENA countries, some of which are already at high prevalence exceeding 10-15%. The potential for larger HIV epidemics in these countries was predicted using HCV prevalence levels which suggest high levels of sharing and connectivity of injecting networks (Chapter 3). Considerable HIV epidemic potential was also predicted in several countries where the HIV PWID epidemic is currently at low-level or of unknown status (Chapter 3).

All of these findings suggest that there is or could be substantial incidence occurring among PWID in MENA, and that, if appropriate interventions are not implemented, the region may witness large HIV epidemics among PWID. This is even more of a concern in a region where the HIV response to the growing HIV epidemics among PWID lags far behind other regions and behind current needs [78]. ART coverage levels in MENA are the lowest in the world and the HIV treatment cascade among PWID suggest even lower ART coverage and retention in care than in all those living with HIV [62]. In a region where the HIV epidemic appears to be strongly driven by injecting drug use, reducing incidence among this pivotal population group is essential to reach the Fast-Track target of reducing the number of new infections by 75% in MENA by 2020 [65].

In this study, mathematical modeling is used to estimate HIV incidence among PWID in MENA countries and the impact of interventions on incidence. The study further explores the role of injecting drug use as a driver of HIV incidence in the wider population, mainly through onward transmission to sexual partners.

5.2. UPDATED RISK GROUP SIZE ESTIMATES AND HIV IBBSS PREVALENCE DATA

The mathematical model used in this chapter was parameterized mainly using country-specific bio-behavioural data extracted as part of the systematic review of PWID in MENA conducted in Chapter 2.

The size of the PWID population and HIV prevalence among PWID at country-level are two central parameters in the estimations of HIV incidence in this study. To check whether any important new data were generated after my systematic review was conducted, the evidence on these two measures were updated with recent data, as provided by partner international organizations and national country-level collaborators and stakeholders conducting/overseeing main mapping studies and IBBSS in the region.

A number of PWID risk group size estimates were performed in several countries of the region since research paper 1 was published. These estimates were compiled and provided by WHO-EMRO [79]. In total, there were ten new estimates of the number of PWID in the following countries: Afghanistan, Bahrain, Egypt, Kuwait, Lebanon, Morocco, Pakistan, Syria, and Tunisia. Table 5.1 below is an updated version of Table 2 in research paper 1. It summarizes available national estimates of the number of PWID in MENA countries. The table also includes updated estimates of the total adult population in each country (for the year 2015 versus 2010 in the publication of research paper 1).

In this study, HIV incidence was conducted in countries with epidemiological evidence indicating HIV prevalence greater than 1%. At the time that estimations were conducted, no new (since Research paper 1 was published) IBBSS were conducted among PWID and that found HIV infections among PWID. HIV prevalence data as published in Research paper 1 was therefore used in parameterizing the model.

Table 5.1. Updated national estimates of the number and prevalence of people who inject drugs in the Middle East and North Africa.

		PWID estimate (number)				
Country	**Population 15-64 years [41]**	**Low**	**Middle**	**High**	**Year of estimate**	**Source**
Afghanistan	17,398,120	22,720	34,080	45,440	*	[80]
		6,870	6,900	6,930	2005	[6]
		18,000	20,000	23,000	2009	[81]
					2009	[82]
		1,465	17,640	23,000	2012	[79]
Algeria	25,990,793	26,333	40,961	55,590	*	[80]
Bahrain	1,048,273	337	674	1,011	*	[80]
			3,200	30,000	2006	[79]
Djibouti	560,045	--	--	--	--	--
Egypt	56,386,786	56,970	88,618	120,265	*	[80]
		86,000	93,000	119,000	2014	[79]
Iran	56,428,180	70,000	185,000	300,000	*	[80]
			180,000		2004	[6]
			250,000		2007	[83]
Iraq	20,382,898	23,115	34,673	46,230	*	[80]
Jordan	4,609,030	3,200	4,850	6,500	*	[80]
Kuwait	2,946,556	2,700	4,100	5,500	*	[80]
			4,000	12,000	2014	[79]
Lebanon	3,970,975	2,200	3,300	4,400	*	[80]
		812	3,114	5,416	2015	[79]
Libya	4,120,317	4,633	7,206	9,779	*	[80]
			1,685		2001	[6]
Morocco	22,898,757		18,500		*	[80]
			18,000		2011	[79]
			3,000		2013	[84]
Oman	3,453,143	2,800	4,250	5,700	*	[80]
OPT	2,652,509	1,200	1,850	2,500	*	[80]
Pakistan	114,295,357	54,000	462,000	870,000	*	[80]
		125,000	130,460	150,000	2006	[6]
			102,042		2006	[85]
			99,000		2010	[83]
			104,804		2011	[79]
Qatar	1,861,947	780	1,190	1,600	*	[80]
Saudi Arabia	21,622,717	15,172	23,600	32,028	*	[80]
			10,000		2008	[83]
Somalia	5,444,348		1,000		*	[80]
Sudan	22,599,407	24,319	37,828	51,337	*	[80]
Syria	10,881,822	4,000	6,000	8,000	*	[80]
			10,000		2011	[79]
Tunisia	7,770,711	8,462	13,163	17,864	*	[80]
			9,000		2009	[83]
		9,000	11,000		2013	[79]
UAE	7,776,519	3,200	4,800	6,400	*	[80]
Yemen	15,280,727	12,710	19,770	26,830	*	[80]

OPT: Occupied Palestinian Territories, UAE: United Arab Emirates

* The specific year of the estimate was not mentioned in the original report, but the report covered data from 1998-2005

5.3. RESEARCH PAPER 4 - MATHEMATICAL MODELLING STUDY

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Ghina Mumtaz
Principal Supervisor	Prof. Helen Weiss
Thesis Title	The Epidemiology of HIV Infection Among People Who Inject Drugs in the Middle East and North Africa

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Journal of the International AIDS Society (JAIDS)
Please list the paper's authors in the intended authorship order:	
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am first and corresponding author on this paper. I conducted all the simulations and analyses, interpreted findings, and wrote the first draft of the manuscript.

Student Signature: _____ _____ **Date:** January 10, 2017

Supervisor Signature: ___  _____ **Date:** January 10, 2017

HIV INCIDENCE AMONG PEOPLE WHO INJECT DRUGS IN THE MIDDLE EAST AND NORTH AFRICA: MATHEMATICAL MODELING ANALYSIS

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ABSTRACT

Introduction Emerging HIV epidemics have been documented among people who inject drugs (PWID) in the Middle East and North Africa (MENA). This study estimates HIV incidence among PWID that is due to sharing needles/syringes in MENA. It also delineates injecting drug use role as a driver of the epidemic in the population, and estimates impact of interventions.

Methods A mathematical model of parenteral HIV transmission among PWID was applied in the seven MENA countries with sufficient epidemiological evidence and HIV prevalence ≥ 1%. Estimations of incident and/or prevalent infections among PWID, ex-PWID, and sexual partners of infected current and ex-PWID were conducted.

Results Estimated HIV incidence rate among PWID ranged between 0.7% per person-year (ppy) in Tunisia and 7.8% ppy in Pakistan, with Libya being an outlier (24.8% ppy). The number of annual incident infections was lowest in Tunisia (n=79) and Morocco (n=99), and highest in Iran and Pakistan (about n=6,700 each). In addition, 20-2,208 and 5-837 incident annual infections were estimated across countries among sexual partners of PWID and ex-PWID, respectively. Since epidemic emergence, the number of total incident infections across countries was 706-90,015 among PWID, 99-18,244 among PWID sexual partners, and 16-4,360 among ex-PWID sexual partners. The estimated number of prevalent infections across countries was 341-23,279 among PWID, 119-16,540 among ex-PWID, 67-10,752 among PWID sexual partners, and 12-2,863 among ex-PWID sexual partners. Increasing ART coverage to the global target of 81% - factoring in ART adherence and current coverage - would avert about half of total incident infections among PWID and their sexual partners. Combining ART with harm reduction could avert as much as 90% and 70% of incident infections among PWID and their sexual partners, respectively.

Conclusions We estimated considerable HIV PWID incidence among PWID in MENA. Of all incident infections due to injecting drug use, about 75% are occurring among PWID and the rest among sexual partners. Out of all prevalent infections attributed to injecting drug use as epidemic driver, about half are among PWID, 30% among ex-PWID, and 20% among PWID/ex-PWID sexual partners. These findings call for scale up of services for PWID and their retention throughout the treatment cascade.

INTRODUCTION

As part of the global commitment to end the AIDS epidemic by 2030, the Joint United Nations Programme on HIV/AIDS (UNAIDS) stipulated the ambitious '90-90-90' target calling to diagnose 90% of all people living with HIV/AIDS (PLHIV), provide antiretroviral therapy (ART) for 90% of those diagnosed, and achieve viral suppression for 90% of those treated, all by 2020 for all countries [1]. With gaps persisting along this HIV cascade, the United Nations General Assembly agreed in 2016 that staying on the Fast-Track to ending AIDS by 2030 would only be possible if key populations at higher risk of infection (KPs) have access to comprehensive prevention services [2]. These populations and their sexual partners were estimated to account for 36% of new HIV infections globally in 2015; yet are among those with the least access to HIV prevention, care, and treatment services [2].

The Middle East and North Africa (MENA), which includes 24 countries extending from Morocco in the West to Afghanistan and Pakistan in the East, is one of the few regions where the number of new HIV infections increased between 2010 and 2015 [2]. The vast majority of these infections seem to be occurring among KPs, including people who inject drugs (PWID) and their sexual partners [2]. Emerging HIV epidemics have been recently documented among PWID in one-third of MENA countries, with a risk environment suggesting potential for further HIV spread [3, 4]. As a central population to the epidemic in several MENA countries [3], PWID are a priority population if the Fast-Track target of reducing the number of new HIV infections by 75% by 2020 is to be achieved [5].

PWID remain, globally and more so in MENA, one of the hardest-to-reach KPs. They face stigma, discrimination, and criminalization which hinder the delivery of HIV prevention, diagnosis, and treatment services. This also impedes the collection of epidemiological data to track PWID through the HIV cascade and inform policy and programs [5-8]. Despite noticeable progress in the collection of HIV prevalence data among PWID in MENA, HIV incidence data remain scarce [3]. Quantifying HIV incidence among PWID in MENA is urgently needed to provide baseline data to track progress towards UNAIDS target of reducing the number of new HIV infections.

In this study, we use mathematical modeling to estimate, at country-level in MENA, HIV incidence among PWID due to sharing non-sterile injecting equipment. We also estimate HIV incidence among sexual partners of PWID due to heterosexual sex with infected PWID, and

delineate the role of injecting drug use as a driver of the HIV epidemic in the population. Our approach is to explore and quantify HIV dynamics surrounding PWID from a comprehensive perspective that factors in the different HIV transmission pathways that are initiated by injecting drug use.

The specific objectives of our study are to estimate in each country: 1) the number of incident HIV infections among PWID and their sexual partners, 2) the total number of HIV infections that occurred among PWID and their sexual partners since the emergence of the PWID HIV epidemic, 3) the number of HIV infections among ex-PWID and their sexual partners, where ex-PWID are individuals who acquired HIV infection while injecting but are no longer injecting, and hence could be missed by programs targeting current drug users, and 4) the impact of select interventions on HIV incidence among PWID and their sexual partners.

METHODS

Description of the model

We adapted the model developed by Kwon et al [9], a mathematical model of parenteral HIV transmission among PWID, to estimate HIV incidence among PWID. The model assumes that sharing of needles/syringes occurs in groups of specific size, where PWID share in random order, and where each PWID injects once per sharing event. The model uses input data on HIV prevalence, number of times a needle/syringe is reused before disposal, and levels of effective syringe cleaning to estimate number of HIV transmissions per sharing event. The model then estimates HIV incidence in the total PWID population using data on size of the PWID population, frequency of injecting, and levels of sharing. We adapted the model by adjusting for the effect of ART and allowing heterogeneity in injecting risk behavior. We also allowed the number of times a needle/syringe is reused to be a function of the sharing group size, instead of assuming a fixed number. Further details on model structure and equations are in Additional file 1.

To account for heterogeneity in risk behavior, we assumed that the size of the sharing group in each country follows a gamma distribution. With this distribution, the majority share injections in smaller groups whereas a small fraction shares in larger groups (such as at shooting galleries). This pattern is suggested by behavioral and qualitative studies whereby injecting in larger groups has been reported in a few settings in Iran, Pakistan, and Libya; but the most common pattern, even in these countries, appears to be among closed small networks [3, 8]. In absence

of clear data to parameterize the variability in injecting risk behavior, the structure of the model was informed by data on the variability in sexual risk behavior and networking, and assumed that the variance of the gamma distribution is equal to its mean [10].

Data sources

The model parameters, their values, and justifications are listed in Table 1, and are based on recent empirical HIV natural history and epidemiology data. Whenever available, country-specific parameter values were used, as informed mainly by a recent systematic review of PWID in MENA [3]. MENA-wide aggregate data [3] and global data were used to complement country-specific data as needed (Table 1). Model fitting was used to derive one parameter, the average size of the sharing group (mean of the gamma distribution). We used a deterministic compartmental model [11] to fit the trend in HIV prevalence in two countries with sufficient available trend data (Iran and Pakistan), and then used the estimated incidence rate and the present adapted Kwon et al model to predict, using fitting, the value of the sharing group size (Table 1). The fitting was implemented by minimizing the residual sum of squares between all data points and model predictions [12].

Table 1. Model assumptions in terms of parameter values.

Parameter	Value	Source
Biological parameters		
Transmission probability per unsterile injection	0.007	Systematic review and meta-analysis [13] and long-term cohort study [14]
Transmission probability per unprotected coital act (non-commercial)	0.003	Systematic review and meta-analysis [15]
Efficacy of ART in reducing HIV transmission	0.96	Clinical trial of treatment for prevention and other observational data [16, 17]
Effectiveness of ART in reducing HIV transmission	0.69	Calculated as the product of ART efficacy and adherence
Epidemiology parameters		
Total number of PWID	See Table 2	MENA PWID data [3, 18-22]
ART coverage	See Table 2	UNAIDS country estimates for ART coverage among all people living with HIV/AIDS [23]
HIV prevalence among PWID	See Table 2	MENA PWID data [3]
HIV prevalence among sexual partners	One-third of HIV prevalence in PWID	Bio-behavioral survey in Iran [24], consistent with similar modeling work in the region [25]
Natural history parameters		
Natural mortality rate	0.02	Cohort studies [26, 27]
HIV disease mortality rate	0.091	UNAIDS data compilation [28] and cohort studies [29-31]
Behavioral parameters		
Adherence of PWID to ART	0.72	Systematic review and meta-analysis [32]
Stopping injection rate	0.10	MENA PWID data [3]
Number of years of injecting after seroconversion	4.7 years	Estimated from the natural mortality, HIV disease mortality, and stopping injection rates
Average size of sharing group	Ira: 3, Pak: 2, Others: 3	Iran and Pakistan: model fitting to epidemiological data

Parameter	Value	Source
		Others: informed by Iran and Pakistan fitted values and epidemiological data from Iran [33, 34]
Proportion of PWID who inject daily	0.50	Global survey data [9, 35]
Number of injections per PWID per day among those who inject daily	Ira: 3.3, Pak: 2.2, Others: 2.2	Iran and Pakistan: country-specific epidemiological data [3] Others: median of all MENA measures [3]
Average time between two subsequent injections for PWID who inject less frequently than daily	14 days	Global survey data [9]
Average frequency of injecting per PWID per year	Ira: 602, Pak: 402, Others: 402	Calculated as a weighted average of daily and non-daily injectors [9]
Proportion of PWID who share injections	Afg: 0.29, Egy: 0.40, Ira: 0.31, Lib: 0.45, Mor: 0.35, Pak: 0.60, Tun: 0.30	MENA PWID data [3]
Proportion of the injections that are shared for PWID who share injections	Egy: 0.62, Ira: 0.28, Mor: 0.52, Pak: 0.40, others: 0.40	Egypt, Iran, and Pakistan: country-specific epidemiological data [3] Others: calculated using MENA measures [3]
Average number of times a shared needle/syringe is used before disposal	Equal to the size of the sharing group, with a maximum value of 10	
Proportion of PWID with regular sexual partners in the last year	0.660	MENA PWID data [3]
Proportion of PWID with non-regular sexual partners in the last year	0.337	MENA PWID data [3]
Number of yearly coital acts with regular sexual partners	50	Bio-behavioral survey in Iran [24]
Number of yearly coital acts with regular sexual partners	20	Bio-behavioral survey in Iran [24]
Condom use with regular sexual partners	0.295	MENA PWID data [3]
Condom use with non-regular sexual partners	0.359	MENA PWID data [3]
Needle/Syringe cleaning parameters		
Effectiveness of needle/syringe cleaning	0.75	Modeling work [9] based on [36] and [37]
Proportion of shared injections that are cleaned	0.15	MENA PWID data [3], & modeling work [38] based on [39]

Afg: Afghanistan, ART: antiretroviral therapy, Egy: Egypt, Ira: Iran, Lib: Libya, MENA: Middle East and North Africa, Mor: Morocco, Pak: Pakistan, PWID: people who inject drugs, Tun: Tunisia

Plan of analysis

The following estimations were applied to seven MENA countries with sufficient epidemiological evidence and HIV prevalence ≥1% [3]: Afghanistan, Egypt, Iran, Libya, Morocco, Pakistan, and Tunisia. Remaining MENA countries have either zero or unknown HIV prevalence among PWID [3]. The estimations capture the different HIV transmission pathways that arise from injecting drug use in the population and that are described in Figure 1A. They include estimations of incident and/or prevalent HIV infections among PWID, ex-PWID, and sexual partners of infected current and ex-PWID. We estimated incidence due to heterosexual sex between infected PWID and their partners, and did not account for anal sex. In this study, HIV incidence was defined as the number of new HIV infections per year. Incidence *rate* was defined as the number of new HIV infections per susceptible person per year.

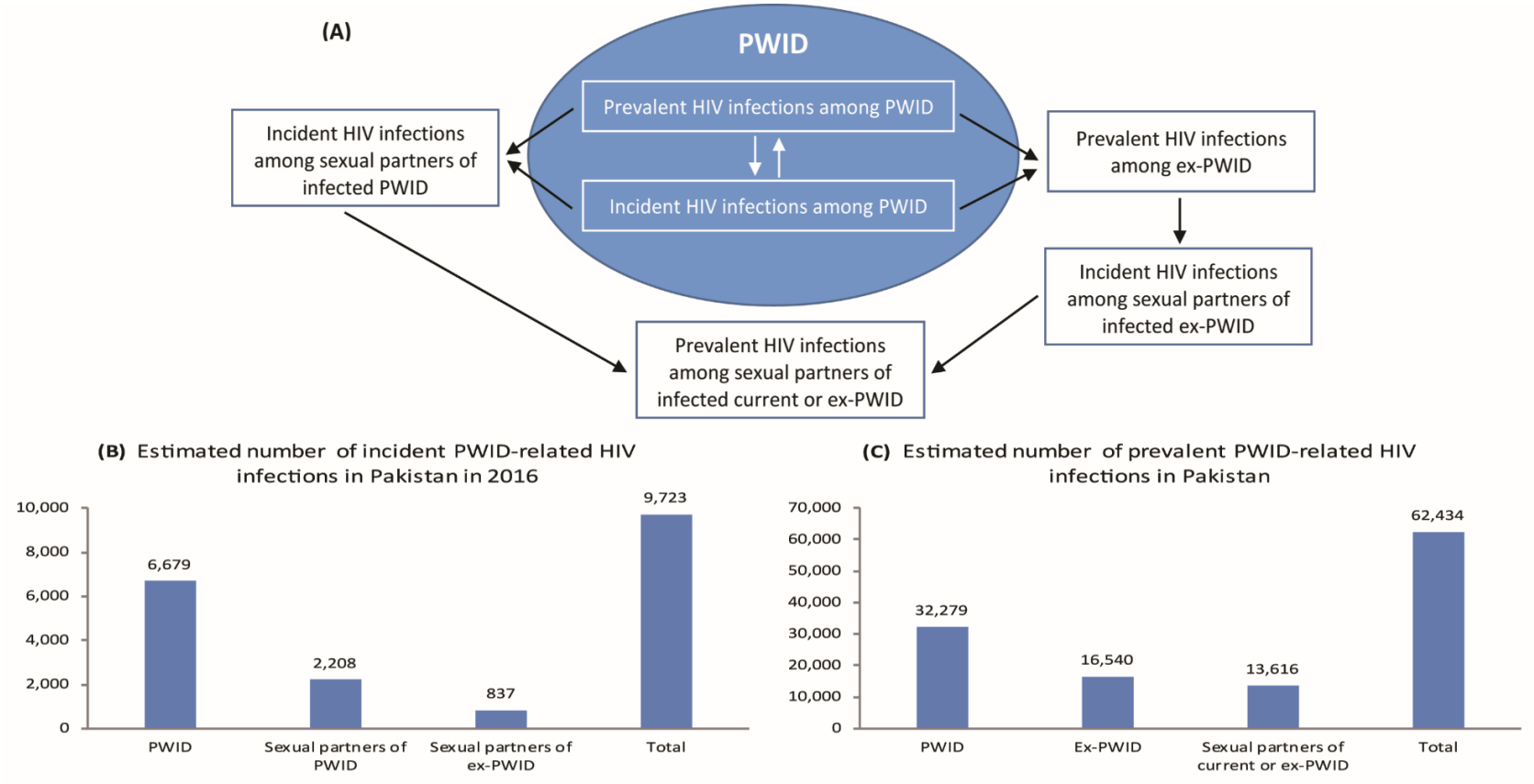

Figure 1. HIV transmission pathways in the population arising from injecting drug use. Panel (A) displays the various HIV transmission pathways that are due to injecting drug use, starting among PWID and percolation of infection to the wider non-injecting community - mainly sexual partners of current and ex-PWID. Panels (B) and (C) provide one example from Pakistan for the number of incident (B) and prevalent (C) infections that are caused by these transmission pathways and that affect the different members of the injecting and non-injecting communities.

Current year estimations

The model was applied to estimate, based on observed HIV prevalence and injecting risk data, HIV incidence for the current year (rate and number of incident infections). The estimated number of incident infections among PWID was compared to the number of incident HIV infections in the total population as estimated by UNAIDS SPECTRUM model [40]. The number of incident infections among sexual partners of PWID living with HIV for the current year was estimated using input data on the proportion of PWID who had a sexual partner in the last year, HIV prevalence among PWID and among their sexual partners, and the annual number of unprotected coital acts per partnership. Separate parameterization and estimations were made for regular and non-regular sexual partners, with their sum being reported in the results. The number of incident infections among sexual partners of infected ex-PWID were similarly estimated.

Analysis of past exposures

We estimated the total number of HIV infections that occurred since the start of the epidemic among PWID in each country. This was done by retracing the course of the HIV epidemic among PWID starting from the year of epidemic emergence, informed by epidemiological data [3] (Table 2). We started with an HIV prevalence of 1% and, in each country ran the model the number of times equal to the years since HIV epidemic emergence. HIV prevalence in each year was recalculated by adding the number of incident HIV infections in this year to the number of prevalent HIV infections from previous years, while adjusting for PWID who left injection or died from natural or HIV disease mortality.

Iterating this process over time provides an estimate for HIV prevalence in the last year. As the observed HIV prevalence in the last year tended to be higher than the estimated prevalence in that year, we increased the level of risk behavior in the first iteration, to account for higher risk behavior in earlier years of the epidemic, and used linear interpolation in order to reach observed levels of risk behavior and HIV prevalence at the last year. In Libya, the measured HIV prevalence (87% [41]) was not consistent with reported levels of current risk behavior. With these levels, the maximum HIV prevalence the model could reach was 52%; and hence, estimations of past exposures were not possible in Libya.

The past exposures model was also used to estimate the total number of incident cases that ever happened among sexual partners of infected current and ex-PWID since HIV epidemic

emergence. The prevalent number of infected individuals in the different affected population groups were also estimated (current and ex-PWID, and their partners).

Endemic HIV prevalence

We estimated HIV prevalence at endemic equilibrium among PWID at country level. This calculation is based on a generic deterministic compartmental model for HIV infection (Additional file 1). It uses input data on the estimated HIV incidence rate, rate of leaving injection, and natural and HIV disease mortality rates.

Uncertainty analysis

Multivariate uncertainty analysis was conducted to specify the range of uncertainty in the estimated HIV incidence among PWID and their sexual partners. All biological and behavioral parameters were varied within 25% of their point estimates, as a reasonable range for uncertainty, except for HIV prevalence among PWID which was varied within its measured 95% confidence intervals (Table 2). We implemented 10,000 runs of the model using Monte Carlo sampling from uniform probability distributions for the uncertainty in the parameters. 95% uncertainty intervals (UI) for the estimates were determined.

Impact of interventions

We examined the impact of several HIV interventions targeted at PWID. Specifically, we assessed the effect of: 1) Reducing current sharing of needles/syringes by 25%, 50%, and 75% on HIV incidence among PWID, 2) Expanding ART coverage among PWID based on most recent test-and-treat World Health Organization (WHO) guidelines [42, 43] to reach coverage levels of 25%, 50%, and the global target of 81% [2], on HIV incidence among PWID and their sexual partners, and 3) Increasing current condom use by 25%, 50%, and 75% on HIV incidence among sexual partners. Of note that the impact of ART is dependent on adherence and existing coverage levels in each country.

We also examined the impact of two packages that include a combination of the above interventions. These intervention packages bracket the realm of plausibility for interventions within the MENA context. The less optimistic scenario includes reducing sharing by 25%, increasing ART coverage to 50%, and increasing condom use by 25%. The more optimistic scenario includes reducing sharing by 75%, increasing ART coverage to 81%, and increasing condom use by 75%.

RESULTS

Results of all main estimations of HIV infection among PWID and their sexual partners are in Table 2. The estimated incidence rate among PWID was lowest in Tunisia and Afghanistan at 0.7% (95% UI: 0.4-1.4%) and 1.2% (95% CI: 0.8-2.4%) per person-year (ppy), respectively, and highest in Pakistan at 7.8% ppy (95% UI: 4.3-13.4). Libya, at an HIV prevalence of 87% among PWID [41], was an outlier with an estimated incidence rate of 24.8% ppy (95% UI: 13.3-41.3). The incidence rate in remaining countries was around 4% ppy. The estimated number of incident infections for the current year was lowest in Tunisia (n=79) and Morocco (n=99), and highest in Iran and Pakistan (around 6,700 each). These PWID incident infections represent over 90% of all incident cases in the total population in Iran, 39% in Pakistan, 16-21% in Tunisia and Afghanistan, and 8% in Morocco. In addition, 20-2,208 and 5-837 new infections were estimated at country-level among sexual partners of current and ex-PWID for this year, respectively (Table 2).

In total, we estimated that about 82,000-90,000 infections happened among PWID since the start of the PWID HIV epidemic in Iran and Pakistan each; over 12,250 happened in Egypt; 1,753 happened in Afghanistan; and over 760 happened in Morocco and Tunisia each (Table 2). Similarly, up to 18,244 and 4,360 HIV infections were among sexual partners of current and ex-PWID, respectively, in each of Iran and Pakistan since the start of the PWID HIV epidemic. After accounting for stopping injection and mortality, we estimated that there are currently, at country-level, 347-32,279 prevalent HIV infections among current PWID, 119-16,540 among ex-PWID, and 67-10,752 and 12-2,863 among sexual partners of current and ex-PWID, respectively. The lowest numbers of prevalent infections were in Morocco and Tunisia, while the highest were in Iran and Pakistan (Table 2). The estimated incidence rates suggest that HIV prevalence may increase in Egypt and Morocco to reach, at endemic equilibrium, 15%. Little or no further increase in HIV prevalence is predicted in the remaining countries, based on current estimated incidence rates (Table 2).

Table 2. HIV infection estimations among people who inject drugs and their heterosexual sex partners in the Middle East and North Africa.

Country		Afghanistan	Egypt	Iran	Libya	Morocco	Pakistan	Tunisia
HIV PWID epidemic characteristics								
Total number of PWID [3, 18-22]	**n**	18,820	90,809	185,000	4,446	3,000	117,632	11,000
Date of HIV epidemic emergence among PWID [3]	**Year**	2009	2008	2001	2000	2008	2004	2009
HIV epidemic state among PWID [3]	**Level-trend**	Concentrated - Emerging	Concentrated - Emerging	Concentrated - Established	Concentrated-Unknown	Concentrated - Emerging	Concentrated - Emerging	Low-level
Most recent representative HIV prevalence [3]	**%**	4.4	7.2	15.1	87.1	11.5	27.2	3.1
	(95% CI)	(3.3-5.7)	(5.2-9.6)	(13.7-16.6)	(81.5-91.9)	(9-14.5)	(26.0-28.5)	(3.1-1.9)
HIV incidence in the total population [40]	**n**	1,000	1,500	7,100	No data	1,200	17,000	500
	(range)	(500-2,700)	(1,000-2,800)	(4,400-16,000)		(1,000-1,600)	(12,000-30,000)	(200-500)
Number of PLHIV [40]	**n**	6,900	11,000	73,000	No data	24,000	100,000	2,600
ART coverage among PLHIV [23]	**%**	5.3	18.7	8.7	16.7*	36.7	6.1	28.3
Current year estimations of:								
HIV incidence rate in PWID	**% ppy**	1.2	3.8	4.4	24.8	3.7	7.8	0.7
	(95% UI)	(0.8-2.4)	(2.1-6.6)	(2.3-7.1)	(13.3-41.3)	(2.0-6.3)	(4.3-13.4)	(0.4-1.4)
HIV incidence in PWID	**n**	214	3,217	6,773	142	99	6,679	79
	(95% UI)	(124-446)	(1,639-5,847)	(3,328-11,842)	(73-262)	(49-175)	(3,369-11,997)	(41-152)
Contribution of PWID to total incidence	**%**	21.4	NA	95.4	No data	8.2	39.3	15.9
	(95% UI)	(12.4-44.6)		(46.9-100)		(4.1-14.6)	(19.8-70.6)	(8.2-30.4)
HIV incidence in sexual partners of infected current PWID	**n**	62	442	1,977	193	20	2,208	22
	(95% UI)	(33-109)	(226-787)	(1,112-3,218)	(109-311)	(11-35)	(1,239-3,566)	(10-42)
HIV incidence in sexual partners of infected ex-PWID	**n**	15	87	720	--†	5	837	6
	(95% UI)	(9-26)	(49-148)	(441-1,095)		(3-8)	(521-1,261)	(3-11)
Estimated total number of incident HIV infections, since epidemic emergence, among:								
PWID	**n**	1,753	12,257	82,069	--†	706	90,015	764
Sexual partners of infected current PWID	**n**	331	1,892	17,369	--†	99	18,244	125
Sexual partners of infected ex-PWID	**n**	54	301	4,360	--†	16	4,338	21
Estimated total number of prevalent HIV infections among:								
Current PWID	**n**	829	6,553	28,139	--†	347	32,279	341
Ex-PWID	**n**	303	1,875	14,484	--†	119	16,540	136
Sexual partners of infected current PWID	**n**	224	1,293	9,640	--†	67	10,752	84
Sexual partners of infected ex-PWID	**n**	40	219	2,692	--†	12	2,863	16
Estimated HIV prevalence at endemic equilibrium in PWID	**%**	5.3	15.2	16.9	53.9	14.9	26.8	3.4

* No data were available - the median ART coverage across all MENA countries was used
† The measured HIV prevalence in Libya was not consistent with reported levels of risk behavior; hence estimations of past exposures were not possible
CI: Confidence interval, PLHIV: people living with HIV/AIDS, PWID: people who inject drugs, pyr: per person-year, UI: Uncertainty interval

Table 3. Number and proportion of HIV infections averted due to select interventions in comparison with baseline (current year) estimations of incidence among people who inject drugs and their heterosexual sex partners in the Middle East and North Africa.

	Afghanistan	Egypt	Iran	Libya	Morocco	Pakistan	Tunisia
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
People who inject drugs							
Reducing sharing needles/syringes by 25%	53 (25)	804 (25)	1,693 (25)	36 (25)	25 (25)	1,670 (25)	20 (25)
Reducing sharing needles/syringes by 50%	107 (50)	1,608 (50)	3,386 (50)	71 (50)	49 (50)	3,340 (50)	40 (50)
Reducing sharing needles/syringes by 75%	160 (75)	2,412 (75)	5,080 (75)	107 (75)	74 (75)	5,009 (75)	60 (75)
Increasing ART coverage among PWID to 25%	30 (14)	161 (50)	810 (12.0)	9 (6.5)	NA*	909 (13.6)	NA*
Increasing ART coverage to 50%	68 (32)	798 (24)	2,053 (30)	37 (26)	12 (12)	2,112 (32)	15 (19)
Increasing ART coverage to 81%	116 (54)	1,588 (49)	3,595 (53)	71 (50)	40 (41)	3,604 (54)	36 (45)
Intervention packages:							
Less optimistic scenario†	105 (49)	1,402 (44)	3,233 (48)	63 (45)	34 (34)	3,254 (49)	31 (39)
More optimistic scenario ‡	189 (89)	2,809 (87)	5,978 (88)	125 (88)	84 (85)	5,910 (88)	69 (86)
Sexual partners							
Increasing ART coverage to 25%	8 (14)	21 (5)	228 (12)	12 (6)	NA*	289 (13)	NA*
Increasing ART coverage to 50%	19 (31)	106 (24)	581 (29)	49 (25)	2 (12)	677 (31)	4 (18)
Increasing ART coverage to 81%	33 (53)	214 (48)	1,028 (52)	95 (49)	8 (40)	1,167 (53)	10 (44)
Increasing condom use by 25%	7 (11)	47 (11)	210 (11)	21 (11)	2 (11)	234 (11)	2 (11)
Increasing condom use by 50%	13 (21)	94 (21)	421 (21)	41 (21)	4 (21)	470 (21)	5 (21)
Increasing condom use by 75%	20 (32)	142 (32)	635 (32)	62 (32)	6 (32)	709 (32)	7 (32)
Intervention packages:							
Less optimistic scenario†	24 (38)	142 (32)	731 (37)	64 (33)	4 (21)	841 (38)	6 (27)
More optimistic scenario ‡	43 (68)	288 (65)	1,337 (68)	127 (66)	12 (60)	1,506 (68)	14 (62)

ART: Antiretroviral therapy
* Baseline ART coverage is greater than 25%
† Reducing sharing needles/syringes by 25%, increasing ART coverage to 50%, and increasing condom use by 25%
‡ Reducing sharing needles/syringes by 75%, increasing ART coverage to 81%, and increasing condom use by 75%
Note: The effectiveness of ART in reducing HIV transmission is non-optimal due to adherence issues among PWID (Table 1)

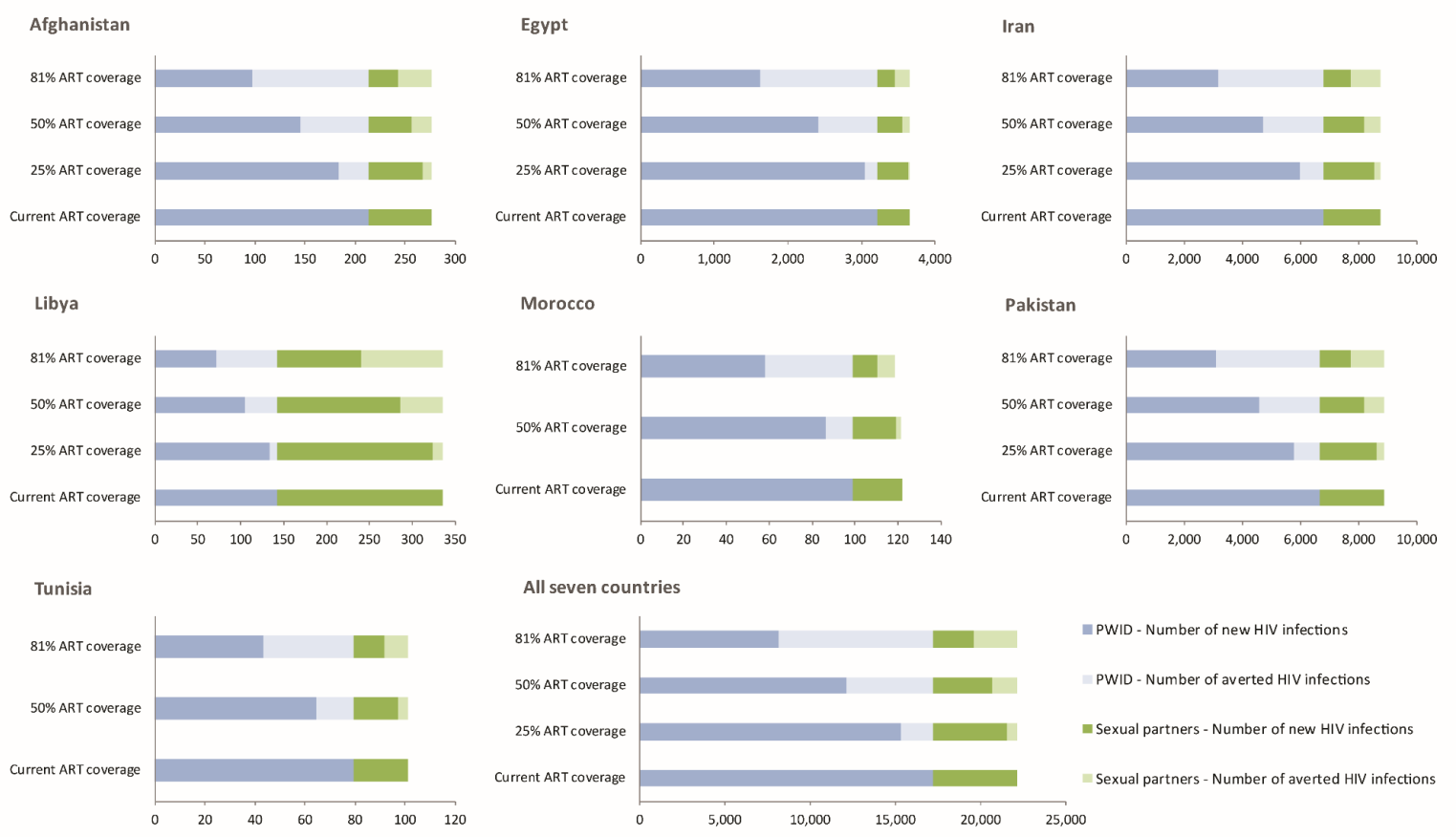

Figure 2. Effect of expanding antiretroviral therapy coverage (ART) on HIV incidence among people who inject drugs (PWID) and their heterosexual sex partners in the Middle East and North Africa (MENA). The graphs display, at various ART coverage levels, the number of new HIV infections and the number of infections averted in comparison with baseline (current year) estimations of HIV incidence among PWID and their heterosexual sex partners.

The impact of select interventions on HIV incidence among PWID and/or their sexual partners is summarized in Table 3 and Figures 2 & 3. Reducing sharing by 25%, 50%, and 75% respectively was associated with a similar proportional reduction in the number of incident infections among PWID. Reducing sharing by 25% would avert 20-53 infections per year in Afghanistan, Libya, Morocco and Tunisia; over 800 infections in Egypt; and about 1,700 infections in Iran and Pakistan each. A reduction of sharing by 75% would avert over 5,000 infections per year in each of Iran and Pakistan (Table 3).

Increasing ART coverage to 25%, 50%, and 81% of all infected PWID would reduce incidence among PWID and their sexual partners at country-level by 5-14%, 12-32%, and 40-54%, respectively (Table 3, Figure 2). In all seven countries combined, 50% ART coverage would result in 5,100 and 1,400 infections averted per year among PWID and their sexual partners, respectively (Figure 2). Increasing condom use by 25%, 50%, and 75% would result in 11%, 21%, and 32% reduction in the number of annual infections among sexual partners of PWID (Table 3).

Finally, implementing the less optimistic intervention package would avert 47% (n=31-3,254 at country-level) and 37% (n=4-481) of incident infections per year among PWID and their sexual partners, respectively, while the more optimistic scenario would avert 88% (n=69-5,978) and 68% (n=12-1,337) of these infections, respectively (Table 3, Figure 3).

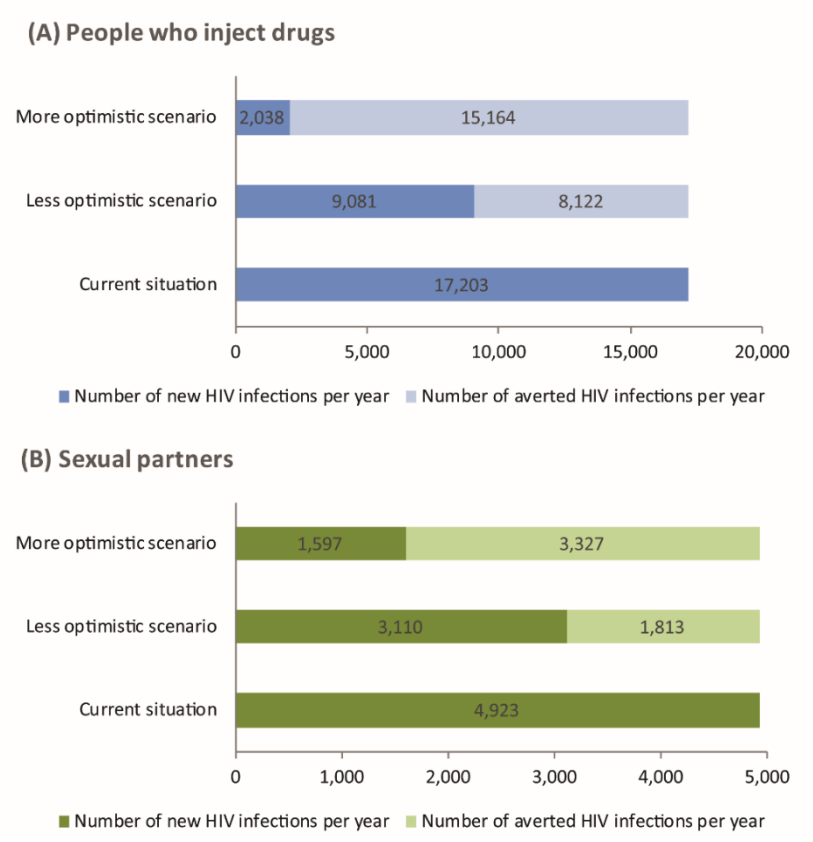

Figure 3. Effect of two comprehensive intervention packages on HIV incidence among people who inject drugs (PWID) (A) and their heterosexual sex partners (B) in all seven Middle East and North Africa (MENA) countries. The package with the less optimistic scenario includes reducing sharing by 25%, increasing ART coverage to 50%, and increasing condom use by 25%. The package with the more optimistic scenario includes reducing sharing by 75%, increasing ART coverage to 81%, and increasing condom use by 75%. The graphs display the number of new HIV infections and the number of infections averted in comparison with baseline (current year) estimations of HIV incidence among PWID and their heterosexual sex partners.

DISCUSSION

A relatively high HIV incidence rate among PWID was found in most MENA countries with at least 1% prevalence (range: 4-25% ppy), supporting recent analyses indicating concentrated and at times rapidly growing HIV epidemics among PWID [3]. A lower incidence rate of about 1% ppy was estimated in Afghanistan, where epidemiological data points to a nascent localized HIV epidemic among PWID [3], and in Tunisia where the PWID HIV epidemic appears to be at low-level [3].

Our estimates of HIV incidence among PWID are overall consistent with our epidemiological understanding of the HIV epidemic among PWID in each country [3], and are congruent with the estimated size of the epidemic and HIV incidence in the *whole population* per most recent UNAIDS SPECTRUM estimates [40]. For example, we found that PWID contribute the vast majority of HIV infections in Iran, a country with an established HIV epidemic among PWID [3, 4, 11] and where injecting drug use is the main driver of the epidemic at the national level [3, 44]. A small contribution of PWID to total HIV incidence was found in Tunisia and Morocco, which is also in agreement with our epidemiological understanding that the HIV epidemic in these two countries is mainly focused among men who have sex with men (MSM) and female sex workers and their clients, respectively [25, 45-48].

We also found that a substantial number of HIV infections in the general population are linked to infections among PWID, due to individuals who acquired the infection in the past through drug injection, but are no longer injecting, and due to onward transmission to sexual partners. We estimated that about 30% of incident HIV infections are among sexual partners of current and ex-PWID, and about half of prevalent HIV infections are among ex-PWID and sexual partners of current and ex-PWID (Figure 1B and C). Figure 1 highlights how injecting drug use drives HIV transmission not only among current PWID but also among individuals with no or no recent injecting drug use. Our findings agree with recent Mode of Transmission analyses in the region that estimated a substantial number of HIV infections among sexual partners/spouses of persons engaging in HIV high risk behavior such as PWID, clients of female sex workers, and MSM [25, 44, 47]. In Iran for example, sexual partners of PWID were found to contribute the second largest number of incident HIV infections in the population after PWID, contributing alone 12% of total incidence [44].

Since injecting drug use in MENA seems to be heavily concentrated among men [3], our findings highlight the vulnerability of PWID sexual partners who are mostly females, and often wives. Indeed, a large number of HIV infections have been documented in MENA among low-risk women who acquired the infection from their PWID husband/sexual partners [24, 49-51]. The context of sexual behavior in MENA, however, suggests limited onward transmission in the population beyond the direct spouses/sexual partners [8, 52].

Despite the growing epidemics among PWID, the region still lags behind other regions in HIV response. With a median ART coverage of 17% among PLHIV in 2015, MENA has the lowest ART

coverage globally [53], and could not reach the 2015 mid-term regional objective of 50% coverage under WHO's initiative to end MENA's HIV treatment crisis [54]. The treatment cascade among PWID seems to suggest an even harsher reality. According to unpublished data provided by the WHO, 27% of infected PWID know their status, 20% are ever enrolled in care, 4% are on ART, and it is unknown how many are virally suppressed. The striking gap between regional figures and the set 90-90-90 target is of great concern, especially in a region where the epidemic is strongly driven by injecting drug use. The punitive legal environment, stigma around HIV testing, and fear of discrimination are all challenges that hamper uptake of treatment by PWID [2]. In some settings, active injecting drug use is a criterion for ART exclusion, even after registration at a service delivery program [54]. These challenges need to be addressed to scale up testing, access to ART, and retention in care. Our study estimated that increasing ART coverage to the global target of 81% (90% of 90%), would alone avert close to half of incident infections among PWID and their sexual partners. Combining scale up of ART with harm reduction services, including needle and syringe programmes (NSP) and condom distribution, as part of an optimistic intervention package would avert close to 90% of infections among PWID and close to 70% of infections among their sexual partners (Figure 3).

Despite improvement in initiation of harm reduction services in recent years, they remain overall limited in most of MENA. By 2014, NSP were available in nine countries, and opioid substitution therapy (OST) in five [55]. Increased political will, the integration of harm reduction in national strategies, and further engagement of civil society organizations are needed to enhance and implement harm reduction approaches. Lessons could be learned from the successful experience of Iran, a leader in harm reduction in the region [55], and from other settings with similar socio-cultural background such as Malaysia and Indonesia [56, 57], to find innovative ways to integrate harm reduction services within the socio-cultural and health services framework of the region.

There were several limitations in our study. Though we used an elaborate mathematical model structure to capture the complexity of HIV dynamics, our results may depend on the type of model structure used. For example, our model did not include sexual transmission of HIV among PWID, and we did not account for onward transmission beyond the direct spouses/sexual partners. We also did not assess transmission through anal sex between infected PWID and their same-sex partners, even though behavioral data suggest not insignificant levels of male same-sex sex among PWID in MENA [3].

As with all modeling work, the robustness of our findings depend on the quality of input data. This study used the best-available data in the region, collected through the comprehensive MENA PWID systematic review [3]. Most data came from quality integrated bio-behavioral surveillance surveys (IBBSS) using state-of-the-art sampling methodologies for hard-to-reach populations and using large samples [3]. Still, many studies were limited by reliance on self-reported behavioral data. The availability and quality of data varied between countries, and there were no MENA-specific data on some parameters. There were also no country-specific data on ART coverage among PWID. For this reason, we used country-specific estimates of HIV coverage among all PLHIV [23]. Unpublished MENA-wide aggregate data suggest that ART coverage among PWID could be lower than that among PLHIV, suggesting that we may have underestimated HIV incidence. To accommodate for the uncertainty in input parameters, we conducted uncertainty analyses with wide uncertainty ranges for parameters, including non-MENA specific parameters that may not be precisely measured such as HIV transmission probability and syringe cleaning efficiency.

This study aimed to estimate incidence at national level, and hence assumed that HIV bio-behavioral data in each country is representative of the epidemic at national level, which may not be the case. For example, in Libya, the data came from one city, Tripoli [41], and the scale of the epidemic in other parts of Libya is unknown. Similarly, HIV prevalence in each of Cairo and Alexandria was 7%, but no other localities in Egypt were covered by the IBBSS [58]. In Morocco, we used average HIV prevalence of two cities where studies were conducted, and estimated an incidence rate of 3.7% ppy. Running our model separately in the two localities generated an incidence of 0.1% ppy in Tanger and 7.4% ppy in Nador, highlighting the diversity of the epidemic within Morocco (data not shown). There is however solid epidemiological evidence that the HIV PWID epidemic in both Iran and Pakistan has reached high levels at the national level.

We also assumed that current HIV prevalence is the same as the most recent representative HIV prevalence. Although this may not necessarily be true, all studies were conducted in the last few years [3]. If there have been any changes in prevalence, it is most likely to be an increase given the overall emerging nature of the HIV PWID epidemic [3], suggesting that we may have underestimated HIV incidence in some countries. In Iran and Pakistan, however, it is unlikely that there have been substantial changes in HIV prevalence. In Iran, multiple data sources

indicate an established HIV epidemic among PWID with stable prevalence of about 15% over the last few years [3, 59, 60]; while in Pakistan it is predicted that the HIV PWID epidemic may be approaching saturation [4].

Despite these limitations, this study fills an important gap in estimating HIV infection levels in MENA. HIV-related estimates in MENA are typically produced through established mathematical models that are applied globally such as UNAIDS SPECTRUM [40] and the Global Burden of Disease (GBD) models [61]. While these models provide two different approaches for HIV estimations, their focus is on total population-level estimates. For example, the GBD model uses input data from vital registration and/or antenatal care clinics, in addition to population-based surveys [61]. However, these approaches may overlook the dynamics of infection among hidden KPs such as PWID and MSM. In this study, we model HIV transmission specifically among PWID, and use quality input data derived from this same population. Such 'microscopic' approach could potentially offer more realistic estimations since it is focused on the populations where HIV is actually being transmitted. The GBD model estimated 32,190 incident HIV infections in 2015 in the whole of MENA [61], about half of UNAIDS SPECTRUM estimates for this region, a result that is not surprising given that UNAIDS SPECTRUM factors in data on KPs, in addition to other data sources [62]. In this study, we estimated over 17,000 incident infections only among PWID in seven MENA countries, suggesting that GBD may have underestimated HIV incidence in this region, and that approaches focused on total population dynamics could be missing hidden epidemics among KPs.

Though our estimates for HIV incidence among PWID were overall in line with UNAIDS estimates of total incidence in the population and with our country-specific knowledge of HIV epidemiology, there were some notable differences. For example, our estimated contribution of PWID to total incidence in Afghanistan and Pakistan was lower than expected, given that the epidemic is largely driven by injecting drug use in these countries [3]. This may suggest that UNAIDS SPECTRUM estimate for total incidence in these two countries is larger than actual incidence, or that we underestimated incidence among PWID given the relatively low levels of reported risk behavior. The potential underreporting of injecting risk behavior in Afghanistan and Tunisia could also explain the low estimated endemic HIV prevalence, whereas other prediction methods using measured levels of hepatitis C virus (HCV) suggest larger HIV epidemic potential in these countries [4]. In Egypt, our estimate of incident infections among PWID exceeded the estimated total number of infections in the population by UNAIDS. While UNAIDS

may have underestimated total incidence in this country (despite such a large PWID population), it could be also that the concentrated HIV epidemic among PWID in Egypt is limited to the two cities where the IBBSS studies were conducted. Careful triangulation of multiple sources of evidence is needed to alleviate some of these apparent contradictions, which in truth may reflect incomplete understanding of HIV epidemic dynamics [45].

In addition to providing estimates of incidence, our study provided insights into HIV epidemic dynamics among PWID. Our analyses indicated that current levels of injecting risk behavior could not explain observed prevalence nor the speed at which these epidemics rose. While it could be partially due to underreporting of risk behavior, this suggests that the epidemic was initially spreading among PWID sub-groups with higher levels of risk behavior. These findings agree with the contextual understanding of these epidemics. For example, the HIV PWID epidemics in Iran and Pakistan started in prisons, where they were ignited by limited access to clean needles/syringes and considerable levels of sharing – there are reports of syringes being reused 30-40 times in Iranian prisons [63]. In Libya, even assuming extreme levels of risk behavior at onset of epidemic, we could not retrace the course of the epidemic in this country. Although the data in Libya came from a quality IBBSS [41], the observed prevalence was extremely high (87%), one of the highest ever reported among PWID globally [41, 64]. Since PWID are a population characterized with relatively short injecting careers and high turnover, it is difficult to understand how HIV prevalence has reached such high level. Possibly, this prevalence may reflect a very recent HIV sub-epidemic among the PWID group that was sampled in Tripoli.

CONCLUSION

We estimated substantial HIV incidence among PWID in MENA. This is especially the case because some of the largest countries, such as Iran and Pakistan, are affected by large HIV PWID epidemics with high HIV prevalence. In several countries, PWID were found to contribute dominantly to HIV incidence. Concerted efforts are needed to bypass the persistent barriers from governments, society, and health systems to improve service delivery to PWID and their retention throughout the cascade [6]. Comprehensive programs that include ART, NSP, OST, voluntary testing and counselling, and prevention of sexually transmitted infections should be established and extended to include settings of vulnerability such as prisons [65].

We further estimated that for each currently infected PWID there is one other HIV infected person in the general population who acquired the infection through HIV PWID dynamics, either as an ex-PWID or as a sexual partner of current or ex-PWID (Figure 1). These populations also need to be linked to care and prevention but are usually missed by programs targeted at PWID. Innovative, context-sensitive approaches are needed to reach these populations, a large fraction of whom are women, for appropriate interventions. Recruiting sexual partners of PWID through their PWID partner could be a starting point [24]. Recruitment of ex-PWID remain a more challenging task, and service delivery models need to be explored to reach this population. Recruitment through peers or previous records at harm reduction centers could be plausible mechanisms. Also, with the availability of direct-acting antivirals, birth cohort screening for HCV infection, in countries considering such programs, may identify ex-PWID who are co-infected with HCV.

Finally, HIV surveillance among PWID must be expanded in MENA. Specifically, there is an immediate need to continue with repeated rounds of IBBSS to provide longitudinal data in countries where such surveys have been initiated, and to start implementing them in countries who still have not established a surveillance base. Where possible, inclusion of sexual partners of PWID should be considered, as well as population size estimations. Generating such strategic epidemiological data will help monitor HIV epidemics, improve quality of input data for estimation studies, guide policy and programs, and track PWID through the HIV treatment cascade.

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COMPETING INTERESTS

The authors have no competing interests to declare

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AUTHORS' CONTRIBUTIONS

GM contributed to the conception of the study, conceived and generated simulations, conducted analyses, and wrote the first draft of the manuscript. SFA contributed to the coding and simulations. HAW contributed to the conception and design of the study. LJA conceived the study and simulations, and contributed to analyses. All authors have read and agreed with the final version of the manuscript.

LIST OF ABBREVIATIONS

ART: antiretroviral therapy, GBD: Global Burden of Disease, HCV: hepatitis C virus, IBBSS: integrated bio-behavioral surveillance survey, KP: key population at higher risk of HIV infection, MENA: Middle East and North Africa, MSM: men who have sex with men, NSP: needle and syringe programme, OST: opioid substitution therapy, PLHIV: people living with HIV/AIDS,

PWID: people who inject drugs, ppy: per person-year, UI: uncertainty interval, UNAIDS: Joint United Nations Programme on HIV/AIDS, WHO: World Health Organization

5.4. SUPPLEMENTARY ONLINE MATERIAL OUTLINE

The following is the outline of the supplementary online material as cited in Research paper 4. The corresponding files are found in Appendix D.

Additional file 1. Mathematical models description and other analyses

5.5. SUMMARY OF FINDINGS

Overall high HIV incidence rates were estimated among PWID in most countries where estimations were conducted. Estimates of HIV incidence among PWID are overall consistent with our epidemiological understanding of the PWID HIV epidemic in each country as informed by Research papers 1 and 3. Injecting drug use caused a substantial number of infections among PWID since the start of the HIV epidemic among PWID at country-level.

Injecting drug use drives incidence not only among current PWID, but also among sexual partners of current/ex-PWID through onward transmission. Moreover, considerable levels of prevalent HIV infections are found among ex-PWID. For each currently infected PWID there is one other HIV infected person in the general population who acquired the infection through HIV PWID dynamics, either as an ex-PWID or as a sexual partner of a current or ex-PWID.

Increasing ART coverage, alone or in combination with harm reduction services, substantially reduces incidence among PWID and their sexual partners. The gaps in the HIV treatment cascade among PWID in MENA are enormous and call for an urgent scale up of ART and harm reduction services in order to be on track with global targets.

6. DISCUSSION

The overarching aim of this thesis was to address a gap in our understanding of HIV epidemiology among PWID in MENA. The following main research questions were addressed:

1) What is the status of the HIV epidemic among PWID in MENA?
2) What is current HIV incidence among PWID in MENA and what is the role of injecting drug use as a driver of HIV transmission in the general population in MENA?
3) Could HCV prevalence levels predict future endemic HIV prevalence among PWID?
4) What is the estimated HIV epidemic potential among PWID in MENA based on existing HCV prevalence levels?
5) What is the effect of select interventions on HIV incidence among PWID in MENA?

The first section of this chapter brings together key findings in relation to these research questions from the more extensive Discussion sections of their respective chapters. The findings are summarized under two broad themes: HIV epidemiology among PWID in MENA, and theoretical and ecological explorations of the HCV-HIV association among PWID. The implications of the findings in terms of HIV/drug use policy and programming are discussed in the second section of the chapter and in Research paper 5, which also includes a summary of the main thesis findings in terms of HIV and HCV epidemiology among PWID in MENA. Recommendations for future research are discussed and, finally, the main scientific contributions of the thesis are summarized.

6.1. SUMMARY OF FINDINGS

6.1.1. HIV epidemiology among PWID in MENA

A summary of some of the main findings and estimations in relation to HIV prevalence, incidence, epidemic state, and epidemic potential at country-level are found in Table 6.1.

A large body of evidence

Contrary to common perceptions, this thesis identified a large volume of HIV-related biological and behavioural data among PWID in MENA. Although the quantity and quality of data varied between and within countries, there is a noticeable improvement in the quality of the data over

time [86], with a number of IBBSS conducted in several countries in the last few years. These surveys used innovative sampling methodologies for hard-to-reach populations such as respondent-driven sampling and time location sampling, and benefited from overall large samples.

A pattern of emerging HIV epidemics with high incidence

There was epidemiological evidence of sufficient quality to characterize the status of the HIV epidemic among PWID in 13 of the 23 MENA countries (Figure 6.1 & Table 6.1). Rigorous methodology was used based on triangulation and synthesis of multiple sources of data and incorporating quality assessment of HIV biological data.

Evidence for HIV epidemics was found in one-third of all MENA countries, with the most common pattern being that of concentrated emerging HIV epidemics. HIV prevalence was overall in the range of 10-15%. Most of the observed epidemics are recent and evolved only in the last decade. High HIV incidence rate was estimated in almost all countries with concentrated HIV epidemics (range: 4-25% ppy), supporting the epidemiological data and observed epidemic patterns. A relatively lower incidence rate of 1.2% ppy was estimated in Afghanistan, where the epidemic seems to be recent and mainly localized in one setting. Iran is the only country where the epidemic appears to be established at a national level. Although HIV prevalence might have saturated at stable levels, HIV incidence in this country was estimated at a high of 4.4% ppy (leading to 6,773 annual incident infections), sustaining an HIV prevalence of 15%. It was estimated that injecting drug use has resulted, since HIV PWID epidemic emergence at country-level, in a large number of incident HIV infections among PWID ranging between 706 in Morocco and 82,000-90,000 in each of Iran and Pakistan.

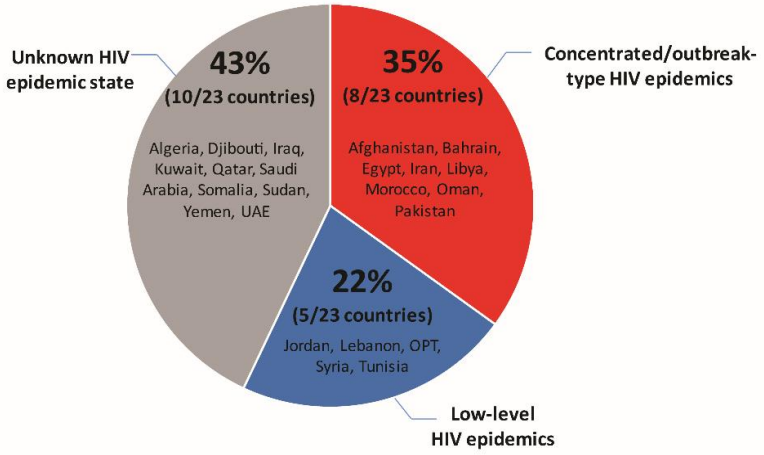

Figure 6.1. Distribution of countries by HIV epidemic state among people who inject drugs.

Table 6.1. Summary of key thesis findings: HIV prevalence, incidece, epidemic state, and epidemic potential among people who inject drugs at country-level in the Middle East and North Africa.

Epidemiological characteristics					Thesis findings and estimations						
	Reported HIV and HCV prevalence				Epidemic state				Incidence	Epidemic potential	
Country	HIV prevalence in most recent IBBSS	Number of cities/ provinces	Year of HIV estimate	Mean HCV prevalence [87]	Level of HIV prevalence	Trend in HIV prevalence	Geographical distribution	Quality & scope of evidence	Estimated HIV incidence	HIV epidemic potential[a]	Estimated endemic HIV prevalence [b]
	(%)	n (HIV % range)		(%)					(% ppy)		(%)
Iran	15.1 [88]	10 (2.0-32.0)	2010	47.1	Concentrated	Established	National	Conclusive	4.4	Low	15.7-17.0
Pakistan	25.2 (37.8[c]) [89]	16 (3.3-49.6)		60.7	Concentrated	Emerging	National	Conclusive	7.8	Low	19.9-26.8
Afghanistan	4.4 [90]	5 (0.3-13.3)[c]	2012	34.2	Concentrated	Emerging	At least localized	Good	1.2	Medium	5.3-12.5
Egypt	7.2 [73]	2 (6.5-6.8)[c]	2010	63.0	Concentrated	Emerging	At least localized	Good	3.8	High	15.2-22.7
Morocco	11.5 [91] 7.1 (3.7[c]) [92][d]	2 (0.4-25.1)[c] 1	2010-2 2013-4	57.6	Concentrated	Emerging	At least localized	Good	3.7	Medium	14.9-20.8
Libya	89.6 (87.1[c]) [93]	1	2010	94.2	Concentrated	Unknown	At least localized	Good	24.8	--	--
Bahrain	--	--	--	--	≥ Outbreak-type	--	--	Limited	--	--	--
Oman	--	--	--	--	≥ Outbreak-type	--	--	Poor	--	--	--
Jordan	0.0 [94]	3	2009		Low-level	--	--	Good	--		
Lebanon	0.0 [95]	1	2007-8	29.0	Low-level	--	--	Good	--	High	10.5-11.4
OPT	0.0 [96][d]	3	2013	43.8	Low-level	--	--	Good	--	High	14.8-15.8
Syria	--	--	--	60.5	Low-level	--	--	Limited	--	High	18.8-21.8
Tunisia	3.0 [97]	2 (0.0-2.9)[c]	2011	22.6	Low-level	--	--	Good	0.7	Medium	3.4-10.2
Saudi Arabia	--	--	--	60.5	Unknown	--	--	Poor	--	High	19.8-21.8

[a]Predictions based on HCV prevalence levels

[b]Range of estimates generated using different methodologies (predictions based on HCV prevalence data and/or predictions based on estimated HIV incidence rates)

[c]Population-adjusted estimate

[d]Updated data from IBBSS conducted after research paper 1 was published

IBBSS: Integrated bio-behavioural surveillance survey, OPT: Occupied Palestinian Territories, UAE: United Arab Emirates

NB1: The table includes countries where the status of the HIV epidemic is known or where there was sufficient data to make estimations of HIV incidence or epidemic potential

NB2: HIV incidence estimations were conducted in 7 countries where there is evidence for HIV transmission among PWID (HIV prevalence ≥ 1%)

NB3: HIV epidemic potential estimations were conducted in 10 countries with HCV prevalence data among PWID

Geographical patterns

There was sufficient evidence that the observed HIV epidemics among PWID in two countries, Iran and Pakistan, are national. A large number of geographically representative settings were included in the IBBSS in these two countries, almost all having substantial HIV prevalence [88, 89, 98-101]. In the other countries however, the HIV epidemic among PWID seems to be limited to one or two settings. For example, in Morocco, there was substantial HIV prevalence among PWID in Nador, but limited prevalence in the remaining cities [91, 102]. Similarly in Afghanistan, Herat, which is at the Iranian borders, is the only city with a large HIV epidemic among PWID [90, 103]. In Kabul, HIV prevalence seems to be consistently around 2-3% across consecutive surveys, whereas HIV prevalence in the remaining three cities was below 1% [90, 103-106]. Since this could be a reflection of the small number of sites covered by the IBBSS, the concentrated HIV epidemics in these countries was qualified as “at least localized”.

Interestingly, there appears to be links between HIV epidemics among PWID of neighbouring countries. For example, molecular epidemiology studies have linked HIV subtypes in Afghanistan, Iran, and Pakistan [107]. This suggests that strains have been circulating between these countries following drug trade routes in the region, and probably facilitated by population movements across borders such as through the return of Afghani refugees from Iran following the fall of the Taliban [107-109].

Possibility of hidden HIV epidemics

In close to half of the MENA countries, the status of the HIV epidemic among PWID remains unknown due to the lack of, or poor quality of data (Figure 6.1). In these countries, there could be undetected HIV transmission among PWID. Previous experience in MENA has proven that there could be hidden HIV epidemics that are discovered, often too late, when IBBSS are conducted. For example, the first IBBSS among PWID in Tripoli, Libya, was implemented recently in 2010, revealing a major HIV epidemic with alarming prevalence of 87% [93]. Similarly, the first IBBSS conducted in Nador, Morocco, unveiled a hidden HIV epidemic among PWID with a prevalence of 37.8% in 2008 [102], which was confirmed by a subsequent survey that found a prevalence of 25% in 2011 [91]. As mentioned above, there could also be unidentified HIV sub-epidemics in countries where the IBBSS were conducted in only a few

settings such as in Morocco and Tunisia. The possibility of hidden HIV epidemics suggests that the full scale of the epidemic among PWID at the regional level could be underestimated.

Role of prisons

There is evidence that prisons played a principal role in initiating and amplifying the HIV epidemic among PWID in Iran, and that they may have contributed to the epidemic in other countries such as Pakistan [110]. In these countries, the first major outbreaks of HIV were identified in prisons [111-117], and some of the highest HIV prevalence measures were among incarcerated PWID, reaching 24% in Iran [118] and 60% in Libya [117]. The very high HIV incidence reported among incarcerated PWID in Iran further testifies to the vulnerability of the prison environment [119]. Overcrowding, availability of drugs, sharing of injecting equipment, unprotected sex, and poor services are some of the factors contributing to the vulnerability of the prison environment in MENA [110]. Overall in the region, about two-thirds of PWID have ever been incarcerated and as many as half have ever injected while in prison [110]. Sharing of injecting equipment in prisons is common in MENA [110], and it has been reported that syringes are used 30 to 40 times in Iranian prisons before disposal [120]. The incarcerated population is overall highly mobile in MENA favouring the bridging of the infection from prisons to the wider PWID community and vice versa. This pattern in MENA is similar to that in other regions where outbreaks of HIV among prisoners, driven by injecting drug use, have been reported in multiple countries [117, 121-123].

HIV epidemic potential

In one-fifth of MENA countries, the HIV epidemic was found to be at low-level, with multiple surveys consistently reporting no or very limited HIV infections among PWID (Figure 6.1 & Table 6.1). However, the behavioural data indicates an overall high risk environment, even in countries at low-level. This suggests that if HIV is introduced into PWID, there could be large and possibly rapid HIV spread, depending on injecting networks and stochastic effects. The overlap of risk behaviour with other KPs who might be experiencing HIV epidemics, such as MSM, could also bridge the infection and ignite PWID HIV epidemics in settings with a risk environment that is favourable of epidemic expansion, as seems to have happened in Egypt.

There have been examples in the region where HIV prevalence among PWID increased considerably over a short period of time, such as in Karachi – Pakistan, where HIV prevalence

increased from near zero to 23% in less than six months [70]. This is not surprising given that when HIV prevalence was still very low in Karachi, HCV prevalence was over 85% [124, 125], indicating substantial use of non-sterile injecting equipment and suggesting connectivity of injecting networks. In Iran, the substantial HCV prevalence (up to 80%) was also predictive of the large HIV epidemic that occurred subsequently.

Within this context, this thesis made predictions of HIV epidemic potential among PWID in MENA countries using the results of an analysis of the association between HCV and HIV prevalence data (discussion in section 6.1.2 below). The main findings are summarized in figure 6.2.

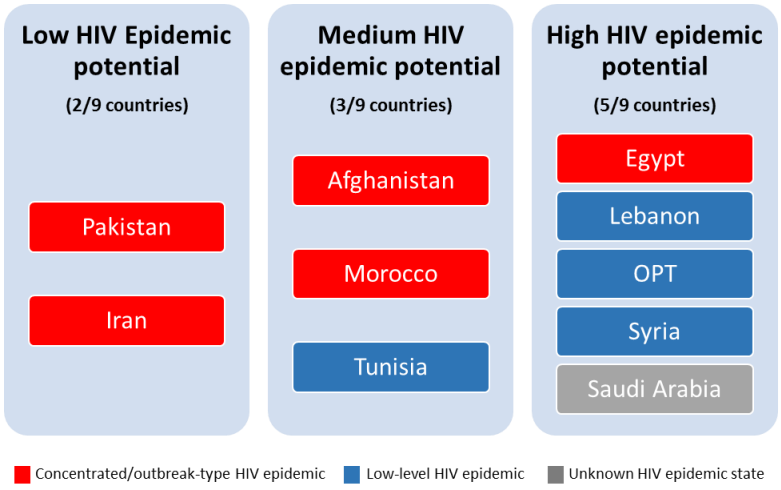

Figure 6.2. Summary of HIV epidemic potential among people who inject drugs in the Middle East and North Africa as predicted using HCV prevalence levels.

Based on existing HCV prevalence levels, there is predicted room for further HIV growth in most countries, many of whom are currently low-level HIV epidemic settings. Out of nine countries with HCV prevalence data, five have high and three moderate HIV epidemic potential, highlighting the emerging and potentially growing nature of the HIV epidemic among PWID in MENA. The high HIV incidence rate estimated in Egypt (3.8% ppy) and Morocco (3.7% ppy) suggests that the predicted HIV epidemic growth could materialize soon; whereas in Afghanistan and Tunisia, the lower estimated incidence of 1.2% ppy and 0.7% ppy, respectively, suggest that the epidemic will take longer to reach its peak, and explains why estimated endemic prevalence will be lower in these two countries.

Although HIV prevalence in Pakistan showed an increasing trend in repeated IBBSS reaching 27% in the last round [89, 99-101], predictions based on HCV prevalence data suggest that the HIV epidemic could be reaching saturation with limited potential for further growth. Still, HIV incidence rate remains considerable in such settings of high HIV prevalence. Pakistan had the highest estimated HIV incidence rate at 7.8% ppy of all MENA countries where estimations were possible (apart from the outlier case of Libya). The limited HIV epidemic potential therefore should not be interpreted as low priority for prevention interventions.

Injecting drug use as a driver of the HIV epidemic in the population

In addition to the documented growing HIV prevalence and estimated substantial HIV incidence rate among PWID in several MENA countries, injecting drug use was found to be a source of substantial number of HIV infections in the general population, due to individuals who acquired the infection in the past through drug injection but are no longer injecting, and due to onward transmission to sexual partners of PWID and ex-PWID. About half of prevalent HIV infections and 30% of incident infections that are due to injecting drug use were estimated to be found or occurring among ex-PWID and/or sexual partners of current and ex-PWID, that is among individuals with no or no recent injecting drug use. These findings agree with recent mode of transmission analyses in the region that estimated a substantial number of HIV infections among sexual partners/spouses of persons engaging in HIV high risk behaviour such as PWID, clients of FSWs, and MSM [126, 127].

Impact of interventions

The impact of select interventions, each independently and in combination, on HIV incidence among PWID and/or their sexual partners was estimated at country-level, taking into consideration ART adherence and current coverage. It was estimated that increasing ART coverage to the 2015 unmet medium-objective of 50% under WHO's initiative to end MENA's HIV treatment crisis [78] would reduce HIV incidence among PWID and their sexual partners at country-level by 12-32%. Increasing ART coverage to the global target of 81% of those living with HIV would alone avert about half of incident HIV infections among PWID and their sexual partners.

Combining scale up of ART with harm reduction services, including NSP and condom distribution, as part of an optimistic intervention package scenario was estimated to avert close to 90% of HIV infections among PWID and close to 70% of infections among sexual partners.

6.1.2. Theoretical and ecological explorations of the HCV-HIV association among PWID

This thesis investigated and characterized the poorly-understood association between HCV and HIV infections among PWID using both mathematical modelling and ecological analyses of epidemiological data.

Mathematical modelling predictions indicated a positive association between HCV and HIV prevalence at endemic equilibrium. The nature and magnitude of the association between HCV and HIV endemic prevalence varied according to six dynamical regimes depicting the overlapping epidemiology of the two infections among PWID (Figure 6.3).

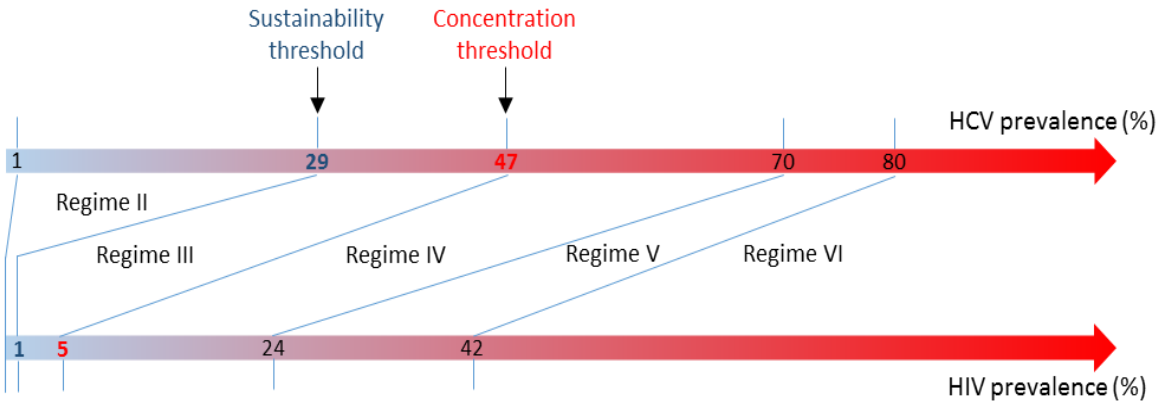

Figure 6.3. Summary of the overlapping epidemiology of HCV and HIV infections among people who inject drugs. The figures displays the different dynamical regimes and the HCV thresholds for sustainable and concentrated HIV epidemics.
(Note: Regime 1, where the prevalence of both infections is less than 1%, is not displayed on the graph)

The association was characterized by the presence of two epidemiologically and programmatically important thresholds: 1) the sustainability threshold which is the minimum HCV prevalence below which HIV will not be sustainable in a PWID population (i.e. HIV prevalence < 1%), estimated at 29% (95% UI: 21-40%), and 2) the concentration threshold which

is the minimum HCV prevalence needed for a concentrated HIV epidemic of HIV prevalence larger than 5%, estimated at 47% (95% CI: 37-57%) (Figure 6.3). These thresholds were largely insensitive to the uncertainty in biological parameters and the details of injecting risk behaviour, except near extreme values of mixing pattern and variation in risk behaviour among the different risk groups in a PWID population.

These findings indicate that HCV prevalence levels in a PWID population can predict future HIV prevalence, and the predictive association depends on the regime existing HCV prevalence levels belong to in this population. It was demonstrated that HIV prevalence predictions across the entire spectrum of HCV prevalence are overall robust with regards to behavioural uncertainty, further confirming the applicability of the concept. HCV acts like a temperature scale of the level of risk behaviour in an injecting network and can be used as an index to measure the risk and severity of potential HIV epidemics among PWID

The ecological analysis of the HCV-HIV prevalence data extracted from the conducted systematic review among PWID in MENA was in line with the above theoretical mathematical explorations. HCV prevalence was the only significant predictor of HIV prevalence in settings of established HIV epidemics where both infections are at endemic levels. Based on MENA data, a meta-analysis of the risk ratio of HCV to HIV endemic prevalence suggested that HIV prevalence will reach at endemic equilibrium about one-third of HCV prevalence in a given PWID population where HIV is introduced.

6.2. POLICY AND PROGRAMMING RECOMMENDATIONS

This thesis work filled an important gap in our understanding of HIV epidemiology among PWID in MENA. Through its comprehensive assessment and estimations of HIV epidemic scale and potential at country- and regional-levels, it provided the scientific basis for evidence-informed and data-driven policy and programming in the region. Part of the research involved partners at international organizations leading HIV efforts in the region, which facilitates dissemination of findings to national stakeholders and improves the chances of incorporating them into policy and practice [128].

One of the main findings of this research work is the documentation of the emerging HIV epidemics among PWID in several MENA countries. Since these epidemics are for the most part recent and still growing, there is a window of opportunity for prevention that should not be missed before the epidemics reach their full potential. These findings defied a general feeling of complacency in the region that is driven by the low HIV prevalence found in sporadic samples at low-risk of infection, overlooking transmission dynamics in hard to reach and stigmatized KPs where most HIV infections are happening. The documented rising HIV epidemics among PWID confront political leaders with a reality, and subsequent policy choices, that they have to face and may not afford to overlook.

Overall, the region lags behind in responding to the emerging HIV epidemics among PWID. Despite some improvements in the initiation of harm reduction services in recent years, they remain overall limited and insufficient to meet current needs. By 2014, NSP were available in nine countries, and OST in five, with only four countries having both programs operational (Table 6.2) [37]. There is an urgent need to prioritize PWID for interventions and to scale up harm reduction services. Lessons could be learned from the successful experience of Iran, the leader in harm reduction in the region [37], and of other settings with similar socio-cultural background such as Malaysia and Indonesia [129, 130], to find innovative ways to integrate harm reduction within the prevailing socio-cultural framework. Iran has the highest coverage of NSP in MENA [64, 131], and appears to be the only country to provide such services in prisons [131, 132]. Morocco is yet another example of a MENA country that has been pioneering in its HIV response and that proves that harm reduction is feasible and acceptable in this region.

Table 6.2. State of needle and syringe programs and opioid substitution therapy programs in Middle East and North Africa countries, 2014 [37].

	NSP operational	OST operational
Afghanistan	Yes	Yes
Iran	Yes	Yes
Lebanon	Yes	Yes
Morocco	Yes	Yes
Egypt	Yes	No
Jordan	Yes	No
OPT	Yes	No
Pakistan	Yes	No
Tunisia	Yes	No
UAE	No	Yes
Algeria	No	No
Bahrain	No	No
Djibouti	No	No
Iraq	No	No
Kuwait	No	No
Libya	No	No
Oman	No	No
Qatar	No	No
Saudi Arabia	No	No
Somalia	No	No
Sudan	No	No
Sudan (South)	No	No
Syria	No	No
Yemen	No	No

Source: Harm Reduction International. The Global State of Harm Reduction 2014. Found at http://www.ihra.net/files/2015/02/16/GSHR2014.pdf, Last accessed August 15, 2016. 2014.

Increased political will, the integration of harm reduction in national strategies, and further engagement of civil society organizations are needed to advocate and implement harm reduction approaches among PWID in MENA. Civil society organizations play a central and influential role in harm reduction policy development, service delivery, and community progress in the region, but need to be strengthened and further supported by local and national governments [133]. Efforts, such as through outreach and peers, need to be made to reach PWID populations that may be reluctant to approach facility-based services, and those with multiple and overlapping risks. Programs should also be extended to settings of vulnerability such as prisons, which can be a catalyst of large HIV PWID epidemics [110, 117]. Programs need to be supported on public health and human rights grounds with a need for governments to move away from law enforcement which has proven ineffective globally and also regionally [28]. One example is Libya, where the large HIV epidemic among PWID appears to have been exacerbated by restrictions imposed on the sale of needles/syringes at pharmacies in the late 1990s [63, 134].

Alongside prevention interventions, there is a pressing need to alleviate MENA's "HIV treatment crisis", as described by the WHO [78]. With a median ART coverage of 17% among people living with HIV in 2015, MENA has the lowest ART coverage of all regions globally [62]. The HIV treatment cascade among PWID shows an even harsher reality. According to unpublished data provided by the WHO, 27% of infected PWID know their status, 20% are ever enrolled in care, only 4% are on ART, and it is unknown how many are virally suppressed. These figures are very worrisome, especially in a region where the HIV epidemic is strongly driven by injecting drug use, and clearly indicate that MENA is far from the 90-90-90 target [135]. This thesis work estimated substantial reduction in HIV incidence among PWID (and their sexual partners) with scale up of ART as a standalone intervention, and more so if in combination with other prevention interventions. The punitive legal environment, stigma around HIV testing, and fear of discrimination are all challenges that hamper uptake of treatment by PWID in MENA [3] and that need to be alleviated to scale up HIV testing, access to ART, and retention in care.

The recent availability of highly effective direct-acting antivirals to treat HCV offers hope for the almost half of PWID in MENA who are infected with HCV. The planned/ongoing manufacturing of generics at affordable prices will facilitate scale-up of HCV treatment among PWID, especially in countries affected by large HCV epidemics. HCV treatment should be integrated within comprehensive intervention packages for PWID that include ART, NSP, OST, voluntary testing and counselling, and prevention of sexual transmitted infections.

In addition to PWID, this thesis highlighted the need of programs to include ex-PWID and sexual partners of PWID/ex-PWID. These two population groups acquired the infection through the dynamics of injecting drug use, but since they currently have no identifiable risk factor, are missed by programs targeted at PWID. It was estimated that for each currently infected PWID there is one other HIV infected person in the general population who acquired the infection through the dynamics of injecting drug use, and that needs to be linked to care and prevention. Innovative, context-sensitive approaches are needed to reach these populations, a large fraction of whom are women, for appropriate interventions. Peer recruitment for ex-PWID and recruitment of sexual partners/spouses through their PWID partners are plausible mechanisms.

While the immediate priority should be settings already at known high incidence and with concentrated HIV epidemics, this thesis identified settings currently at low-level HIV PWID epidemics, but whose injecting risk environment, as measured by HCV prevalence, predicts that

they might experience further HIV epidemic growth and potentially large HIV epidemics among PWID. These findings highlight the need to implement intervention packages in such settings as well (where there could be complacency in view of the current low HIV prevalence) to prevent the infection from taking root in PWID.

The concept that was proposed and demonstrated in this thesis to predict HIV epidemic potential among PWID based on existing HCV prevalence levels has important policy, programming, and resource allocation implications. Even though predictions may not be very precise, this approach can be effective in pinpointing settings that are likely to experience substantial HIV epidemics in the future, and accordingly need to be prioritized for prevention interventions. This is a simple applied tool that allows policy makers and program officers to predict HIV epidemic potential in PWID populations using measures of HCV-HIV association that enable such predictions with varying levels of precision. Using existing sources of data is particularly appealing in resource-limited settings with insufficient HIV surveillance, such as most of MENA and other regions. The application has a practical relevance which can be disseminated directly at the level of national stakeholders or in consultation with the international organizations leading the HIV/HCV response in the region (WHO, UNAIDS, and the World Bank).

6.3. RESEARCH PAPER 5 - VIEWPOINT

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SECTION A – Student Details

Student	Ghina Mumtaz
Principal Supervisor	Prof. Helen Weiss
Thesis Title	The Epidemiology of HIV Infection Among People Who Inject Drugs in the Middle East and North Africa

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

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Viewpoint

Hepatitis C virus and HIV infections among people who inject drugs in the Middle East and North Africa: a neglected public health burden?

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Introduction

People who inject drugs (PWID) are a key population at risk of hepatitis C virus (HCV) and HIV infections. Globally, 63% of PWID are HCV infected [1,2] and 19% are HIV infected [2], leading to an estimated 10 million and 3 million HCV- and HIV-infected PWID, respectively [1–3]. The Middle East and North Africa (MENA), a region comprising 23 countries from Morocco in the West to Pakistan in the East, is at the centre of major drug production and trade, creating a context of vulnerability to injecting drug use [4]. PWID in MENA are a large, mostly young and stigmatized population experiencing a substantial HCV and HIV burden, with potential for even further HIV epidemic growth. Yet, they lack access to comprehensive and confidential HCV and HIV testing, prevention and treatment services [5].

A large population at risk

MENA is home to an estimated 626,000 current PWID (range: 335,000–1,635,000) [6], with Iran, Pakistan and Egypt bearing the largest numbers [6]. The population proportion of PWID, at 0.24 per 100 adults, is comparable to global figures [2], but highest in the Eastern part of the region, such as in Iran at 0.43 per 100 adults [6].

A substantial HCV infection burden

Overall, about half of PWID in MENA are HCV infected (median: 44%; interquartile range (IQR): 31–64%), and prevalence as high as 90% has been reported among some PWID populations [6] (Figure 1). In addition to the estimated 300,000 HCV-infected current PWID [6], there could be as many as 2 million HCV-infected people who acquired the infection through past drug injection, but are no longer injecting. In the United States, for example, the number of HCV-infected previous PWID is more than seven times the number of HCV-infected current PWID [7].

The high HCV prevalence and the injecting risk behaviour environment suggest substantial ongoing HCV transmission [6]. This is affirmed by measured and estimated HCV incidence among PWID. In one study in Afghanistan, for example, an HCV incidence rate of 67 per 100 person-years (pyr) has been reported [8]. Preliminary mathematical modelling results suggest that PWID are a major driver of HCV incidence in MENA (Mumtaz *et al.*, under preparation).

Emerging and growing HIV epidemics

Recent evidence has documented HIV epidemics among PWID in one-third of MENA countries [6]. The scale of the epidemic among PWID could be underestimated as the epidemic status remains unknown in half of MENA countries [6]. In some settings, HIV prevalence has reached unprecedented levels, such as in Tripoli, Libya at 87.2% [9]. The common pattern, however, remains that of emerging concentrated epidemics such as in Afghanistan and Egypt [6]. Most epidemics occurred only in the last decade and HIV prevalence hovers around 10–15% [6].

There is also evidence for substantial HIV incidence among PWID. HIV incidence rates of 1.7 [10], 2.2 [8] and 17.2 [11] per 100 pyr have been reported in Pakistan, Afghanistan and Iran, respectively. Modelling work has estimated high incidence in Iran with the majority of infections being due to drug injection [12]. Case notifications also suggest a dominant contribution of PWID to HIV incidence in Afghanistan and Libya [6].

The early phase of the HIV epidemics and the prevalence of risky injecting and sexual practices suggest potential for further HIV epidemic growth among PWID [6]. Recent predictions suggest moderate to high HIV epidemic potential among PWID in countries such as Afghanistan, Egypt, Lebanon, Morocco, Palestine, Saudi Arabia, Syria and Tunisia [13].

Moving forward

There is an urgent need to prioritize PWID for interventions and to scale up harm reduction services in MENA. In 2014, needle/syringe exchange programmes (NSPs) were implemented in ten MENA countries, and opioid substitution therapy (OST) in six [14]. These do not include Libya and Saudi Arabia, countries with high HCV prevalence among PWID (Figure 1). Among the other countries with substantial HCV infection burden, Morocco is the only one with operational NSP and OST programmes, while in Pakistan and Egypt

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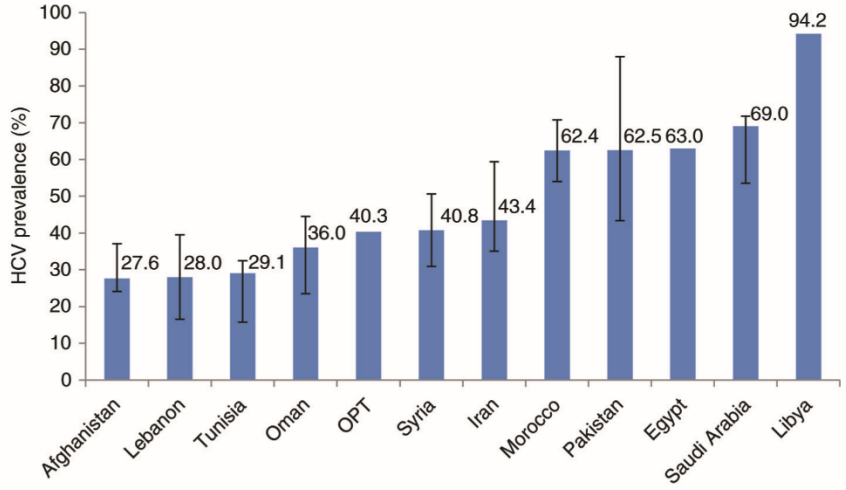

Figure 1. Median HCV prevalence among people who inject drugs in the Middle East and North Africa as per available studies [6]. Error bars represent the lower and upper bounds of the interquartile range if more than one data point was available per country.

only NSPs are provided. Iran remains the leader in harm reduction with an NSP coverage of 55–77% among PWID in 2014, and provision of OST through 4200 centres [14]. Limited funding, low and heterogeneous coverage of services, socio-cultural stigma and fear of arrest persist as major barriers for access and provision of harm reduction services [14]. MENA countries could benefit from Iran's experience in implementing harm reduction within the regional social-cultural context. With most PWID starting injecting at a young age, harm reduction should be adapted for young people and linked to other sectors such as education and employment [15].

Alongside prevention interventions, the recent availability of highly effective direct-acting antivirals to treat HCV offers hope for HCV-infected PWID. The prohibitively expensive cost of the drugs remains a major challenge for scale-up. Ensuring affordable access to treatment will only be possible with generic competition or with substantial price reductions on existing or upcoming drugs such as the 99% price discount negotiated by Egypt [16] and a similar discount negotiated recently by Pakistan. Generics are planned to be manufactured within the region, such as in Egypt and Morocco. Generics are being produced in India for as little as $750 for a full treatment course, and production costs may go down to $100 within a few years [17]. As the first Global Health Sector Strategy on Viral Hepatitis is being drafted, concerted efforts are needed for the development of National Strategic Plans for Viral Hepatitis, and possibly Viral Hepatitis Programmes, at country level in MENA, as is already materializing in a few countries including Bahrain, Egypt, Lebanon and Iran. Such programmes can furnish the logistical framework for supporting HCV-related services among PWID through initiatives including testing, treatment and optimally harm reduction, in tandem with National AIDS Control Programme services.

As for HIV treatment, much remains to be accomplished in a region that has one of the lowest antiretroviral therapy (ART) coverages worldwide with a median coverage of 16% (IQR: 6–17%) [18]. Limited HIV testing, the cost of ART to burdened health care systems, and poor access are obstacles for ART uptake and scale-up [19]. The median prevalence of lifetime HIV testing among PWID is 33% (IQR: 16–56%), and is very low in many countries with concentrated HIV epidemics such as in Afghanistan, Pakistan and Egypt [6]. While Voluntary Counselling and Testing (VCT) has been initiated in most countries, uptake of services has been overall weak, partially because of weak non-governmental organizations (NGO) involvement, limited engagement of PWID, and social stigma [5]. Morocco is one exception where the strong civil society has facilitated broad and sizable access to VCT services for different populations [5]. Provision and access to HCV testing is even more limited because of the poor commitment to HCV treatment. Managing the structural barriers of social stigma, poverty, homelessness, criminalization and incarceration will facilitate both HIV and HCV testing, treatment and prevention scale-up for PWID in MENA [20].

Conclusions

There is a large marginalized population of over half a million PWID in MENA, half of whom are already HCV infected. There is also a larger population of HCV-infected previous injectors who are progressing through the natural course of disease without knowing the status of their infection or the opportunity of treatment. PWID in MENA are also enduring rising HIV epidemics, some of which have already reached high HIV prevalence. Advantage should be taken from the global momentum for tackling viral hepatitis, and courageous decisions are needed at the national level to develop or expand programmes that can tackle HCV and HIV public health burden among PWID. Scale-up of treatment and harm reduction services should be a main pillar of such programmes, alongside innovative strategies to overcome the challenges imposed by social stigma and criminalization.

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Competing interests
The authors have no competing interests to declare.

Authors' contributions
GM wrote the first draft of the manuscript. All authors provided critical input to the manuscript and approved the final version.

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6.4. RECOMMENDATIONS FOR FUTURE RESEARCH

This thesis identified a large volume of HIV epidemiological data that enabled the objectives of the PhD to be addressed, but also identified limitations and gaps in the available literature, and highlighted ways to improve future research including data collection and reporting.

One the most striking issues identified during the thesis is the magnitude of the gaps in the HIV treatment cascade among PWID in the MENA region. Generation of this cascade by WHO was challenging due to the scarcity of the data that quantifies the different steps of the cascade in the vast majority of countries. There is a need to expand data collection and routine monitoring along the continuum of care (HIV testing, linking to care, ART administration, and adherence), to implement CD4 testing and to track viral suppression (currently almost absent), and to improve country reporting mechanisms. There is also a need for research, at country-level, looking into the barriers to testing, linkage to care, and retention in care [78], to improve on the treatment cascade. This includes investigation of systemic and structural barriers such as criminalization, police practices, stigma and discrimination – even in health care settings and by health care providers, referral mechanisms, coordination between NGOs (points of testing) and care services, exclusion of active PWID from ART, drugs stock outs, among others [78, 136].

With regards to sero-surveys, there has been a recent noticeable improvement in the quality of HIV bio-behavioural data with the recent conduct of multiple IBBSS using state of the art sampling methodologies and using large samples. However, HIV surveillance in the region needs to be further expanded and improved. IBBSS were conducted in ten out of 23 countries, with repeated rounds available in six of them. Within the context of emerging HIV epidemics among PWID, and with over half of countries still lacking any data to inform the status of the HIV PWID epidemic, there is an urgent need to further develop HIV surveillance through the conduct of IBBSS in the region. This includes implementing subsequent rounds in countries that have already established their surveillance base to generate time trends, and conducting first rounds in settings where such surveys have not been conducted yet.

A number of suggested improvements could be made to the study design and instruments of surveys in the region. One of the main issues encountered was the inclusion, in the sample of many studies, of non-injecting drug users, with results of both injectors and non-injectors being reported aggregately. In such cases, to maximize the number of studies included in Chapter 2

systematic review, while at the same time minimizing bias, only studies where over 50% of the sample consisted of PWID were eligible for inclusion. It is necessary that future studies restrict their samples to PWID or, alternatively, stratify results by injectors versus non-injectors. The definition of PWID also varied across studies. Some defined PWID as persons who have injected a non-therapeutic drug in the past month, others in the past two months, six months, or in the past year. These inconsistencies make comparison between studies, and synthesis of findings across studies, more difficult. It would be beneficial if UNAIDS/WHO can lead a process to harmonize risk group definitions for use of these definitions in all IBBSS.

Other suggested improvements in data collection tools and/or reporting include more precise specification of: 1) type of behaviour (such as distinguishing between receptive and distributive sharing of needles/syringes and distinguishing between sharing and reuse), 2) time frame of behaviour (such as when sharing occurred: last act, ever, last month…), 3) denominators in reported proportions (such as whether the denominator is all PWID or only those sexually active when reporting the prevalence of condom use), and 4) missing data. It would also enhance the usability of data, particularly for mathematical modelling parameterization, if some key continuous variables (such as the frequency rate of injections, the duration of injecting career, the number of sexual/injecting partners…) are reported using summary measures of continuous data (medians, means, quartiles…) instead of using categories which are usually inconsistent between studies and also not optimal for modelling studies.

Although the evidence suggests that injecting drug use in MENA is heavily concentrated among men, data on women who inject drugs are very limited. Women who inject drugs are one of the most stigmatized and hidden populations, and hence could be under-represented and underestimated in epidemiological PWID studies in MENA. A global review has identified that women comprise one third of PWID, with data suggesting higher HIV prevalence among women compared with men PWID [137]. Little is known about their risk practices, vulnerabilities, and HIV infection burden in MENA. Trying to reach and include women who inject drugs in future IBBSS in MENA is important to advocate for programs tailored for their needs [137].

The thesis work identified gaps in some key indicators for monitoring, evaluation, and modelling studies. Although mapping exercises have been recently conducted in a few countries such as Pakistan [85, 138] and Morocco [84], many countries have no or no recent national estimates on the number and proportion of PWID. The quality and methodology used to derive some of

the available PWID population size estimates are also unknown. PWID population size estimates are needed for a better estimation of HIV infection burden and for informing policy on the scale of PWID prevention and treatment services in the region. Other key indicators of importance for modelling studies and which are currently limited include the number of sharing partners per PWID (size of sharing network), number of acts of sharing per partner, frequency of coital acts within sexual partnerships (heterosexual and male same sex sex), among others.

The proposed methodology of using HCV prevalence as a predictor of future HIV spreads calls for the need to collect quality and representative HCV prevalence data among PWID. This could be done by including HCV serology in HIV IBBSS among PWID. Although cost and tight budget are one of the main considerations when implementing IBBSS in the region, the additional suggested HCV test is ultimately cost-effective, as it enables predictions of future HIV epidemic scale, and helps prioritize most-at-risk PWID populations which significantly improves the cost-effectiveness of interventions [139].

Finally, there is a need in MENA to complement the bio-behavioural data with qualitative research that focuses on the social and cultural aspects that affect exposure, risk-taking, and care seeking. Mapping and ethnographic studies are needed for a better understanding of the profile and injecting/sexual networks of PWID, and to investigate the social and structural determinants of the infection in this hidden KP in this region [140]. Such evidence is central to inform policy, and to design and implement interventions that are tailored to specific settings of risk and vulnerability. Mathematical modelling studies could be implemented to estimate the impact of social policy change on curbing the spread of the emerging HIV epidemics among PWID in MENA.

6.5. MAIN SCIENTIFIC CONTRIBUTIONS OF THESIS

This thesis addressed a neglected area of research concerned with a culturally sensitive infection, HIV, in a hidden and stigmatized population, PWID, within the specific context of MENA - a region that includes about 10% of the world's population and that has several social and structural vulnerabilities for HIV. Multiple methodologies were used to answer the various research questions, including systematic review and data synthesis, statistical analysis, and different mathematical modelling approaches. The research work undergone has applied, theoretical, and policy and programming contributions listed below:

Applied epidemiology contributions

- Challenged a widely-held misperception that there are limited data on HIV in the MENA region, particularly among KPs
- Identified, analysed, and synthesised a large volume of HIV-related data among PWID in MENA, including unpublished key and novel national data - access to which was facilitated by WHO, UNAIDS and World Bank - these data appeared in the scientific literature for the first time (in Research paper 1)
- Provided the first systematic review and comprehensive characterization of the status of the HIV epidemic among PWID at the regional level
- Provided a detailed analysis and summary of HIV epidemiology among PWID at country-level in MENA
- Facilitates, through the large database of HIV biological and behavioural country-specific data it compiled, the conduct and parameterization of mathematical modelling studies in the region, such as the one in Research paper 4
- Used at country-level in MENA, a mathematical model specifically designed to estimate HIV transmission among PWID, unlike HIV-related estimations in the region which typically produce estimates through mathematical models that focus on total population level dynamics
- Not only estimated HIV incidence among PWID, but also delineated and quantified the role of injecting drug use as a driver of HIV infection in the wider population, namely through history of past injection and onward transmission to sexual partners

- Qualified and quantified future HIV epidemic growth among PWID in MENA using HCV prevalence as a proxy biomarker of risk, thus complementing the behavioural data that suggest a high risk environment and hence potential for further growth

Theoretical epidemiology contributions

- Investigated and characterized the poorly-understood association and epidemiologic overlap between HCV and HIV infections among PWID, through both mathematical and epidemiological/statistical analyses
- Demonstrated a powerful concept of using data on one infection, HCV, to estimate the future size of epidemics of another infection, HIV, among PWID, hence providing theoretical foundation for an innovative approach to identify PWID populations at high risk of future HIV epidemic expansion
- Provided an independent estimate of the HCV to HIV infectiousness ratio, a key epidemiological parameter of interest in its own and also critical to the parametrization of HIV/HCV mathematical models
- Provided important insights into HIV epidemic dynamics among PWID, particularly in relation to injecting risk behaviour dynamics and how it drives the emergence of HIV PWID epidemics

Policy and programming contributions

- Provided a comprehensive characterization of the status and potential future scale of HIV epidemics among PWID, one of the pivotal risk groups for HIV transmission in MENA, thus informing HIV policy and programming nationally and regionally and providing a strategic framework for future HIV scientific and intervention efforts
- Highlighted a window of opportunity for prevention, given that the documented epidemics are recent and most often in their early phase
- Provided baseline HIV incidence data among PWID to track progress towards the global and regional targets of reducing the number of new HIV infections
- Estimated HIV infection levels among ex-PWID who are no longer injecting and HIV transmission to sexual partners of PWID/ex-PWID; two population groups that are usually missed by programs targeted at PWID but who need to be linked to care and prevention

- Provided a tool, using HCV data, for policy makers and program managers to identify PWID populations who should be prioritized for HIV/drug prevention and treatment interventions, hence improving the cost-effectiveness of interventions.
- Maximized the use of existing sources of data (HCV prevalence data) to make future predictions of HIV epidemic scale, an application particularly appealing in resource-limited settings such as most of MENA
- Highlighted countries where the HIV epidemic among PWID is still at low-level or has just emerged, but where HIV prevalence is predicted to grow, highlighting the need to prioritize these PWID populations for prevention interventions to be ahead of the growing epidemics
- Estimated the impact of select interventions on HIV incidence among PWID and their sexual partners, thus guiding the formulation of prevention and treatment efforts in the region
- Provided a scientific basis to advocate for appropriate interventions and mobilization of resources targeted specifically to the needs of PWID (and their sexual partners) in MENA, who remain marginalized, with poor support networks, and poor access to HIV testing, prevention, and treatment services
- Provided a scientific basis to advocate for more leadership and political action to manage the HIV epidemic and increase commitment to HIV/AIDS surveillance among and beyond PWID

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8. APPENDICES

8.1. APPENDIX A – RESEARCH PAPER 1 SUPPLEMENTARY ONLINE MATERIAL

Outline

Text S1
PRISMA Checklist

Section/topic	*#*	*Checklist item*	*Subsection (paragraph number)*
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	All
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	All
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	(1-4)
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	(5)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Study selection (1-3)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Data sources and search strategy (1-3)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Text S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Study selection (1-3)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Data extraction (1-2)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Study selection (1)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Scope and quality of the evidence (1-2)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Analysis (1-4)
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Scope and quality of the evidence (1, 4)

Section/topic	*#*	*Checklist item*	*Subsection (paragraph number)*
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results of search strategy (1), Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Scope and quality of the evidence (2), Table S1 and S2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 1-6, Tables S1-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Scope and quality of the evidence (1, 3-4)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	Injecting drug use in MENA (1), Emerging HIV epidemics and HIV epidemic potential among PWID (1-3), Bridging of the HIV epidemic to other population groups (1-2)
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	Study limitations (1-2)
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusion (1-4)
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	52

Text S2
Search criteria

The following criteria were used to search the different data sources.

Pubmed

("Drug Users"[Mesh] OR "Substance Abuse, Intravenous"[Mesh] OR "Needle Sharing"[Mesh] OR "Heroin Dependence"[Mesh] OR Drug use*[Text] OR Drug-use*[Text] OR Substance abuse*[Text] OR Drug abuse*[Text] OR Drug-abuse*[Text] OR Injecting-drug use*[Text] OR Intravenous-drug use*[Text] OR Injection-drug use*[Text] OR IDU*[Text] OR IVDU*[Text] OR Drug addict*[Text] OR Drug dependen*[Text]) **AND** ("Middle East"[Mesh] OR "Islam"[Mesh] OR "Arabs"[Mesh] OR "Arab World"[Mesh] OR "Africa, Northern"[Mesh] OR "Sudan"[Mesh] OR "Somalia"[Mesh] OR "Djibouti"[Mesh] OR "Pakistan"[Mesh] OR "Middle East"[Text] OR "Middle-East"[Text] OR "North Africa"[Text] OR "North-Africa"[Text] OR "EMRO"[Text] OR "Eastern Mediterranean"[Text] OR “Arab”[Text] OR “Arabs”[Text] OR “Arab World”[Text] OR "Islam"[Text] OR "Afghanistan"[Text] OR "Algeria"[Text] OR "Bahrain"[Text] OR "Djibouti"[Text] OR "Egypt"[Text] OR "Jordan"[Text] OR "Kuwait"[Text] OR "Lebanon"[Text] OR "Libya"[Text] OR "Iran"[Text] OR "Iraq"[Text] OR "Morocco"[Text] OR "Oman"[Text] OR "Pakistan"[Text] OR "Qatar"[Text] OR "Saudi Arabia"[Text] OR "Somalia"[Text] OR "Sudan"[Text] OR "Syria"[Text] OR "Tunisia"[Text] OR "United Arab Emirates"[Text] OR "Dubai"[Text] OR "Abu Dhabi"[Text] OR "Abu-Dhabi"[Text] OR “Sharjah”[Text] OR "West Bank"[Text] OR "Ghaza"[Text] OR "Palestine"[Text] OR"Yemen"[Text])

Embase

(exp drug abuse/ or exp substance abuse/ or exp drug dependence/ or exp heroin dependence/ or (drug use* or drug abuse* or drug addict* or drug dependen* or IDU* or IVDU*).mp.) AND (exp Middle East/ or exp North Africa/ or exp Arab/ or exp Afghanistan/ or exp Djibouti/ or exp Pakistan/ or exp Somalia/ or exp Sudan/ or Middle East.mp. or North Africa.mp. or EMRO.mp. or Eastern Mediterranean.mp. or Arab.mp. or Arabs.mp. or Arab World.mp. or Islam.mp. or Afghanistan.mp. or Algeria.mp. or Bahrain.mp. or Djibouti.mp. or Egypt.mp. or Jordan.mp. or Kuwait.mp. or Lebanon.mp. or Libya.mp. or Iran.mp. or Iraq.mp. or Morocco.mp. or Oman.mp. or Pakistan.mp. or Qatar.mp. or Saudi Arabia.mp. or Somalia.mp. or Sudan.mp. or Syria.mp. or Tunisia.mp. or United Arab Emirates.mp. or Dubai.mp. or Abu Dhabi.mp. or Sharjah.mp. or West Bank.mp. or Ghaza.mp. or Palestine.mp. or Yemen.mp.)

Regional databases

WHO African Index Medicus: Free text search using each MENA country name
WHO Index Medicus for the Eastern Mediterranean Region: A keyword search of “injecting” and a keyword search of “HIV”

Conference abstracts

Free text search using each MENA country name

Text S3
Narrative justification for quality of the evidence and status of the epidemic at the country level

This text relates to Table 5 in main manuscript. Countries are sorted by level of HIV prevalence, trend in HIV prevalence, geographical distribution, quality and scope of evidence, then alphabetical order.

Iran

The number of studies conducted is the largest in MENA and the number of HIV prevalence measures is also substantial, being the second largest after Pakistan. The geographical coverage of conducted studies is national, with a large number of cities/provinces represented. Two rounds of surveillance have also been conducted in 2006 and 2010 which included up to 10 cities each, had a large sample size, and used the probability-based time-location sampling technique. In total, about half of HIV prevalence measures in Iran were from studies using probability-based sampling methodologies and the vast majority had high precision.

The first HIV outbreaks among PWID in Iran were reported around 1996, and it is only in the early 2000s that HIV prevalence started increasing considerably to reach a peak by the mid-2000s (Figure 3A). HIV transmission among PWID after 2005 is still ongoing and seemingly at high levels, but a trend of increasing HIV prevalence does not seem to be apparent. Injecting drug use remains the major mode of transmission in notified HIV cases at 60% in 2011. The totality of the evidence suggests that the HIV epidemic among PWID in Iran is now established at concentrated levels of about 15%.

Pakistan

The number of studies and of HIV prevalence measures is substantial, the latter being the largest in MENA. The geographical coverage of conducted studies is national, with a large number of cities/districts represented. Over one-third of studies conducted included multiple locations. The quality of HIV prevalence measures is good: two-thirds were from studies using probability-based sampling techniques, over half reached their target sample size, and the overwhelming majority had high precision. Pakistan had also four rounds of repeated integrated bio-behavioral surveillance surveys (IBBSS), the highest number in MENA. These surveys used multi-stage cluster sampling, included up to 16 cities per round, and were preceded and informed by ethnographic mapping.

The totality of the evidence indicates that after almost two decades of very limited HIV prevalence among PWID, a trend of increasing prevalence started to be observed after 2003 (Figure 3B). One incidence study conducted in 2002 among PWID in three cities reported an HIV incidence rate of 1.7 per 100 person-years. The trend of increasing HIV prevalence seems to be ongoing, reaching over 40% in several studies, and with no evidence of stabilization or peak in the most recent studies. The trend of an emerging epidemic is also manifest in the repeated rounds of IBBSS using standard and state of the art methodology: HIV prevalence among PWID has steadily increased from 10.8% in 2005, to 15.8% in 2006, to 20.8% in 2008, and reached 25.2% in 2011. There is conclusive evidence of a concentrated emerging HIV epidemic among PWID at the national level in Pakistan.

Afghanistan

A number of well-designed studies have been conducted in Afghanistan, some with respondent-driven sampling (RDS) and others with thoughtful convenience sampling using a variant of time-location sampling. Two round of IBBSS have been implemented in 2009 and 2012. Data are available from four main cities in Afghanistan and overall all studies were adequately powered.

Although data from the earlier years of the epidemic are not available, the first studies conducted in 2005-8 reported low HIV prevalence among PWID at 0-3%. However, a substantial increase in HIV prevalence reaching up to 18% in one city, Herat, was reported in the IBBSS conducted in 2009 and confirmed in the second round at 13.3%. HIV incidence among PWID in Kabul in 2008 was also reported at 2.2 per 100 person-years, despite 72% reported use of harm reduction services among participants.

The totality of the evidence suggests that the epidemic in Afghanistan is recent, emerging in the last few years, and has reached concentrated levels in at least some parts of Afghanistan. Herat is close to the Afghani-Iranian border and molecular investigations have found the same HIV variants among PWID in Iran and in Kabul, Afghanistan, far away from the Iranian border. This suggests that the virus may have been introduced by the return of Afghani refugees from Iran. Iran had already a large HIV epidemic among PWID since the early 2000s. More data and from other cities are needed to confirm the observed trends at the national level.

Egypt

The number of studies conducted is small, but overall of good quality. Prominently, two rounds of repeated IBBSS were conducted. These were adequately powered and used the state of art sampling methodology of RDS. In addition, there is a large number of HIV prevalence measures that were extracted from databases.

The totality of the evidence indicates very limited HIV prevalence among PWID for about two decades, including in the first round of IBBSS in 2006, but a noticeable increase reaching about 7% in the most recent round of surveillance in 2010. Available HIV prevalence measures however cover mainly the two largest cities in Egypt and therefore the evidence cannot be generalized to the national level. Nonetheless, an emerging epidemic among PWID is also apparent in HIV case notification reports whereby 19.6% of notified HIV cases in 2010 were due to injecting drug use, compared to 1.6% of the total notified cases since the beginning of the epidemic until 2008. More data and from various parts of the country are needed to confirm the observed emerging epidemic among PWID at the national level.

Morocco

The number of studies conducted in Morocco is small, but of relatively good quality. With the exception of one point-prevalence measure in the 1990s with unclear methodology and quality, the recent studies conducted in 2008 and 2011 are well-designed, well-powered, and used RDS as a sampling strategy. There is also a number of HIV prevalence measures from databases, including voluntary counseling and treatment (VCT) data and data from sentinel surveillance.

Overall, the data indicate very low HIV prevalence among PWID until recently, starting 2008, when both VCT data and the well-designed RDS studies started to indicate substantial prevalence, particularly in one city, Nador, where HIV prevalence has been reported at 25-38%. It is worth noting that HIV prevalence in the other cities included in the recent RDS studies is still at zero prevalence, suggesting that the epidemic in Morocco is only emerging and still highly localized. The recent nature of the epidemic is also confirmed by HIV case notifications, whereby the contribution of injecting drug use to notified cases in 2011 was only 1.2%. More data and from various parts of the country are needed to confirm the observed trends at the national level.

Libya

Libya has just completed its first study investigating the epidemiology of HIV among PWID. This study is the first round of a planned IBBSS, used RDS, and had a large sample size. There is in addition two data points that were extracted from the various databases. Though the methodology of these data points is unclear, they indicated substantial HIV prevalence at 22.0% and 59.4%, suggesting major outbreaks of HIV among PWID in Libya possibly around the beginning of the last decade or even earlier. These data are now confirmed by the noted first round of IBBSS which reported an alarming HIV prevalence of 87.1% among PWID in Tripoli, the highest prevalence reported in MENA. The evidence therefore is indicative of a concentrated HIV epidemic among PWID in at least part of Libya. Though the epidemic in Tripoli with all likelihood is an established epidemic, the level of evidence overall is not enough to characterize whether the national epidemic is emerging, with few outbreaks in the past; or has been established for some time now with endemic HIV transmission among PWID. The good quality data is restricted to one city, Tripoli, and therefore more data are needed from various parts of the country to indicate whether there is a concentrated epidemic among PWID at the national level.

Bahrain

There is a number of HIV prevalence measures, the vast majority of which are from databases and therefore of unclear methodology and quality. There is only one study which was conducted and for which a report was available. This study had a large sample size and was conducted in a voluntary drug treatment center. It reported a prevalence of 21.1% in Manama in the early 90s. The data from the databases also indicated some HIV spread among PWID in Bahrain with prevalence rates reaching up to 8%. This is further reflected in HIV case notification reports, whereby in 2010, 37.5% of notified HIV cases were due to injecting drug use, suggesting ongoing transmission. The totality of the evidence suggests that there are at least some pockets of HIV among PWID in Bahrain, but the type and quality of available evidence is not enough to indicate whether there is a concentrated epidemic, even if localized.

Oman

There is a number of HIV prevalence measures, the vast majority of which are from databases and therefore of unclear methodology and quality. There is only one study which was conducted and for which a report was available, but with high risk of bias in all domains, including self-reported HIV prevalence. However, the reported HIV prevalence in this study, and

the data extracted from the databases, indicate substantial levels of HIV prevalence reaching up to 27%. Still, the contribution of injecting drug use to the total notified HIV cases remains small at 4.3% until the end of 2011. The totality of the evidence therefore suggests that there have been at least some pockets of HIV among PWID in Oman, but the type and quality of available evidence is not sufficient to indicate whether there is a concentrated epidemic, even if localized.

Jordan

There is a number of HIV prevalence measures from databases starting from 1990, in addition to one round of IBBSS in 2009 that used RDS and covered four cities. All prevalence measures indicated zero prevalence among PWID. This is further reflected in case notifications whereby in 2011, 0% of the notified HIV cases were due to injecting drug use. The totality of the evidence therefore suggests that the HIV epidemic among PWID in Jordan is a low-level epidemic.

Lebanon

The number of HIV prevalence measures in Lebanon is small, but includes a round of IBBSS that used RDS and was conducted in 2007-8. The study found zero HIV prevalence among PWID. Although this study failed to reach its target sample size, possibly due to disconnectivity in the PWID networks in this country, all the other data available, whether from studies or databases, report very low HIV prevalence among PWID. This is also reflected in the HIV case notifications, whereby in 2011, 2% of notified cases were due to injecting drug use. The totality of the evidence therefore points towards a low-level HIV epidemic among PWID in Lebanon.

Occupied Palestinian Territories (OPT)

The number of HIV prevalence measures among PWID in the OPT is very small, but includes a first round of IBBSS that used RDS. The study found no infections among PWID in East Jerusalem, suggesting that the epidemic is at low-level. Also, only 2.8% of notified AIDS cases until the end of 2011 were due to injecting drug use. More data and from various parts of the country are needed to confirm this low-level epidemic state at the national level.

Tunisia

Two rounds of IBBSS have been conducted among PWID in Tunisia in 2009 and 2011. The studies had a large sample size and used RDS. They reported an HIV prevalence of 3.1% and 2.4%, respectively. The several HIV prevalence measures extracted from databases indicate

limited prevalence since 1992. Still, by the end of 2009, 24.4% of all notified cases were due to injecting drug use, suggesting that HIV transmission is ongoing among PWID in Tunisia. The totality of the evidence therefore suggests that although the HIV epidemic among PWID in Tunisia appears to be a low-level epidemic, there could be somewhat significant ongoing HIV transmission among PWID. This low-intensity epidemic however does not appear to have reached high enough levels to be qualified as a concentrated epidemic.

Syria

A number of HIV prevalence measures among PWID in Syria are available from databases from 1988 and until 2007. All of them indicate zero prevalence. In addition, there is one study which was conducted in Damascus using snow-ball sampling. The study reported a prevalence of 0.5%. The limited HIV prevalence among PWID is confirmed in case notifications whereby in 2011, 0% of the notified HIV cases were due to injecting drug use. The totality of the evidence therefore suggests that the HIV epidemic among PWID in Syria is a low-level epidemic. More data and from various parts of the country are needed to confirm this epidemic state at the national level.

Table S1. Precision and risk of bias of individual HIV prevalence measures among predominantly male people who inject drugs in the Middle East and North Africa as extracted from eligible reports

Country	Year	HIV prevalence (%)	Precision	Risk of bias		
				HIV ascertainment	Sampling	Response rate
Afghanistan	2012	13.3 [1]	Good precision	Low ROB	Low ROB	Low ROB
	2012	2.4 [1]	Good precision	Low ROB	Low ROB	Low ROB
	2012	0.3 [1]	Good precision	Low ROB	Low ROB	Low ROB
	2012	1.0 [1]	Good precision	Low ROB	Low ROB	Low ROB
	2012	0.9 [1]	Good precision	Low ROB	Low ROB	High ROB
	2009	18.2 [2]	Good precision	Low ROB	Low ROB	High ROB
	2009	3.2 [2]	Good precision	Low ROB	Low ROB	Low ROB
	2009	1.0 [2]	Good precision	Low ROB	Low ROB	High ROB
	2007-9	2.1 [3]	Good precision	Low ROB	Low ROB	Unclear
	2006-8	3.2 [4]	Good precision	Low ROB	Low ROB	Unclear
	2006-8	0.0 [4]	Low precision	Low ROB	Low ROB	Unclear
	2006-8	0.0 [4]	Good precision	Low ROB	Low ROB	Unclear
	2005-6	3.0 [5]	Good precision	Low ROB	Low ROB	Unclear
Bahrain	1991	21.1 [6]	Good precision	Low ROB	High ROB	Low ROB
Egypt	2010	6.5 [7]	Good precision	Low ROB	Low ROB	Low ROB
	2010	6.8 [7]	Good precision	Low ROB	Low ROB	Low ROB
	2008-11	1.4 [8]	Good precision	Low ROB	High ROB	Unclear
	2006	0.6 [9]	Good precision	Low ROB	Low ROB	Low ROB
	1994	0.0 [10]	Good precision	Low ROB	High ROB	Unclear
	--	0.0 [11]	Low precision	Low ROB	High ROB	Unclear
	--	7·6 [12]	Low precision	Low ROB	High ROB	Unclear
	--	0·0 [13]	Low precision	Low ROB	High ROB	Unclear
Iran	2012-3	7.7 [14]	Good precision	Low ROB	High ROB	Unclear
	2011	2.9 [15]	Good precision	High ROB	High ROB	Unclear
	2010	31.9 [16]	Good precision	Low ROB	High ROB	Unclear
	2010	26.4 [16]	Good precision	Low ROB	High ROB	Unclear
	2010	23.9 [16]	Good precision	Low ROB	High ROB	Unclear
	2010	18.3 [16]	Good precision	Low ROB	High ROB	Unclear
	2010	16.8 [16]	Good precision	Low ROB	High ROB	Unclear
	2010	9.4 [16]	Good precision	Low ROB	High ROB	Unclear
	2010	7.0 [16]	Good precision	Low ROB	High ROB	Unclear
	2010	6.2 [16]	Good precision	Low ROB	High ROB	Unclear
	2010	3.6 [16]	Good precision	Low ROB	High ROB	Unclear
	2010	2.2 [16]	Good precision	Low ROB	High ROB	Unclear
	2010	9.4 [17]	Good precision	Low ROB	High ROB	Low ROB
	2009-10	9.9 [18]	Good precision	Low ROB	High ROB	Unclear
	2009	1.2 [19]	Low precision	Low ROB	High ROB	Unclear
	2009	1.0 [19]	Good precision	Low ROB	High ROB	Unclear
	2009	1.7 [19]	Good precision	Low ROB	High ROB	Unclear
	2009	3.5 [19]	Good precision	Low ROB	High ROB	Unclear
	2009	1.5 [19]	Good precision	Low ROB	High ROB	Unclear
	2008-9	1.1 [20]	Good precision	Low ROB	High ROB	Unclear
	2008-9	6.4 [21]	Good precision	Low ROB	High ROB	Unclear
	2008	18.8 [22]	Good precision	Low ROB	High ROB	Unclear
	2008	0.7 [23]	Good precision	Low ROB	Low ROB	Low ROB
	2007-8	3.7 [24]	Good precision	Low ROB	High ROB	Unclear
	2007-8	2.4 [25]	Good precision	Low ROB	High ROB	Unclear
	2007-9	18.2 [26]	Low precision	Low ROB	High ROB	Unclear
	2007	6.6 [27]	Good precision	Low ROB	Low ROB	Unclear
	2007	30.0 [28]	Low precision	Low ROB	High ROB	Unclear
	2006-7	10.7 [29]	Good precision	Low ROB	High ROB	Unclear
	2006	24.4 [30]	Good precision	Low ROB	High ROB	Low ROB
	2006-7	8.2 [31]	Good precision	Low ROB	Low ROB	Unclear
	2006-7	24.7 [31]	Good precision	Low ROB	Low ROB	Unclear

Country	Year	HIV prevalence (%)	Precision	Risk of bias		
				HIV ascertainment	Sampling	Response rate
	2006-7	20.8 [31]	Good precision	Low ROB	Low ROB	Unclear
	2006-7	30.5 [31]	Good precision	Low ROB	Low ROB	Unclear
	2006-7	6.5 [31]	Good precision	Low ROB	Low ROB	Unclear
	2006-7	4.2 [31]	Good precision	Low ROB	Low ROB	Unclear
	2006-7	35.7 [31]	Good precision	Low ROB	Low ROB	Unclear
	2006-7	11.6 [31]	Good precision	Low ROB	Low ROB	Unclear
	2006-7	2.1 [31]	Good precision	Low ROB	Low ROB	Unclear
	2006-7	14.4 [31]	Good precision	Low ROB	Low ROB	Unclear
	2006-7	25.0 [32]	Good precision	Low ROB	Low ROB	Unclear
	2005-6	47.7 [33]	Good precision	Low ROB	High ROB	Unclear
	2004	6.3 [34]	Good precision	Low ROB	High ROB	Unclear
	2004	0.8 [35]	Good precision	Low ROB	High ROB	Low ROB
	2004-5	72.1 [36]	Low precision	Low ROB	High ROB	Low ROB
	2004	23.2 [37]	Good precision	Low ROB	High ROB	Low ROB
	2003-6	45.7 [38]	Low precision	Low ROB	High ROB	Unclear
	2003	14.0 [39]	Good precision	Low ROB	High ROB	Unclear
	2003-4	15.2 [40]	Good precision	Low ROB	High ROB	Unclear
	2003	24.0 [41]	Good precision	Low ROB	High ROB	Low ROB
	2003	22.0 [41]	Good precision	Low ROB	High ROB	Low ROB
	2003	9.7 [42]	Low precision	Low ROB	High ROB	Unclear
	2002-6	18.0 [43]	Good precision	Low ROB	High ROB	Unclear
	2002	15.1 [44]	Good precision	Low ROB	Low ROB	Unclear
	2002-3	18.2 [45]	Low precision	Low ROB	Low ROB	Unclear
	2002-4	35. 7[46]	Good precision	Low ROB	High ROB	Unclear
	2002	0.7 [47]	Good precision	Low ROB	Low ROB	Unclear
	2001-2	7.8 [48]	Low precision	Low ROB	High ROB	Unclear
	2001-2	17.0 [48]	Good precision	Low ROB	Low ROB	Unclear
	2001-6	1.6 [49]	Good precision	Low ROB	High ROB	Unclear
	2001-6	12.7 [50]	Good precision	Low ROB	High ROB	Unclear
	2001-3	67.5 [51]	Good precision	Low ROB	High ROB	Unclear
	2001-2	0.0 [52]	Good precision	Low ROB	High ROB	Unclear
	2001-2	6.9 [52]	Good precision	Low ROB	High ROB	Low ROB
	2001	19.2 [53]	Good precision	Low ROB	High ROB	Unclear
	2000-5	25.8 [54]	Low precision	Low ROB	High ROB	Unclear
	1998	1.2 [55]	Good precision	Low ROB	High ROB	Unclear
	1996	0.0 [56]	Good precision	Low ROB	Low ROB	Unclear
		41.7 [57]	Good precision	Low ROB	High ROB	Unclear
	--	0.0 [58]	Low precision	Low ROB	Low ROB	Unclear
	--	20.5 [59]	Good precision	Low ROB	Low ROB	Unclear
	--	8.8 [60]	Low precision	Low ROB	High ROB	Unclear
Jordan	2009	0. 0 [61]	Good precision	Low ROB	Low ROB	Unclear
	2009	0.0 [61]	Low precision	Low ROB	Low ROB	Unclear
	2009	0.0 [61]	Low precision	Low ROB	Low ROB	Unclear
Lebanon	2007-8	0.0 [62]	Low precision	Low ROB	Low ROB	High ROB
	2000-2	0.0 [63]	Low precision	Low ROB	High ROB	Unclear
Libya	2010	87.1 [64]	Good precision	Low ROB	Low ROB	Low ROB
Morocco	2011-12	25.1 [65]	Good precision	Low ROB	Low ROB	Low ROB
	2010-11	0·4 [65]	Good precision	Low ROB	Low ROB	Low ROB
	2008	0.0 [66]	Unclear	Low ROB	Unclear	Unclear
	2008	37.8 [66]	Good precision	Low ROB	Low ROB	Unclear
	1991-9	33.0 [67]	Good precision	Low ROB	High ROB	Unclear
Oman	--	12.0 [68]	Low precision	High ROB	High ROB	High ROB
	--	27.0 [68]	Low precision	High ROB	High ROB	High ROB
	--	18.0 [68]	Low precision	High ROB	High ROB	High ROB
OPT	2010	0.0 [69]	Good precision	Low ROB	Low ROB	Unclear
Pakistan	2011	49.6 [70]	Good precision	Low ROB	Low ROB	Low ROB
	2011	52.5 [70]	Good precision	Low ROB	Low ROB	Low ROB
	2011	46.2 [70]	Good precision	Low ROB	Low ROB	High ROB

Country	Year	HIV prevalence (%)	Precision	Risk of bias		
				HIV ascertainment	Sampling	Response rate
	2011	30.8 [70]	Good precision	Low ROB	Low ROB	Low ROB
	2011	24.9 [70]	Good precision	Low ROB	Low ROB	Low ROB
	2011	3.3 [70]	Good precision	Low ROB	Low ROB	Low ROB
	2011	14.9 [70]	Good precision	Low ROB	Low ROB	High ROB
	2011	40.6 [70]	Good precision	Low ROB	Low ROB	Low ROB
	2011	16.0 [70]	Good precision	Low ROB	Low ROB	High ROB
	2011	42.2 [70]	Good precision	Low ROB	Low ROB	Low ROB
	2011	18.6 [70]	Good precision	Low ROB	Low ROB	Low ROB
	2011	19.2 [70]	Good precision	Low ROB	Low ROB	Low ROB
	2011	7.9 [70]	Low precision	Low ROB	Low ROB	High ROB
	2011	20.0 [70]	Good precision	Low ROB	Low ROB	High ROB
	2011	7.1 [70]	Good precision	Low ROB	Low ROB	Low ROB
	2011	21.4 [70]	Good precision	Low ROB	Low ROB	Low ROB
	2009	8 [71]	Good precision	Low ROB	High ROB	Low ROB
	2009	52 [71]	Good precision	Low ROB	High ROB	Low ROB
	2009	23 [71]	Good precision	Low ROB	High ROB	Low ROB
	2009	21 [71]	Good precision	Low ROB	High ROB	Low ROB
	2008	13 [72]	Good precision	Low ROB	High ROB	Low ROB
	2008	10 [72]	Good precision	Low ROB	High ROB	Low ROB
	2008	41 [72]	Good precision	Low ROB	High ROB	Low ROB
	2008	18.6 [73]	Good precision	Low ROB	Low ROB	Low ROB
	2008	12.3 [73]	Good precision	Low ROB	Low ROB	Low ROB
	2008	30.5 [73]	Good precision	Low ROB	Low ROB	Low ROB
	2008	23.1 [73]	Good precision	Low ROB	Low ROB	Low ROB
	2008	14.5 [73]	Good precision	Low ROB	Low ROB	Low ROB
	2008	28.5 [73]	Good precision	Low ROB	Low ROB	Low ROB
	2008	12.8 [73]	Good precision	Low ROB	Low ROB	High ROB
	2008	22.8 [73]	Good precision	Low ROB	Low ROB	Low ROB
	2007	2.6 [74]	Good precision	Low ROB	Low ROB	Unclear
	2007	0.0 [74]	Good precision	Low ROB	Low ROB	Unclear
	2006-7	1.4 [75]	Low precision	Low ROB	Low ROB	High ROB
	2006-7	13.3 [75]	Good precision	Low ROB	Low ROB	Low ROB
	2006-7	1.0 [75]	Good precision	Low ROB	Low ROB	Low ROB
	2006-7	29.8 [75]	Good precision	Low ROB	Low ROB	Low ROB
	2006-7	30.1 [75]	Good precision	Low ROB	Low ROB	Low ROB
	2006-7	6.5 [75]	Good precision	Low ROB	Low ROB	Low ROB
	2006-7	16.5 [75]	Good precision	Low ROB	Low ROB	Low ROB
	2006-7	0.0 [75]	Good precision	Low ROB	Low ROB	Low ROB
	2006-7	2.2 [75]	Good precision	Low ROB	Low ROB	High ROB
	2006-7	9.5 [75]	Good precision	Low ROB	Low ROB	High ROB
	2006-7	51.3 [75]	Good precision	Low ROB	Low ROB	Low ROB
	2006-7	5.3 [75]	Good precision	Low ROB	Low ROB	Low ROB
	2005	0.0 [76]	Unclear	Low ROB	High ROB	Unclear
	2005	9.5 [77]	Good precision	Low ROB	Low ROB	Unclear
	2005	2.5 [77]	Good precision	Low ROB	Low ROB	Unclear
	2005	12.0 [77]	Good precision	Low ROB	Low ROB	Unclear
	2005	1.0 [77]	Good precision	Low ROB	Low ROB	Unclear
	2005	13.3 [78]	Good precision	Low ROB	Low ROB	Low ROB
	2005	25.3 [78]	Good precision	Low ROB	Low ROB	Low ROB
	2005	3.8 [78]	Good precision	Low ROB	Low ROB	Low ROB
	2005	0.3 [78]	Good precision	Low ROB	Low ROB	Low ROB
	2005	0.4 [78]	Good precision	Low ROB	Low ROB	High ROB
	2005	9.5 [78]	Good precision	Low ROB	Low ROB	High ROB
	2005	19.2 [78]	Good precision	Low ROB	Low ROB	Low ROB
	2004	23.1 [79]	Good precision	Low ROB	Low ROB	Low ROB
	2004	0.5 [79]	Good precision	Low ROB	Low ROB	Low ROB
	2004	24.0 [80]	Low precision	Low ROB	High ROB	Unclear
	2004-5	26.0 [81]	Good precision	Low ROB	Low ROB	Unclear

Country	Year	HIV prevalence (%)	Precision	Risk of bias		
				HIV ascertainment	Sampling	Response rate
	2004-5	0.5 [81]	Good precision	Low ROB	High ROB	Unclear
	2004	8.3 [82]	Good precision	Low ROB	High ROB	Unclear
	2003	0.3 [83]	Good precision	Low ROB	High ROB	Unclear
	2003	0.6 [84]	Good precision	Low ROB	High ROB	Low ROB
	2003	0.0 [85]	Good precision	Low ROB	High ROB	Unclear
	2003	0.0 [85]	Low precision	Low ROB	High ROB	Unclear
	2003	9.7 [86]	Good precision	Low ROB	High ROB	Unclear
	2002	0.0 [87]	Low precision	Low ROB	High ROB	Unclear
	2002	3.4 [88]	Good precision	Low ROB	High ROB	Unclear
	2002	0.0 [89]	Good precision	Low ROB	High ROB	Unclear
	1999	0.0 [90]	Good precision	Low ROB	High ROB	Unclear
	1996	0.4 [91]	Good precision	Low ROB	High ROB	High ROB
	1994	0.0 [92]	Good precision	Low ROB	High ROB	Unclear
	1987-4	0.0 [93]	Low precision	Low ROB	High ROB	Unclear
	--	37.2 [94]	Low precision	Low ROB	High ROB	Unclear
	--	0.0 [95]	Good precision	Low ROB	Unclear	Unclear
Syria	2006	0. 5 [96]	Good precision	Low ROB	High ROB	Unclear
Tunisia	2011	2.9 [97]	Good precision	Low ROB	Low ROB	Low ROB
	2011	0.0 [97]	Good precision	Low ROB	Low ROB	High ROB
	2009	3.1 [98]	Good precision	Low ROB	Low ROB	Unclear

OPT: Occupied Palestinian Territories, ROB: Risk of Bias

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Table S2. Summary of precision and risk of bias of HIV prevalence measures as extracted from eligible reports

	n	%*
Precision of estimates		
High precision	159	83.7
Low precision	29	15.3
Missing	2	1.1
Risk of bias quality domains		
HIV ascertainment		
Low risk of bias	186	97.9
High risk of bias	4	2.1
Unclear	--	--
Sampling methodology		
Low risk of bias	100	52.6
High risk of bias	88	46.3
Unclear	2	1.1
Response rate		
Low risk of bias	64	33.7
High risk of bias	20	10.5
Unclear	106	55.8
Total	190*	100.0

	n	%
Low risk of bias		
In at least one quality domain	186	97.9
In at least two quality domains	117	61.6
In all three quality domains	47	24.7
High risk of bias		
In at least one quality domain	104	54.7
In at least two quality domains	5	2.6
In all three quality domains	3	1.6

* Out of a total of 190 HIV prevalence measures among predominantly male PWID

Table S3. Subnational estimates of the number and prevalence of people who inject drugs in the Middle East and North Africa

Country	City/province	Year	N (range)	% (range)	Source
Afghanistan	Mazar-i-Sharif, Kabul, Jalalabad	2006-7	1,465 (55-1,251)	0.22 (0.15-0.24)	[1]
	Herat	2012	1,211		[2]
	Jalalabad	2012	1,471		[2]
	Kabul	2012	12,541		[2]
	Mazar-i-Sharif	2012	1,496		[2]
Egypt	Greater Cairo	--	85,000		[3]
Iran	Hamadan	2012	11,333		[4]
	Hormozgan	2006		0.1	[5]
	Kerman city	--	1,640 (1,368-1,911)		[6]
	Kerman city	--	3,805 (57-11,254)		[6]
	Kermanshah	2006		0.7	[7]
	Khoshropdpey	2003		0.0	[8]
	Tehran	2006		1.0	[5]
Pakistan	19 cities	2011	46,351 (39,793-52,896)	0.37	[9]
	8 cities	2005	24,390 (20,770-28,010)	0.47	[10]
	Bannu	2006	250	0.08	[11]
	Faisalabad	2005	(2,400-2,550)		[12]
	Faisalabad	2006	8030	1.07	[11]
	Gujranwala	2005	(466-607)		[12]
	Gujranwala	2006	2650	0.62	[11]
	Hyderabad	2006	2600	0.66	[11]
	Islamabad	2006		5.9	[13]
	Karachi	2006	9000	0.25	[11]
	Kech	2007		0.4	[14]
	Lahore	2005	(1,754-2,110)		[12]
	Lahore	2006	3350	0.18	[11]
	Larkana	2006	800	0.65	[11]
	Mandi Bahauddin	2005	(713-928)		[12]
	Multan	2006	900	0.21	[11]
	Peshawar	2006	150	0.04	[11]
	Quetta	2006	150	0.07	[11]
	Rawalpindi	2005	(348-451)		[12]
	Rawalpindi	2006	123	0.02	[11]
	Sarghoda	2005	(1,000-1,100)		[12]
	Sarghoda	2006	2450	0.87	[11]
	Sheikhukupura	2005	(367-460)		[12]
	Sialkot	2005	(600-800)		[12]
	Sukkur	2006	1350	0.59	[11]
Tunisia	Bizerte	2112	654		[15]
	Tunis	2012	1,573		[15]

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Table S4. HIV point-prevalence measures among people who inject drugs as extracted from various databases including the US Census Bureau database, the WHO/EMRO testing database, the UNAIDS epidemiological fact sheets databases, and other sources of data with unidentified reports

	Afg	Bah	Dji	Egy	Irn	Irq	Jor	Kuw	Leb	Lib	Mor	Oma	OPT	Pak	SA	Sud	Syr	Tun	Yem
Year	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1984																			
1987																			
1988									103 (3.9)								51 (0.0)		
1989		728 (7.8)		1932 (0.2)										97 (0.0)					
1990		1436 (2.9)			135 (0.0)		240 (0.4)												
							24 (4.2)												
1991		609 (2.1)		122 (0.0)	579 (0.2)			840 (0.4)						18 (0.0)					
				72 (0.0)															
				50 (0.0)															
1992		393 (1.0)		266 (0.8)	2098 (0.1)		4 (100.0)							24 (0.0)			963 (0.1)	801 (1.6)	
				106 (2.8)															
				4 (0.0)															
1993		139 (1.4)		75 (1.3)	1295 (0.2)	(0.0)	26 (0.0)	208 (1.0)	46 (2.2)					698 (0.3)			157 (0.0)	822 (1.1)	
				616 (0.0)															
				214 (0.0)															
1994		191 (1.6)		385 (0.0)	349 (0.3)	(0.0)		59 (0.0)	32 (3.1)					342 (0.0)			1419 (0.1)	1224 (0.9)	
				102 (0.0)													1379 (0.3)		
1995		183 (0.0)		1085 (0.0)	1232 (0.0)	(0.0)		110 (0.0)	15 (0.0)					703 (5.4)			834 (0.0)	1571 (0.7)	
																	165 (0.0)		
1996		439 (1.1)	(0.0)	96 (0.0)	2747 (5.7)	(0.0)		172 (0.6)						19 (0.0)			153 (0.0)	1518 (1.0)	
														113 (1.8)					
														242 (0.4)					
														19 (0.0)					
1997		350 (0.0)		138 (0.0)	34120 (1.8)	(0.0)		94 (0.0)						32 (0.0)		(0.1)	314 (0.0)	584 (0.3)	
				438 (0.0)															

	Afg	Bah	Dji	Egy	Irn	Irq	Jor	Kuw	Leb	Lib	Mor	Oma	OPT	Pak	SA	Sud	Syr	Tun	Yem
Year	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1998		336 (0.9)	(0.0)	96 (0.0)	8202 (0.5)	(0.0)		181 (0.0)		400 (0.5)			28 (0.0)	25 (0.0)			1299 (0.0)		13 (0.0)
		128 (2.3)			2827 (12.6)														
1999		78 (0.0)	(0.0)	88 (0.0)	8000 (0.1)	(0.0)		74 (0.0)				135 (5.2)	1 (0.0)	37 (0.0)			595 (0.0)		3 (0.0)
		334 (0.0)		176 (0.0)				(0.0)				(5.0)					301 (0.0)		
2000		291 (0.3)	(0.0)	369 (0.0)	7200 (0.2)			(0.0)				58 (5.5)		207 (0.0)			525 (0.0)		2 (0.0)
2001		158 (1.3)	(0.0)	580 (0.0)	3714 (1.6)			166 (0.6)		(59.4)		73 (5.5)		1516 (0.0)			375 (0.0)		2 (0.0)
														(1.0)					
2002		124 (7.3)	(0.0)	488 (0.0)	76 (19.7)		54 (0.0)	126 (0.0)				34 (8.8)		423 (0.0)			120 (0.8)		
					(29.9)							(5.0)							
												(11.8)							
												(18.6)							
2003		203 (1.5)		512 (0.0)	1688 (14.2)		160 (0.6)	31 (0.0)				93 (1.1)		641 (3.3)	(0.0)		237 (0.0)		
2004		309 (1.3)		342 (0.0)	1705 (7.4)		93 (0.0)	191 (1.6)		(22.0)	19 (5.3)	155 (1.9)		87 (0.0)			258 (0.0)		
				353 (0.0)	(18.0)									395 (26.3)					
														3154 (8.3)					
2005	338 (3.6)	265 (1.1)		293 (0.0)	761 (13.7)		217 (0.0)				133 (0.0)	194 (1.0)		(12.1)			456 (0.0)		
	(1.7)										111 (0.0)			(10.8)					
	(3.4)										22 (0.0)			(9.6)					
	(5.1)																		
2006		238 (0.4)		(0.6)	310 (11.6)		326 (0.0)				(6.5)	191 (0.5)					444 (0.0)	187 (0.0)	
				(2.6)	426 (25.0)						147 (0.0)								
				(4.5)							146 (0.0)								
				281 (0.0)							1 (0.0)								
2007		197 (1.5)									30 (0.0)	224 (0.9)			750 (0.8)		388 (0.0)		1 (0.0)

	Afg	Bah	Dji	Egy	Irn	Irq	Jor	Kuw	Leb	Lib	Mor	Oma	OPT	Pak	SA	Sud	Syr	Tun	Yem
Year	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
											22 (0.0)								
											8 (0.0)								
2008	127 (11.0)										61 (1.6)								
											77 (1.3)								
2009								255 (0.0)	109 (0.9)		66 (0.0)				(0.3)				
											16 (6.3)								
2010		181 (3.9)						454 (0.2)							2925				
															(0.4)				
															(0.8)				
															(1.6)				
2011	4681 (0.9)						304 (0.0)	373 (0.0)			173 (2.3)	929 (1.4)	65 (0.0)		3441		478 (0.0)		
															(0.6)				
									(7.8)										

Afg: Afghanistan, Bah: Bahrain, Dji: Djibouti, Egy: Egypt, Irn: Iran, Irq: Iraq, Jor: Jordan, Kuw: Kuwait, Leb: Lebanon, Lib: Libya, Mor: Morocco, Oma: Oman, OPT: Occupied Palestinian Territories, Pak: Pakistan, SA: Saudi Arabia, Sud: Sudan, Syr: Sria, Tun: Tunisia, Yem: Yemen

Table S5. Measures of injecting risk behavior among people who inject drugs in the Middle East and North Africa

	Afghanistan	Algeria	Bahrain	Egypt	Iran	Jordan	Lebanon	Libya	Morocco	Oman	OPT	Pakistan	Syria	Tunisia
Shared needles or syringes (%)														
Ever	8 [1], 11 [2], 17 [3], 27 [2], 34 [2], 50 [4]			59 [5]	12 [6], 12 [7] 14 [8], 18 [9] 20 [10], 25 [11] 28 [12], 31 [13] 31 [14], 32 [15] 32 [16], 34 [17], 35 [18], 36 [19], 36 [20], 37 [21], 48 [22] 49 [9], 49 [18] 50 [23], 66 [23] 76 [24], 70 [25], 71 [25], 95 [26,27]	63 [28], 64 [28], 71 [29]	41 [30], 65 [31]	85 [32]	47 [33]	90 [34], 94 [34], 97 [34]		14 [35], 17 [36], 41 [35], 46 [37], 50 [38], 53 [39], 56 [38], 56 [38], 58 [40], 63 [38], 63 [38], 64 [41], 67 [36], 74 [38], 68 [41], 69 [39], 70 [39], 79 [39],	46 [42]	
Last 6 months	16 [43], 28 [44], 29 [44], 34 [43], 45 [43]				47 [45], 64							47 [46]		
Last 3 months	6 [3]													
Last month				23 [47], 32 [48], 41 [47], 53 [48], 55 [5], 86 [49]	8 [13], 12 [50], 13 [51], 14 [50], 14 [52], 18 [50], 21 [25], 40 [25], 73 [53], 100 [54]				30 [55], 33 [55], 36 [55], 36 [55]			54 [56]	28 [42]	
Last week					9 [57], 23 [57]									
Last injection				25 [49]	6 [26], 11 [22]	61 [29]	17 [31], 21 [58]	18 [32]			11 [59], 19 [60]	18 [61], 18 [62], 18 [62], 22 [63], 23 [61], 23 [64], 23 [65], 24 [62], 24 [62], 25 [65], 28 [63], 30 [65], 31 [64], 35 [66], 47 [66], 82 [65]		
Currently										44 [34], 65 [34], 70 [34]		48 [67], 57 [68], 66 [69], 72 [67]		

	Afghanistan	Algeria	Bahrain	Egypt	Iran	Jordan	Lebanon	Libya	Morocco	Oman	OPT	Pakistan	Syria	Tunisia
Unspecified		41 [70]	79 [71]	11 [72], 15 [73], 40 [74], 43 [75],	0 [76], 29 [77], 31 [78], 33 [79], 36 [80], 48 [81], 50 [82], 59 [83], 70 [84]						39 [85], 47 [85]	8 [86], 46 [87], 52 [88], 80 [38], 86 [89], 88 [38], 90 [90], 95 [91]		
Clean used needle before use (%)														
Always	14 [5]				14 [45]	34 [29]		86 [32]	70 [55], 85 [55]			43 [92], 64 [36]	60%[42]	
In the last month	34 [47], 83 [47]													
Last injection											54 [59]	49 [93]		
Unspecified						83 [28]					36 [85]			
Method of cleaning (%)														
Water				72 [5]		79 [28]		82 [32]	89 [55], 97 [55]		68 [59] 84 [85]	34 [36], 39 [65], 54 [93], 78 [46], 84 [92], 100 [65]	40 [42]	82 [94]
Bleach								9 [32]	4 [55], 7 [55]			0 [46], 5 [93]	3 [42]	8 [94]
Last time injected with (%)														
Friends/acquaintances												56 [65], 64 [63], 64 [61], 67 [66], 72 [65], 81 [64]		
Strangers												0 [64], 0 [66], 0 [61], 1 [63], 2 [65], 3 [65]		
Alone											45 [85], 61 [59]	15 [65], 18 [36], 18 [64], 27 [66], 32 [63], 34 [61], 36 [65], 42 [93]		
Place of last injection (%)														
Public place									21 [33], 46 [55], 51 [55]		47 [85]	25 [40], 66 [63], 78 [66], 79 [65], 82 [61], 89 [65], 91 [64]		

	Afghanistan	Algeria	Bahrain	Egypt	Iran	Jordan	Lebanon	Libya	Morocco	Oman	OPT	Pakistan	Syria	Tunisia
Home									33 [55], 41 [33], 46 [55]		54 [85]	3 [65], 5 [64], 9 [61], 11 [65], 11 [66], 14 [63], 68 [40]	74 [42]	
Used "street doctors" (%)														
Ever												26 [63], 42 [38], 77 [65], 84 [38], 99 [38], 100 [38]		
Last injection												247 [66], 32 [61], 44 [64]		
Unspecified												11 [67], 11 [67], 19 [93], 46 [39], 58 [39], 59 [69], 61 [39], 71 [39], 73 [36], 85 [36]		
Average # of injections														
/day	5.7 [3]				3.3 [95]							1.1 [36], 2 [69], 2 [56], 2.2 [65], 2.2 [63], 2.2 [61], 2.3 [96], 2.3 [65], 2.3 [66]		
/week					7.7 [97], 21.1 [98], 21.3 [97],									
/last month					54.0 [19], 92.6 [25], 104.3 [99], 110.3 [25]							20 [100], 63 [101], 67 [101]	41 [42]	
Age at first injection														
Mean (years)	25.8 [3], 26.4 [4]			23.1 [47], 23.3 [5], 27.0 [47]	23.6 [13], 23.7 [102], 23.9 [103], 24.0 [79], 24.0 [15], 25.0 [18], 25.9 [51], 26.0 [50], 26.3 [50], 26.5 [50], 27.0 [104], 27.3 [76], 27.4 [104], 28.1 [18]				32.9 [33]	20 [34], 22 [34], 22 [34]	28.8 [59]	25.0 [39], 25.2 [38], 25.6 [64], 27.0 [105], 27.0 [63], 27.2 [36], 27.9 [66], 28.1 [38], 28.3 [38], 28.5 [61], 29.1 [38], 31.6 [36]	27.0 [42]	

	Afghanistan	Algeria	Bahrain	Egypt	Iran	Jordan	Lebanon	Libya	Morocco	Oman	OPT	Pakistan	Syria	Tunisia
Median (years)	26.0 [43]				25.0 [22], 25.0 [14]				21.0 [55], 28.0 [55]			25.0 [46]		
Duration of injecting														
Mean (years)	1.3 [106], 1.4 [106], 1.7 [2], 2.1 [2], 2.3 [106], 2.4 [106], 2.5 [2], 2.9 [106], 3.3 [43], 4.0 [3], 4.4 [4]			6.4 [47], 9.3 [47]	1.6 [76], 2.0 [18], 2.6 [18], 3.8 [23], 4.1 [107], 4.5 [79], 4.5 [15], 4.8 [23], 4.8 [25], 4.9 [25], 5.4 [13], 5.8 [95], 6.7 [98], 7.4 [26], 8.4 [27], 12 [99]							2.1 [105], 4.2 [65], 4.4 [36], 4.6 [65], 4.6 [61], 4.9 [64], 5.3 [63], 5.9 [66], 6.1 [35], 7.6 [35], 7.7 [36]		
Median (years)					6 [22]				8.0 [55], 8.7 [55]			3 [41], 7 [41]		
Re-injecting own blood (%)														
Ever	69 [43], 70 [3], 73 [43], 81 [43], 83 [44]											70 [38], 91 [41], 92 [41], 92 [38], 94 [38], 96 [38]		
Selling or donating blood (%)														
Ever	5 [4]			30 [5]	56 [108]							3 [35], 8 [46], 12 [105], 23 [69], 27 [35], 28 [96], 31 [36], 44 [68]	23 [42]	
Last 12 months												1 [62], 2 [62]		
Last 6 months												1 [38], 5 [61], 5 [38], 9 [38], 11 [38]		

OPT: Occupied Palestinian Territories

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Table S6. Measures of sexual risk behavior and sexually transmitted infections prevalence among people who inject drugs in MENA

	Afghanistan	Bahrain	Egypt	Iran	Jordan	Lebanon	Libya	Morocco	Oman	OPT	Pakistan	Syria	Tunisia
Sexually active (%)													
Currently			30 [1], 73 [2]	95 [3]									
Ever	83 [4], 86 [4], 92 [5], 93 [4], 94 [4]	91 [6]	95 [7], 96 [7], 96 [8]	75 [9], 77 [10], 81 [11], 84 [12], 85 [13], 86 [14], 87 [14], 88 [14]			77 [15]		91 [16], 94 [16], 100 [16]		77 [17], 79 [17], 84 [18], 89 [19], 89 [20], 93 [21], 94 [19], 95 [22]		96 [23], 97 [24]
Last year			71 [8], 76 [7], 80 [7]	39 [25], 54 [25]	64 [26]	73 [27]					52 [28]	78 [29]	
Last 12 months								55 [30], 61 [30]					87 [24]
Last 6 months	58 [31], 76 [31], 78 [31], 80 [31], 85 [31]										22 [32], 91 [33]		
Last month			54 [2]				23 [15]			63 [34]		68 [29]	
Married (%)													
Currently	30 [35], 34 [35], 37 [31], 39 [31], 42 [31], 43 [35], 52 [36], 53 [31], 61 [31], 68 [37]	27 [6]	29 [7], 38 [38], 39 [8], 49 [7]	9 [39], 26 [40], 28 [14], 29 [41], 33 [42], 33 [43], 33 [25], 33 [14], 33 [25], 35 [44], 36 [14], 39 [45], 45 [46], 45 [47], 45 [48], 48 [49], 48 [50], 52 [51], 54 [52], 56 [53], 64 [47], 67 [54], 79 [54], 89 [55]	49 [26]	21 [56]	12 [15]	19 [57], 20 [30], 21 [30]	3 [16], 26 [16], 28 [16]	67 [58]	24 [59], 26 [60], 26 [17], 28 [61], 30 [32], 30 [62], 31 [28], 33 [63], 34 [21], 35 [64], 41 [22], 42 [65], 45[20], 45 [63], 45 [63], 45 [18], 48 [63], 53 [66], 53 [66], 55 [33], 68 [19], 73 [67], 77 [19]	44 [29]	16 [24]
Ever	38 [68], 46 [5], 52 [68], 64 [69]		34 [7], 56 [8], 56 [7]	19 [70], 35 [12], 43 [71], 44 [13], 52 [72], 54 [14], 54 [39], 55 [14], 55 [73], 56 [14], 57 [11], 65 [73]		33 [56]					26 [74], 43 [74]		20 [24]
Had sex with regular female partners (%)													
Last year			83 [7], 86 [7], 89 [8]	43 [14], 57 [14], 58 [14]		66 [56]							
Last 6 months											26 [21], 38 [22], 42 [20], 46 [18]		

	Afghanistan	Bahrain	Egypt	Iran	Jordan	Lebanon	Libya	Morocco	Oman	OPT	Pakistan	Syria	Tunisia
Last month						62 [75]	73 [15]						77 [24]
Had sex with non-regular female partners (%)													
Last year			29 [8], 34 [7], 42 [7]	27 [14], 31 [14], 34 [14]		40 [56]		18 [30], 36 [30]					42 [24]
Last month						34 [75]	28 [15]						
Unspecified				73 [54]									
Had sex with men (%)													
Ever	2 [31], 10 [5], 10 [31], 10 [4], 14 [35], 15 [35], 19 [31], 19 [31], 25 [4], 26 [35], 26 [4], 29 [31], 36 [4]		9 [2], 18 [38]	5 [45], 8 [39], 8 [11], 11 [12], 13 [76], 14 [14], 17 [14], 17 [14], 18, [49], 24 [43], 27 [51], 30 [52], 36 [9], 39 [76]	12 [26]	25 [27]			6 [16], 12 [16], 15 [16], 28 [16], 42 [16], 35 [16]	25 [58]	37 [19], 50 [19]		
Last 5 years											7 [32]		
Last 12 months			8 [7], 9 [8], 14 [7]	2 [25], 2 [25], 7 [14], 8 [14], 10 [14]	7 [26]						2 [77], 14 [77]	4 [29]	
Last 6 months											18 [17], 27 [17]		
Last month				19 [44]		10 [27]							
Unknown/unspecified		9 [6]		12 [3], 14 [78]				14 [57]			24 [28]		
Had sex with a sex worker (%)													
Ever	23 [4], 37 [5], 38 [4], 47 [35] 56 [35], 64 [35], 67 [4], 72 [4]		13 [8]	23 [45], 25 [12], 32 [13], 41 [39]		50 [56]			31 [16], 40 [16], 54 [16], 60 [16], 65 [16], 97 [16]	18 [34]	41 [79], 43 [62], 68 [19], 71 [19], 81 [17], 18 [17]	47 [29]	
Last 12 months				9 [25], 15 [25]	30 [26]						21 [77], 18 [74], 23 [74], 24 [77], 30 [74], 34 [74]		
Last 6 months	5 [68], 6 [68], 19 [68]										7 [21], 8 [61], 13[18], 13 [61], 13 [61], 14 [21], 14 [22], 15 [20], 18 [22], 27 [18] 27 [61], 28 [61]		
Last month						33 [75]	20 [15]				11 [67], 47 [67]	40 [29]	

	Afghanistan	Bahrain	Egypt	Iran	Jordan	Lebanon	Libya	Morocco	Oman	OPT	Pakistan	Syria	Tunisia
Unknown/unspecified											3 [28], 96 [28]		
Sold sex (%)													
Ever				8 [39], 36 [14], 43 [14], 45 [14]		12 [56], 25 [27]							
Last 12 months			26 [38]	18 [14], 22 [14] 26 [14], 29 [78]				18 [30], 24 [30]		8 [34]	5 [74], 11 [74]		
Last 6 months											15 [21], 17 [22], 20 [18]		
Last month				19 [80]									
Unknown/unspecified											9 [66], 14 [61], 19 [28], 20 [61]		
Sold or bought sex (%)													
Ever			51 [2]										
Last 12 months			11 [7], 13 [7]							25 [58]			26 [24]
Unknown/unspecified								68 [57]					
Have multiple partners (%)													
Lifetime				54 [11], 57 [14], 59 [14], 62 [14]									
Last 12 months			39 [7], 45 [7]		46 [26]			51 [57]		29 [58]	51 [28]		60 [24]
Last 6 months											18 [33]		
Last month			49 [2]				23 [15]						
Unknown/unspecified				41 [47]									
Overall condom use (%)													
Ever	10 [4],16 [4], 19 [4],30 [4], 33 [4]		41 [2]	24 [51], 24 [25], 29 [25], 53 [11], 53 [13], 57 [9]		88 [27]		55 [57]	53 [16], 63[16], 69[16]		14 [19], 16 [79], 18 [28], 21 [62], 36 [67], 37 [17], 38 [19]	60 [29]	
Last 12 months								24 [30], 36 [30]					
Last 6 months											33 [32]		
Last act	4 [31], 15 [31], 17 [35],18 [31], 20 [31], 26 [35], 27 [31], 32 [35]			38 [80]	7 [81]		66 [15]			34 [58]			24 [24], 34 [23]
Unknown/unspecified			9 [82]	68 [55]									
Consistent condom use (%)													
Last 12 months			14 [2]						12 [16], 19 [16], 25 [16]			19 [29]	
Last 6 months											7 [32]		

	Afghanistan	Bahrain	Egypt	Iran	Jordan	Lebanon	Libya	Morocco	Oman	OPT	Pakistan	Syria	Tunisia
Last month										30 [58]			
Unknown/unspecified											9 [32]		
Condom use with commercial sex workers (%)													
Ever	18 [4], 19 [4], 34 [4], 39 [4]				65 [26]								
Last 12 months			34 [8]	24 [25], 24 [25]									
Last 6 months											7 [61], 49 [61]		
Last month									67 [16], 75 [16], 75 [16]			49 [29]	
Last act							80 [15]			48 [34]	17 [20], 17 [74], 21 [18], 28 [21], 31 [22], 32 [74]		29 [24], 37 [23]
Condom use during anal sex with male (%)													
Ever	3 [4], 4 [83], 13 [83], 13 [83]												
Last 12 months				0 [25], 33 [25]					0 [16], 40 [16], 42 [16]			0 [29]	
Last act				6 [14], 8 [14], 15 [14]									
Prevalence of:													
Syphilis (%)	0.0 [4], 1.2 [5], 1.2 [4], 1.9 [35], 2.2 [4], 3.3 [31], 3.5 [35], 3.8 [31], 4.0 [31], 4.0 [31], 6.2 [31], 6.9 [31], 13.9 [4], 16.7 [35]		3.0 [84]	0.0 [85], 8.0 [86]							1.2 [87], 3.9 [77], 7.6 [77], 13.1 [67], 14.0 [88], 16.9 [17], 18.2 [88]		
HSV-2 (%)	4.4 [35], 7.7 [35], 20.6 [35]										6.0 [77], 11.0 [77], 19.0 [87]		
Gonorrhea (%)											0.0 [77], 1.0 [88], 1.3 [77], 1.8 [88], 12.8 [87]		
Chlamydia (%)											0.0 [77], 0.2 [88], 0.5 [88], 0.7 [77]		

	Afghanistan	Bahrain	Egypt	Iran	Jordan	Lebanon	Libya	Morocco	Oman	OPT	Pakistan	Syria	Tunisia
Self-reported history of sexually transmitted disease (%)			11.0 [82]	7.6 [45], 22.8 [47]							6.8 [20], 10.0 [17], 10.4 [18], 11.4 [22], 12.1 [79], 18.8 [17], 23.0 [89], 54.1 [19], 65.9 [19]		

OPT: Occupied Palestinian Territories. NB: The denominator in some studies corresponds to sexual active PWID while in other studies the denominator corresponds to the total sample of PWID in the study.

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Table S7. HIV/AIDS knowledge, perception of risk, and HIV testing among people who inject drugs in the Middle East and North Africa

	Afghanistan	Egypt	Iran	Jordan	Lebanon	Morocco	Oman	OPT	Pakistan	Syria	Tunisia
Ever heard of HIV/AIDS (%)	43 [1], 83 [2], 97 [2], 98 [2], 100 [3], 100 [3], 100 [3], 100 [3], 100 [3]	9 [4], 96 [5], 99 [6], 100 [6]	73 [7], 82 [8], 93 [9], 94 [9], 96 [9], 100 [10]						29 [11], 52 [12], 54 [13], 59 [14], 65 [15], 66 [16], 67 [17], 72 [18], 74 [19], 82 [20], 86 [20], 87 [21], 88 [16], 89 [22], 93 [23], 96 [24], 97 [25]	99 [26]	100 [27], 100 [28]
Knowledge of injecting drug use as a mode of transmission (%)	51 [1], 81 [2], 94 [2], 97[2]	5 [4], 22 [29], 33 [5], 98 [6], 98 [6]	63 [7], 85 [9], 91 [9], 96 [30], 96 [9], 100 [31]	43 [32], 96 [33]	97 [34]	54 [35], 90 [36], 97 [36]		96 [37]	15 [38], 46 [16], 53 [16], 65 [24], 68 [19], 71 [18], 72 [23], 77 [17], 80 [15], 81 [39], 82 [14], 87 [21], 88 [22]	47 [26]	80 [27], 93 [28]
Knowledge of sex as a mode of transmission (%)	78 [40]	88 [5]		65 [32]		80 [35]			19 [38], 41 [39], 41 [16], 42 [16], 50 [24], 72 [19], 72 [23], 82 [22], 84 [21], 91 [17]	94 [26]	
Self-perception of risk (%)		20 [5], 29 [41]	43 [9], 47 [9], 54 [9]		45 [42], 50 [34]	69 [35]		73 [37]	13 [16], 30 [24], 31 [19], 33 [16], 34 [17], 58 [18], 63 [25], 64 [21]	27 [26]	63 [27]
Ever tested for HIV (%)	3 [3], 13 [3], 16 [3], 24 [2], 24 [2], 33[2], 58 [3], 60 [3]	1 [5], 6 [43], 10 [6], 10 [6]	28 [44], 29 [8], 39 [9], 44 [31], 45 [10], 45 [9], 47 [45], 47 [46], 48 [9], 60 [30], 66 [47]	15 [32] 27 [33]	61 [34], 80 [42]	13 [35], 33 [36], 48 [36]	73 [48], 94 [48], 97 [48]	66 [37]	2 [12], 6 [19], 21 [22], 25 [21], 55 [25]	36 [26]	29 [27], 30 [28]

OPT: Occupied Palestinian Territories

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8.2. APPENDIX B – RESEARCH PAPER 2 SUPPLEMENTARY ONLINE MATERIAL

Outline

Additional file 1.	Mathematical models description
Additional file 2.	Models assumptions in terms of parameter values
Additional file 3.	Trend of HIV prevalence among PWID in Iran as described by available HIV point-prevalence measures 1990-2013
Additional file 4.	Effect of stochasticity (purple) and of behavioural (blue) and biological (red) uncertainty on the modeling predictions of the endemic HIV prevalence, $RR_{HCV/HIV}$ and $OR_{HCV/HIV}$ at 59.4% HCV prevalence in Iran

Additional file 1
Mathematical models description

1. HIV model structure

We developed a deterministic/stochastic compartmental mathematical model that describes the parenteral transmission of HIV through sharing unsterile needles/syringes among people who inject drugs (PWID) (Figure 1). Other methods of HIV transmission (e.g. sexual) are not considered in the model. The model stratifies the PWID population into compartments according to HIV status, stage of HIV infection, and level of injecting risk behavior.

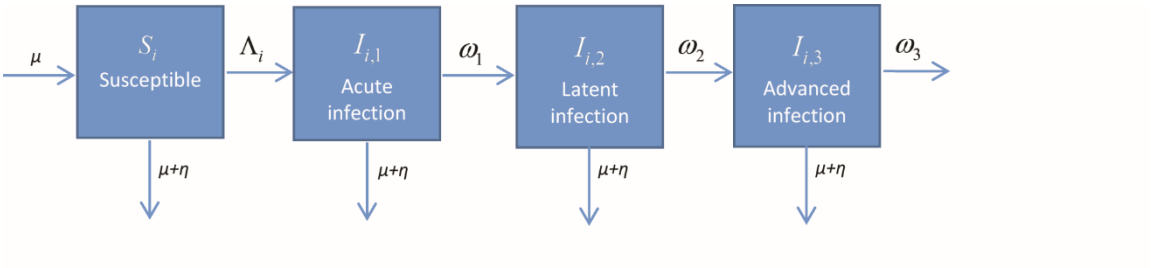

Figure S1. HIV model structure

The model was solved both deterministically and stochastically. The deterministic version of the model was expressed with the below system of coupled nonlinear differential equations for each risk group. For the stochastic version, we used the same transition rates in this deterministic system of equations to generate the stochastic process.

$$\frac{dS_i}{dt} = \mu N_{0,i} - (\mu + \eta)S_i - \Lambda_i S_i \quad \textbf{(1)}$$

$$\frac{dI_{i,1}}{dt} = \Lambda_i S_i - (\mu + \eta)I_{i,1} - \omega_1 I_{i,1} \quad \textbf{(2)}$$

$$\frac{dI_{i,2}}{dt} = \omega_1 I_{i,1} - (\mu + \eta)I_{i,2} - \omega_2 I_{i,2} \quad \textbf{(3)}$$

$$\frac{dI_{i,3}}{dt} = \omega_2 I_{i,2} - (\mu + \eta)I_{i,3} - \omega_3 I_{i,3} \quad \textbf{(4)}$$

To accommodate heterogeneity of injecting risk behavior, we stratified the population into 7 injecting risk groups, defined with the index i ($i = 1, 2, ..., 7$ representing the low to high risk groups). Here S_i is the HIV susceptible population in the i–risk group, and $I_{i,\beta}$ is the HIV infected population in the i–risk group. The index β marks the stage of HIV pathogenesis;

$\beta = 1,2,3$ represent the acute, latent, and advanced stages, respectively. $N_{0,i}$ is the initial population size of each i -risk group. μ is the natural mortality rate, and η is the leaving injecting career rate. The rate of progression from one HIV stage to the next is described by ω_1 and ω_2, while ω_3 is the rate of HIV/AIDS disease mortality. The rate Λ_i is the HIV force of infection (incidence rate of infection) experienced by the S_i susceptible population. Λ_i is given by:

$$\Lambda_i = \rho_{S_i} \sum_{j=1}^{7} \sum_{\beta=1}^{3} t_{I_{j,\beta} \to S_i} \mathcal{G}_{i,j} \frac{\rho_{I_{j,\beta'}} I_{j,\beta'}}{\rho_{S_j} S_j + \sum_{\beta'=1}^{3} \rho_{I_{j,\beta'}} I_{j,\beta'}} \quad \textbf{(5)}$$

where ρ_{P_i} describes the *effective* new partner acquisition rate for any population variable P_i (S_i or I_i) (note further discussion in section 3.2 below).

The parameter $t_{I_{j,\beta} \to S_i}$ defines the HIV transmission probability per partnership between a member of the susceptible population S_i and a member of the HIV infected population $I_{j,\beta}$:

$$t_{I_{j,\beta} \to S_i} = 1 - \left(1 - p^{HIV}_{I_{j,\beta} \to S_i}\right)^{n_{I_{j,\beta} \leftrightarrow S_i}} \quad \textbf{(6)}$$

It is expressed in terms of HIV transmission probability per needle/syringe sharing act per HIV stage in this partnership ($p^{HIV}_{I_{j,\beta} \to S_i}$) and the number of needle/syringe sharing acts per partnership ($n_{I_{j,\beta} \leftrightarrow S_i}$).

The mixing among the different risk groups is dictated by the injecting-mixing matrix $\mathcal{G}_{i,j}$. This matrix provides the probability that an individual in risk group i would choose a partner in risk group j. It is given by:

$$\mathcal{G}_{i,j} = e\theta_{i,j} + (1-e) \frac{\rho_{S_j} S_j + \sum_{\beta=1}^{3} \rho_{I_{j,\beta}} I_{j,\beta}}{\sum_{k=1}^{7} \left(\rho_{S_k} S_k + \sum_{\beta'=1}^{3} \rho_{I_{k,\beta'}} I_{k,\beta'} \right)} \quad \textbf{(7)}$$

Here, $\theta_{i,j}$ is the identity matrix and the parameter $e \in [0,1]$ measures the degree of assortativeness in the mixing. At the extreme $e = 0$, the mixing is proportionate (choosing partners with no preferential bias based on the kind of risk group) while at the other extreme

$e = 1$, the mixing is fully assortative as individuals choose partners only from within their own risk group [1].

2. HCV Model structure

We developed a deterministic/stochastic compartmental mathematical model that describes the parenteral transmission of HCV through sharing unsterile needles/syringes among PWID (Figure 2). The model is similar in structure to the HIV model described above, and also stratifies the PWID population into compartments according to HCV status and stage of infection, and level of injecting risk behavior.

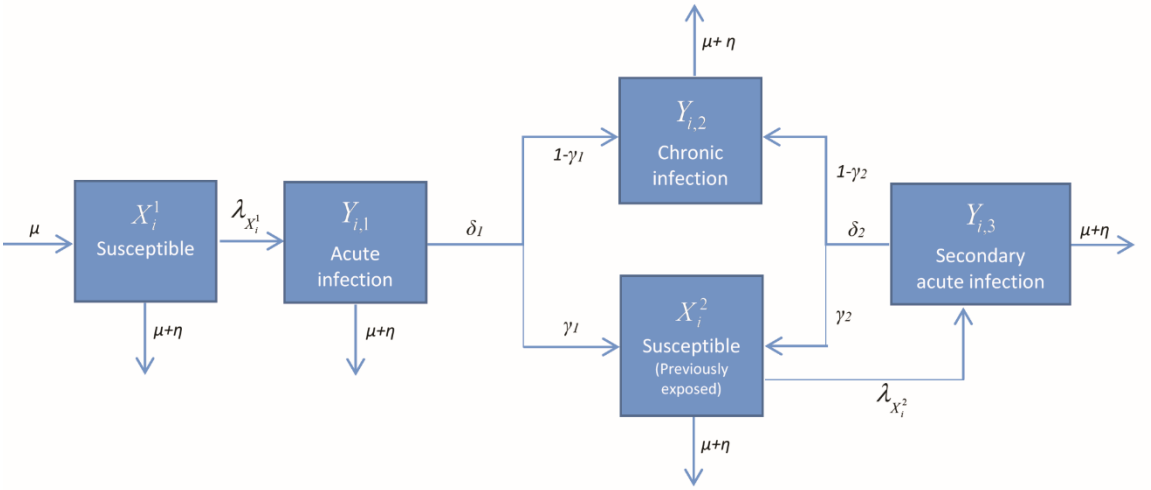

Figure S2. HCV model structure

The model was solved both deterministically and stochastically. The deterministic version of the model was expressed in terms of a system of coupled nonlinear differential equations for each risk group:

$$\frac{dX_i^1}{dt} = \mu N_{0,i} - (\mu + \eta)X_i^1 - \lambda_{X_i^1} X_i^1 \quad \textbf{(8)}$$

$$\frac{dY_{i,1}}{dt} = \lambda_{X_i^1} X_i^1 - (\mu + \eta)Y_{i,1} - \delta_1 Y_{i,1} \quad \textbf{(9)}$$

$$\frac{dY_{i,2}}{dt} = \delta_1 (1-\gamma_1) Y_{i,1} + \delta_2 (1-\gamma_2) Y_{i,3} - (\mu + \eta)Y_{i,2} \quad \textbf{(10)}$$

$$\frac{dX_i^2}{dt} = \delta_1 \gamma_1 Y_{i,1} + \delta_2 \gamma_2 Y_{i,3} - (\mu + \eta)X_i^2 - \lambda_{X_i^2} X_i^2 \quad \textbf{(11)}$$

$$\frac{dY_{i,3}}{dt} = \lambda_{X_i^2} X_i^2 - (\mu + \eta)Y_{i,3} - \delta_2 Y_{i,3} \quad \textbf{(12)}$$

The index i defines the seven injecting risk groups, ($i = 1,2,...,7$ representing the low to high risk groups). Here X_i^1 is the HCV susceptible population in the i –risk group, and $Y_{i,\beta}$ is the HCV infected population in the i –risk group. The index β marks the stage of HCV pathogenesis; $\beta = 1,2,3$ represent the acute, chronic, and secondary acute stages, respectively. X_i^2 is the population, in the i –risk group, that was previously exposed to HCV infection but cleared it and is now susceptible for HCV reinfection. $N_{0,i}$ is the initial population size of each i -risk group. μ is the natural mortality rate, and η is the leaving injecting career rate. The rates of progression from primary and secondary acute HCV infections are δ_1 and δ_2, respectively. γ_1 is the percentage of primary HCV infections that clear, and γ_2 the percentage of HCV reinfections that clear.

The rate $\lambda_{X_i^1}$ is the HCV force of infection experienced by the X_i^1 susceptible population and is given by:

$$\lambda_{X_i^1} = \rho_{X_i^1} \sum_{j=1}^{7} \sum_{\beta=1}^{3} R_{I_{j,\beta} \to X_i^1} \mathcal{H}_{i,j} \frac{\rho_{Y_{j,\beta'}} Y_{j,\beta'}}{\rho_{X_i^1} X_i^1 + \rho_{X_i^2} X_i^2 + \sum_{\beta'=1}^{3} \rho_{Y_{j,\beta'}} Y_{j,\beta'}} \quad \textbf{(13)}$$

We assume here that the susceptible population X_i^2 experiences the same force of infection as the X_i^1 population (no acquired immunity):

$$\lambda_{X_i^2} = \lambda_{X_i^1} \quad \textbf{(14)}$$

ρ_{P_i} describes the *effective* new partner acquisition rate for any population variable P_i (X_i or Y_i) (note further discussion in section 3.2 below).

The parameter $R_{Y_{j,\beta} \to X_i^1}$ defines the HCV transmission probability per partnership between a member of the susceptible population X_i^1 and a member of the HCV infected population $Y_{i,\beta}$:

$$R_{Y_{j,\beta} \to X_i^1} = 1 - \left(1 - p^{HCV}_{Y_{j,\beta} \to X_i^1}\right)^{n_{Y_{j,\beta} \leftrightarrow X_i^1}} \quad \textbf{(15)}$$

It is expressed in terms of HCV transmission probability per needle/syringe sharing act per HCV stage in this partnership $p^{HCV}_{Y_{j,\beta} \to X_i^1}$ and the number of needle/syringe sharing acts per partnership ($n_{Y_{j,\beta} \leftrightarrow X_i^1}$),

The mixing among the different risk groups is dictated by the mixing matrix $\mathcal{H}_{i,j}$. This matrix provides the probability that an individual in risk group i would choose a partner in risk group j. It is given by:

$$\mathcal{H}_{i,j} = e\theta_{i,j} + (1-e)\frac{\rho_{X_j^1}X_j^1 + \rho_{X_j^2}X_j^2 + \sum_{\beta=1}^{3}\rho_{Y_{j,\beta}}Y_{j,\beta}}{\sum_{k=1}^{10}\left(\rho_{X_j^1}X_j^1 + \rho_{X_j^2}X_j^2 + \sum_{\beta'=1}^{3}\rho_{Y_{j,\beta'}}Y_{j,\beta'}\right)} \quad \textbf{(16)}$$

Here, $\theta_{i,j}$ is the identity matrix and the parameter $e \in [0,1]$ measures the degree of assortativeness in the mixing. At the extreme $e = 0$, the mixing is proportionate while at the other extreme $e = 1$, the mixing is fully assortative [1].

3. Injecting risk behavior

3.1. Distribution of injecting risk behavior in the population

The PWID population was stratified into a number of risk groups. In the absence of direct empirical data to inform on the exact distribution of injecting risk behavior in a given PWID population, we assumed that the proportion of the PWID population initially in each risk group i follows a gamma distribution. This assumption was informed by previous theoretical work [2-5] and mathematical modeling of HIV sexual transmission [6, 7], and accommodates wider flexibility [4]. The gamma distribution of the population size across the risk groups is given by:

$$p(i) = \frac{1}{b^a\Gamma(a)} i^{a-1} e^{\frac{-i}{b}} \quad \textbf{(17)}$$

Here a is the shape parameter determined through normalization of the distribution, and b is the scale parameter in the gamma distribution.

3.2. The effective new injecting partner acquisition rate

The ρ_{P_i} parameter describes the number of new injecting partners an individual in a specified risk group acquires, but also effectively other factors that enhance the risk of exposure to the infection such as concurrency and clustering within injecting networks, and variability in injecting risk behavior in the population. Since the exact nature of injecting behavior and injecting networks is not well-understood and varies within and across communities, ρ_{P_i} is effectively a summary measure of the population-specific level of injecting risk behavior, and captures the distribution and strength of the risk of exposure to HIV (or HCV) infection. The

form of the ρ_{P_i} distribution across different risk groups was defined through a power law function as:

$$\rho_{P_i} = Ci^{\alpha} \quad \textbf{(18)}$$

where α is the exponent in the power-law function and C is an overall constant.
This form is motivated by simulations using an individual-based network model developed to explore the diversity of risk in risk networks [8], and also by analyses of the architecture of complex weighted networks [9, 10], and by an analysis of the average separation between individuals in a network or a sub-network [11, 12]. The latter can be seen as a proxy of the size of the "ecology" through which an individual can acquire an infection. Here C is a constant determined by the average risk behavior and α is the exponent parameter that determines the level of variability in the effective new injecting partner acquisition rate [8].

4. Parameter values

The parameters of the model were derived using current empirical data on HIV/HCV epidemiology and natural history, and are listed in Table S1 along with their references.

We assumed that the transmission probability of HIV per sharing needle/syringe is 10 times higher than the probability of transmission per coital act in each HIV stage [13]. The latter were based on recent re-analyses of the Rakai Study data [14-17]. The durations of the acute, latent, and advanced stages of HIV infection were assumed to be 49 days, 9 years, and 2 years, respectively. These choices were based on compilation of data by UNAIDS indicating that the average duration from HIV acquisition to death, in absence of antiretroviral therapy, is about 11 years [18], and based on the classification in Wawer *et al.* [17], re-analysis of the Rakai data for acute infection [14], and measured time from seroconversion to death in several cohort studies [19, 20].

The transmission probability of HCV in the chronic stage was calculated based on the transmission probability of HIV in the latent stage [14-17]. Based on model fitting to empirical data (please see main text), we found HCV transmission probability in the chronic stage to be 7.8 times greater than that of HIV. HCV transmission probability in the primary acute infection was estimated earlier at 2.7 times HCV transmission probability in the chronic stage [21]. We also assumed that HCV transmission probability in the secondary acute stage is half of that in the primary acute stage, based on the 50% reduction in viral load following reinfection

compared to primary infection, as estimated in a cohort study by Obsurn et al. [22]. The durations of primary and secondary HCV acute stages were assumed to be 16.5 weeks and 4.1 weeks, respectively, based on direct measurement in recent prospective cohort studies [22, 23]. The percentage of primary HCV infections and HCV reinfections that clear were assumed to be 25% and 83%, respectively, based on cohort studies data [22, 23].

As for the parameters of injecting risk behavior, the degree of assortativeness (*e*) was fixed at 0.3; a representative value informed by earlier modeling work on HIV [16]. Meanwhile, the scale (*b*), and shape (*a*) parameters (in the gamma distribution of the population across the different risk groups) were fixed at 0.5 and 0.28, respectively, based on our model fitting to a statistical model summarizing the HCV/HIV empirical data [24]. The exponent parameter in the power law function of the distribution of injecting risk behavior (α) was fixed at 2.0, based also on our model fitting to HCV/HIV empirical data [24]. The duration of the injecting career was assumed to be 10 years as informed by empirical data [13].

5. Effect of ART - sensitivity analysis

We assessed the sensitivity of the HCV thresholds for HIV epidemic expansion to antiretroviral therapy (ART) scale up. We assumed that the efficacy of ART in reducing HIV transmission among PWID is 100%, based on clinical trials of treatment for prevention and other observational data [25, 26]. Accordingly, the probability of HIV transmission per needle/syringe sharing act ($p^{HIV}_{I_{j,\beta}\to S_i}$) in a population with ART coverage of ϕ among those eligible for treatment is reduced by a factor of $(1-\phi)$. We assumed that with ART scale up, all infected PWID in the advanced stage and half of those in the latent stage would be eligible for ART treatment, which corresponds roughly to an eligibility treatment criteria of CD4 cell count < 500 cells/µl [27].

We also assumed that ART slows disease progression from onset of infection to death. The average duration of latent infection in the HIV infected population up to treatment initiation was assumed to be $4.5 years + 4.5(1-\phi)$. The average duration from treatment initiation to death was assumed to be $2 years + 15.5\phi$. Accordingly, 100% coverage among those eligible will double the average duration from onset of infection to death in the HIV infected population from 11 years to 22 years.

References of Additional file 1

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Additional file 2

Table S1. Models assumptions in terms of parameter values

Parameter	Symbol	Value	Range of values*	Reference
HIV Biological parameters				
HIV Infectiousness ratio for injecting/sexual transmission	R	10	N/A	[1]
Probability of transmission per shared injection in each HIV stage:				
Acute	$p^{HIV}_{I_{j,1}\to S_i}$	$R \times 0.03604 = 0.360$	N/A	Calculation using R and reference [2]
Latent	$p^{HIV}_{I_{j,2}\to S_i}$	$R \times 0.0008 = 0.008$	N/A	Calculation using R and reference [2]
Advanced	$p^{HIV}_{I_{j,3}\to S_i}$	$R \times 0.0042 = 0.042$	N/A	Calculation using R and reference [2]
Duration of each HIV stage:				
Acute	$1/\omega_1$	49 days	N/A	[3-8]
Latent	$1/\omega_2$	9 years	N/A	[3-8]
Advanced	$1/\omega_3$	2 years	N/A	[3-8]
HCV Biological parameters				
Infectiousness ratio of HCV to HIV	F	7.8	1-15	Model fitting
Probability of transmission per shared injection in each HCV stage:				
Acute	$p^{HCV}_{Y_{j,1}\to S_i}$	$2.7 \times p^{HCV}_{Y_{j,2}\to S_i} = 0.168$	N/A	[1]
Chronic	$p^{HCV}_{Y_{j,2}\to S_i}$	$F \times P^{HIV}_{I_{j,2}} = 0.062$	N/A	Calculation using F
Secondary acute	$p^{HCV}_{Y_{j,3}\to S_i}$	$0.5 \times p^{HCV}_{Y_{j,1}\to S_i} = 0.084$	N/A	[9]
Duration of each HCV stage:				
Acute	$1/\delta_1$	16.5 weeks	N/A	[10]
Secondary acute	$1/\delta_2$	4.1 weeks	N/A	[9]
Proportion of virus clearance among:				
Primary HCV infections	γ_1	25%	N/A	[10]
HCV reinfections	γ_2	83%	N/A	[9]
Behavioral and demographic parameters				
Death rate	μ	$1/70$ years $= 0.014$	N/A	[11]
Duration of injection career	η	10 years	N/A	[1]
Degree of assortative mixing	e	0.3	0-1	[1]
Scale parameter in the gamma distribution of the population across risk groups	b	0.5	0.4-0.6	Model fitting
Shape parameter in the gamma distribution of the population across risk groups	a	0.28	0.05-0.45	Model fitting
Exponent parameter in the power law function of the risk behavior distribution	α	2.0	1.0-2.6	Model fitting
Number of sharing acts per partnership	$n_{I_{j,\beta}\leftrightarrow S_i}$	50	N/A	Representative value

* In the sensitivity analyses

References of Additional file 2

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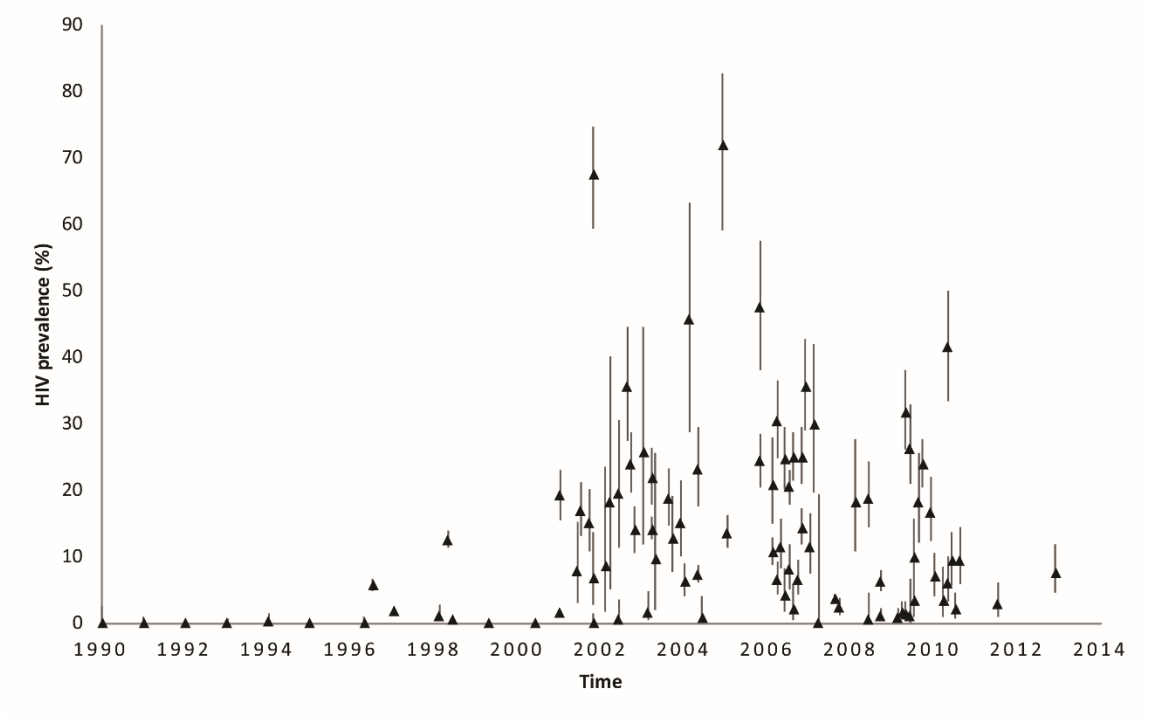
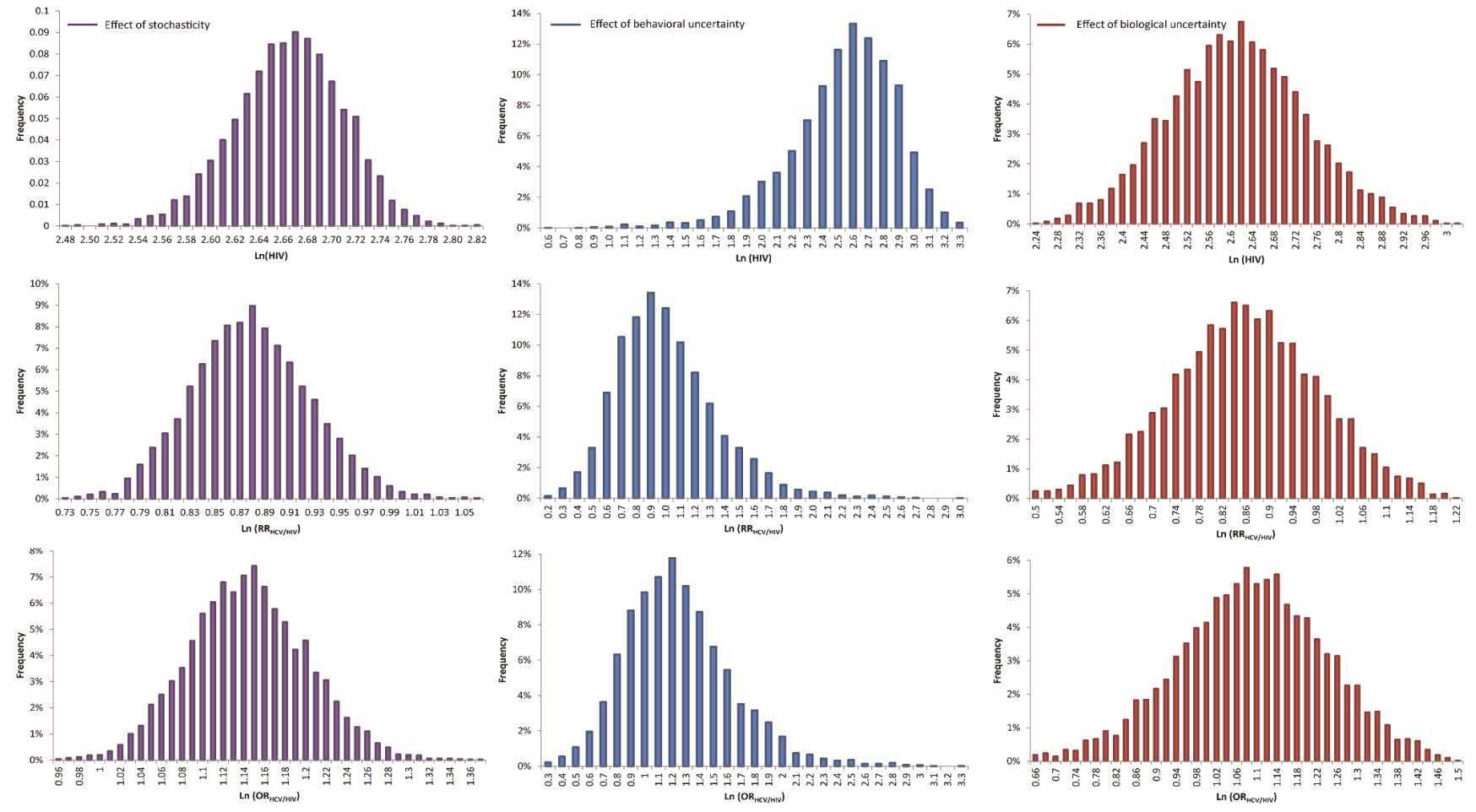
Additional file 3



Additional file 4



8.3. APPENDIX C – RESEARCH PAPER 3 SUPPLEMENTARY ONLINE MATERIAL

Outline

Table S1

Table S1. HIV epidemic states among people who inject drugs in select Middle East and North Africa countries with sufficient data to explore the HCV-HIV association*

	Low level	Emerging	Established
Afghanistan	Before 2009	2009 and after	NA
Iran	Before 2001	2001-2006	After 2006
Morocco	Before 2008	2008 and after	NA
Pakistan	Before 2004	2004 and after	NA
Tunisia	All	N/A	N/A

*Based on findings by Mumtaz et al, 2014 [1]
N/A: Not applicable

Reference of Table S1

1. Mumtaz GR, Weiss HA, Thomas SL, Riome S, Setayesh H, Riedner G*, et al.* HIV among people who inject drugs in the Middle East and North Africa: systematic review and data synthesis. *PLoS Med* 2014,**11**:e1001663.

Table S2

Table S2. Summary of the 54 paired HCV-HIV prevalence data among people who inject drugs in the Middle East and North Africa

Country	Year	City	Sampling	Site	HIV epidemic state	Sample size	HCV	HIV
Afghanistan [1]	2005-6	Kabul	Convenience sampling	Voluntary counseling and testing	Low level	463	36.7%	3.0%
Afghanistan [2]	2006-8	Herat	Convenience sampling	Voluntary counseling and testing	Low level	340	49.1%	3.2%
Afghanistan [3]	2007-9	Kabul	Targeted sampling	Mixed	Low level	483	36.0%	2.1%
Afghanistan [4]	2009	Herat	Respondent driven sampling	N/A	Emerging	159	57.9%	18.2%
Afghanistan [4]	2009	Kabul	Respondent driven sampling	N/A	Low level	286	37.1%	3.1%
Afghanistan [4]	2009	Mazar-i-Sharif	Respondent driven sampling	N/A	Low level	102	25.5%	1.0%
Afghanistan [5]	2012	Herat	Respondent driven sampling	N/A	Emerging	185	70.8%	15.7%
Afghanistan [5]	2012	Jalalabad	Respondent driven sampling	N/A	Low level	236	15.3%	2.5%
Afghanistan [5]	2012	Kabul	Respondent driven sampling	N/A	Low level	369	27.6%	2.4%
Afghanistan [5]	2012	Mazar-i-Sharif	Respondent driven sampling	N/A	Low level	254	23.6%	2.4%
Afghanistan [5]	2012	Charikar	Respondent driven sampling	N/A	Low level	117	28.2%	0.9%
Iran [6]	1998	Shiraz	Convenience sampling	Voluntary drug treatment center	Low level	464	80.2%	1.3%
Iran [7]	2001-2	Tehran	Convenience sampling	Voluntary drug treatment center	Emerging	90	36.4%	7.8%
Iran [7]	2001-2	Tehran	Simple random sampling	Prison	Emerging	371	80.6%	17.0%
Iran [8]	2001-2	Mashhad	Convenience sampling	Prison	Emerging	101	59.4%	6.9%
Iran [9]	2002	Hormozgan	Simple random sampling	Prison	Emerging	249	65.5%	15.3%
Iran [10]	2002	Tehran	Convenience sampling	Voluntary drug treatment center	Emerging	34	64.7%	8.8%
Iran [11]	2002	Hamadan	Simple random sampling	Prison	Emerging	149	31.5%	0.7%
Iran [12]	2002-3	Gorgan	Simple random sampling	Prison	Emerging	22	95.5%	18.2%
Iran [13]	2000-5	Zahedan	Convenience sampling	Clinical setting	Emerging	31	22.6%	25.8%
Iran [14]	2003	Rafsanjan	Convenience sampling	Clinical setting	Emerging	31	16.1%	9.7%
Iran [14]	2003	mix of cities	Convenience sampling	Prison	Emerging	401	76.8%	14.0%

Country	Year	City	Sampling	Site	HIV epidemic state	Sample size	HCV	HIV
Iran [15]	2001-6	Kashan	Convenience sampling	Clinical setting	Emerging	177	11.9%	1.7%
Iran [16]	2001-6	Ahfaz	Convenience sampling	Clinical setting	Emerging	142	52.1%	12.7%
Iran [17]	2002-6	Ahfaz	Convenience sampling	Clinical setting	Emerging	333	30.9%	18.0%
Iran [18]	2004	Shahr-e-Kord	Convenience sampling	Voluntary drug treatment center	Emerging	133	11.3%	0.8%
Iran [19]	2004	Tehran	Convenience sampling	Mixed	Emerging	202	52.0%	23.8%
Iran [20]	2006	Tehran	Convenience sampling	Mandatory drug treatment center	Established	454	80.0%	24.7%
Iran [21]	2006	mix of cities	Random cluster sampling	National	Established	936	43.4%	20.5%
Iran [22]	2006-7	Tehran	Convenience sampling	Mixed	Established	38	44.4%	10.5%
Iran [22]	2006-7	Tehran	Convenience sampling	Mixed	Established	861	34.1%	10.7%
Iran [23]	2007	Tehran	Convenience sampling	Clinical setting	Established	70	35.7%	30.0%
Iran [24]	2008	Tehran	Convenience sampling	Mandatory drug treatment center	Established	258	65.1%	19.4%
Iran [25]	2007-9	Sari	Convenience sampling	Clinical setting	Established	88	37.5%	18.2%
Iran [26]	2008	Foulad-Shahr	Respondent driven sampling	N/A	Emerging	117	60.7%	1.7%
Iran [27]	2008-	Isfahan	Convenience sampling	Harm reduction center	Low level	531	47.1%	1.1%
Iran [28]	2008-9	Isfahan	Convenience sampling	Prison	Low level	943	41.6%	6.6%
Iran [29]	2009-10	mix of cities	Convenience sampling		Established	158	42.4%	10.1%
Iran [30]	2010	mix of cities	Convenience sampling	Harm reduction center	Established	42	35.7%	7.1%
Iran [30]	2010	mix of cities	Convenience sampling	Harm reduction center	Established	226	38.1%	9.3%
Iran [31]	2010	Shiraz	Convenience sampling	Voluntary drug treatment center	Established	144	50.0%	41.7%
Iran [32]	2012-3	Shiraz	Convenience sampling	Voluntary drug treatment center	Established	233	40.3%	7.7%
Morocco [33]	2010-1	Tanger	Respondent driven sampling	N/A	Low level	261	42.1%	0.4%
Morocco [33]	2011-2	Nador	Respondent driven sampling	N/A	Emerging	277	73.0%	22.0%
Pakistan [34]	2002	mix of cities	Convenience sampling	Mixed	Low level	500	42.0%	3.4%
Pakistan [35]	2003	Quetta	Convenience sampling	Voluntary drug treatment center	Low level	300	44.7%	0.3%
Pakistan [36]	2003	Karachi	Convenience sampling	Harm reduction center	Low level	161	93.8%	0.6%

Country	Year	City	Sampling	Site	HIV epidemic state	Sample size	HCV	HIV
Pakistan [37]	2004	Karachi	Time location sampling	Community	Emerging	402	87.0%	23.1%
Pakistan [37]	2004	Lahore	Time location sampling	Community	Low level	397	91.8%	0.5%
Pakistan [38]	2004	Quetta	Convenience sampling	Community	Emerging	50	60.0%	24.0%
Pakistan [39]	2007	Karachi	Convenience sampling	Clinical setting	Emerging	42	45.2%	19.0%
Pakistan [40]	2007	Rawalpindi	Respondent driven sampling	N/A	Low level	302	17.2%	2.6%
Tunisia [41]	2009	mix of cities	Respondent driven sampling	N/A	Low level	715	29.1%	3.1%
Tunisia [42]	2011	Tunis	Respondent driven sampling	N/A	Low level	506	32.8%	4.7%

N/A: Not applicable

Note 1: In studies using respondent driven sampling, unadjusted sample estimates of HIV and HCV prevalence are displayed

Note 2: The sample size displayed refers to the total number of PWID tested for HIV. In some studies, the sample size used for HCV testing might vary slightly.

References of Table S2

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Figure S1

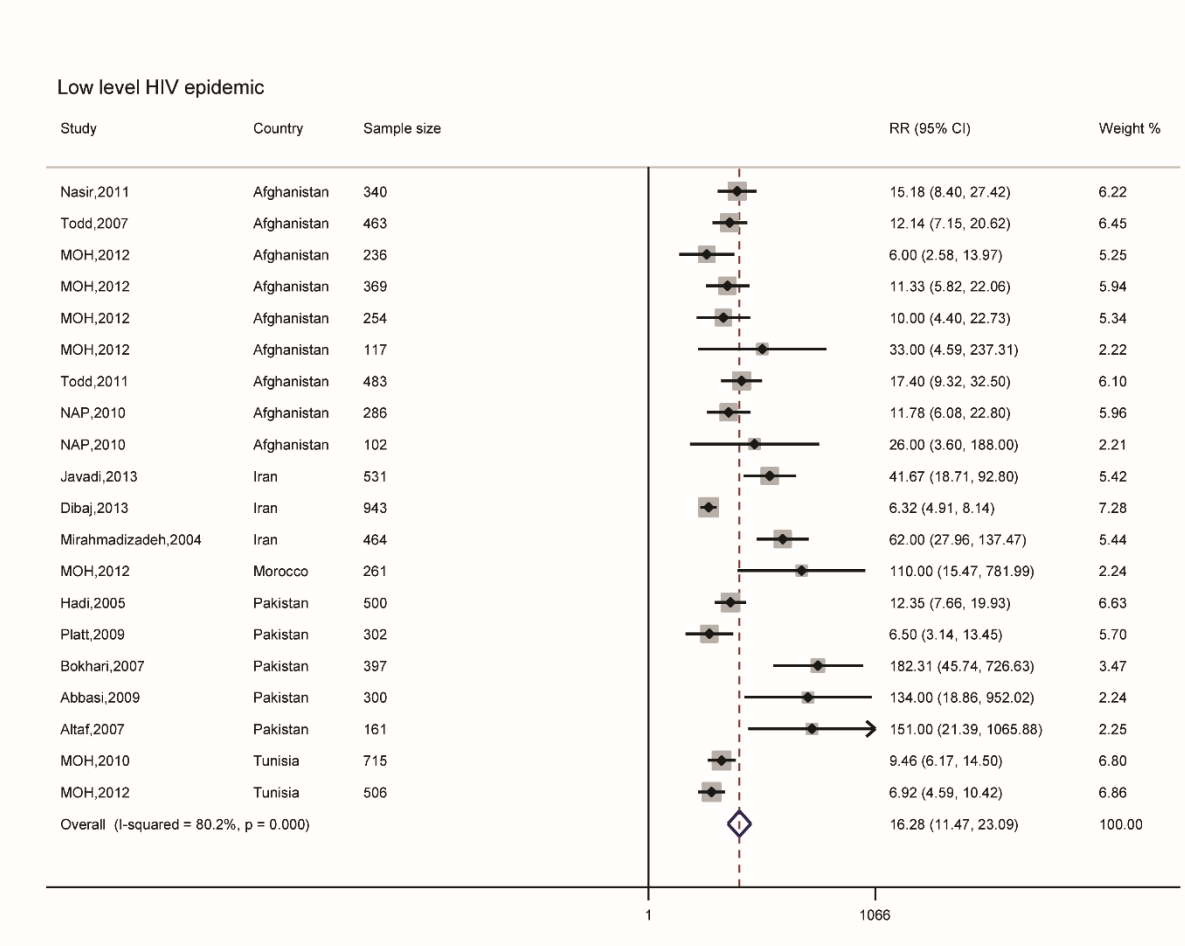

Low level HIV epidemic
Study
Country
Sample size
RR (95% CI)
Weight %
Nasir,2011 Afghanistan 340 15.18 (8.40, 27.42) 6.22
Todd,2007 Afghanistan 463 12.14 (7.15, 20.62) 6.45
MOH,2012 Afghanistan 236 6.00 (2.58, 13.97) 5.25
MOH,2012 Afghanistan 369 11.33 (5.82, 22.06) 5.94
MOH,2012 Afghanistan 254 10.00 (4.40, 22.73) 5.34
MOH,2012 Afghanistan 117 33.00 (4.59, 237.31) 2.22
Todd,2011 Afghanistan 483 17.40 (9.32, 32.50) 6.10
NAP,2010 Afghanistan 286 11.78 (6.08, 22.80) 5.96
NAP,2010 Afghanistan 102 26.00 (3.60, 188.00) 2.21
Javadi,2013 Iran 531 41.67 (18.71, 92.80) 5.42
Dibaj,2013 Iran 943 6.32 (4.91, 8.14) 7.28
Mirahmadizadeh,2004 Iran 464 62.00 (27.96, 137.47) 5.44
MOH,2012 Morocco 261 110.00 (15.47, 781.99) 2.24
Hadi,2005 Pakistan 500 12.35 (7.66, 19.93) 6.63
Platt,2009 Pakistan 302 6.50 (3.14, 13.45) 5.70
Bokhari,2007 Pakistan 397 182.31 (45.74, 726.63) 3.47
Abbasi,2009 Pakistan 300 134.00 (18.86, 952.02) 2.24
Altaf,2007 Pakistan 161 151.00 (21.39, 1065.88) 2.25
MOH,2010 Tunisia 715 9.46 (6.17, 14.50) 6.80
MOH,2012 Tunisia 506 6.92 (4.59, 10.42) 6.86
Overall (I-squared = 80.2%, p = 0.000) 16.28 (11.47, 23.09) 100.00
1
1066

Figure S2

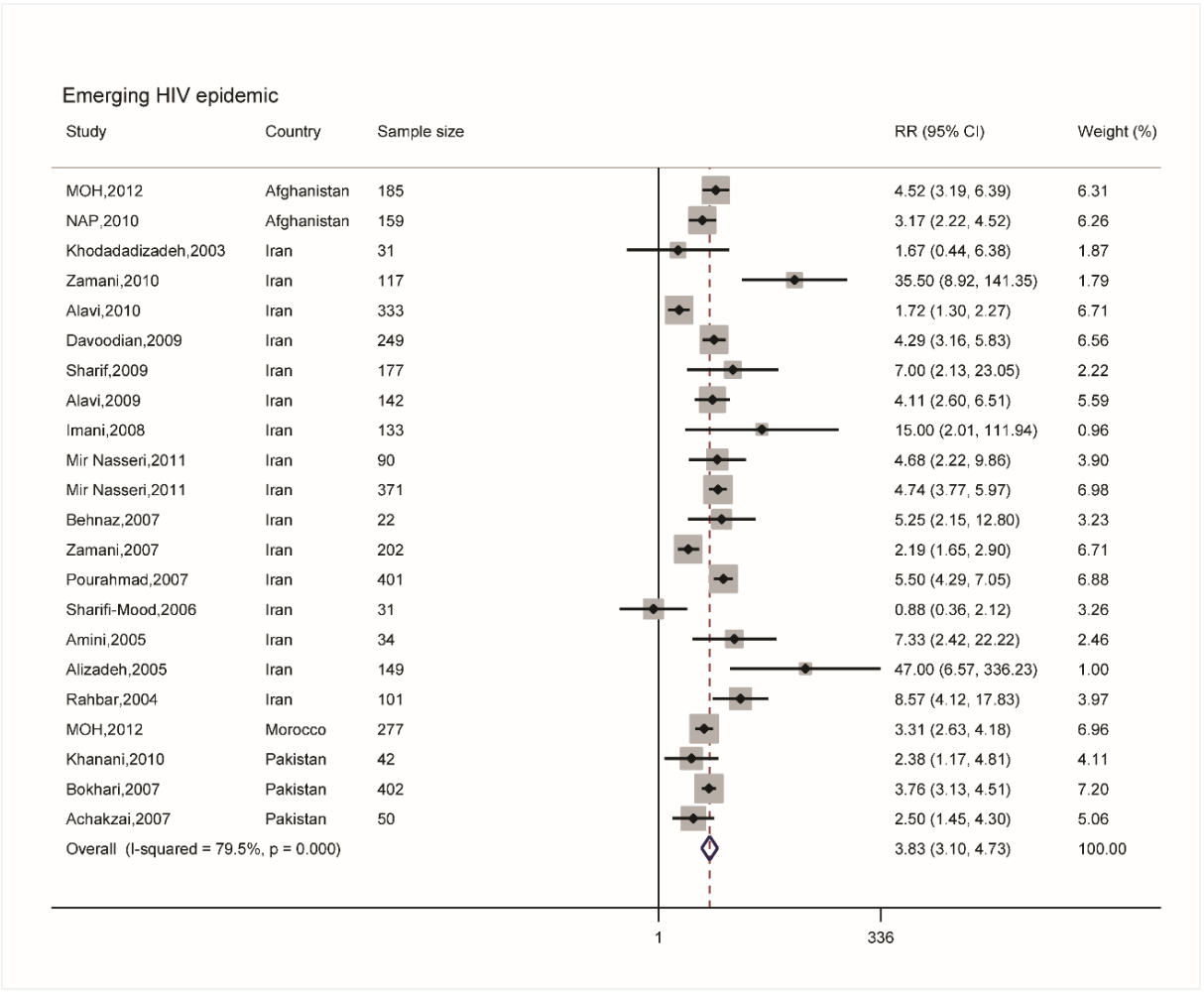
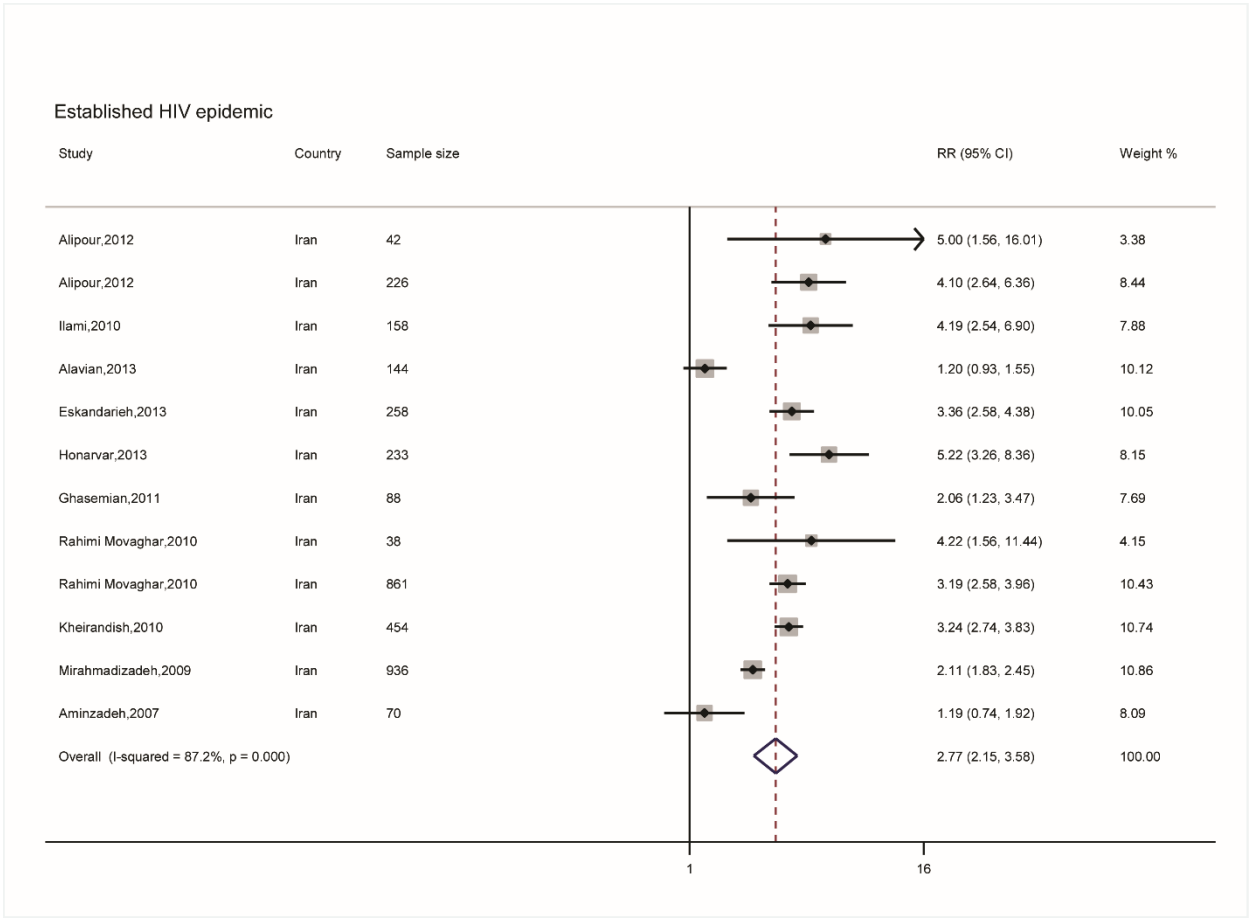

Emerging HIV epidemic
Study
Country
Sample size
RR (95% CI)
Weight (%)
MOH,2012 Afghanistan 185 4.52 (3.19, 6.39) 6.31
NAP,2010 Afghanistan 159 3.17 (2.22, 4.52) 6.26
Khodadadizadeh,2003 Iran 31 1.67 (0.44, 6.38) 1.87
Zamani,2010 Iran 117 35.50 (8.92, 141.35) 1.79
Alavi,2010 Iran 333 1.72 (1.30, 2.27) 6.71
Davoodian,2009 Iran 249 4.29 (3.16, 5.83) 6.56
Sharif,2009 Iran 177 7.00 (2.13, 23.05) 2.22
Alavi,2009 Iran 142 4.11 (2.60, 6.51) 5.59
Imani,2008 Iran 133 15.00 (2.01, 111.94) 0.96
Mir Nasseri,2011 Iran 90 4.68 (2.22, 9.86) 3.90
Mir Nasseri,2011 Iran 371 4.74 (3.77, 5.97) 6.98
Behnaz,2007 Iran 22 5.25 (2.15, 12.80) 3.23
Zamani,2007 Iran 202 2.19 (1.65, 2.90) 6.71
Pourahmad,2007 Iran 401 5.50 (4.29, 7.05) 6.88
Sharifi-Mood,2006 Iran 31 0.88 (0.36, 2.12) 3.26
Amini,2005 Iran 34 7.33 (2.42, 22.22) 2.46
Alizadeh,2005 Iran 149 47.00 (6.57, 336.23) 1.00
Rahbar,2004 Iran 101 8.57 (4.12, 17.83) 3.97
MOH,2012 Morocco 277 3.31 (2.63, 4.18) 6.96
Khanani,2010 Pakistan 42 2.38 (1.17, 4.81) 4.11
Bokhari,2007 Pakistan 402 3.76 (3.13, 4.51) 7.20
Achakzai,2007 Pakistan 50 2.50 (1.45, 4.30) 5.06
Overall (I-squared = 79.5%, p = 0.000) 3.83 (3.10, 4.73) 100.00
1
336

Figure S3


Established HIV epidemic
Study
Country
Sample size
RR (95% CI)
Weight %
Alipour,2012 Iran 42 5.00 (1.56, 16.01) 3.38
Alipour,2012 Iran 226 4.10 (2.64, 6.36) 8.44
Ilami,2010 Iran 158 4.19 (2.54, 6.90) 7.88
Alavian,2013 Iran 144 1.20 (0.93, 1.55) 10.12
Eskandarieh,2013 Iran 258 3.36 (2.58, 4.38) 10.05
Honarvar,2013 Iran 233 5.22 (3.26, 8.36) 8.15
Ghasemian,2011 Iran 88 2.06 (1.23, 3.47) 7.69
Rahimi Movaghar,2010 Iran 38 4.22 (1.56, 11.44) 4.15
Rahimi Movaghar,2010 Iran 861 3.19 (2.58, 3.96) 10.43
Kheirandish,2010 Iran 454 3.24 (2.74, 3.83) 10.74
Mirahmadizadeh,2009 Iran 936 2.11 (1.83, 2.45) 10.86
Aminzadeh,2007 Iran 70 1.19 (0.74, 1.92) 8.09
Overall (I-squared = 87.2%, p = 0.000) 2.77 (2.15, 3.58) 100.00
1
16

8.4. APPENDIX D – RESEARCH PAPER 4 SUPPLEMENTARY ONLINE MATERIAL

Outline

Additional file 1. Mathematical models description and other analyses

Additional file 1
Description of mathematical model and other analyses

A. Original Kwon et al model

Below is the derivation of the original model developed by Kwon et al [1], which we used and further adapted for estimating HIV incidence among people who inject drugs (PWID) in the Middle East and North Africa (MENA). The model is a static mathematical model of HIV transmission among PWID who share needles/syringes. The model assumes that sharing of needles/syringes occurs in sharing groups of specific average size, where PWID share needles/syringes in a random order, and where each PWID injects once per sharing event.

Table 1. Parameters used in the original Kwon et al model [1]

Parameter	Description
N	Total number of PWID
m	Average number of PWID in a sharing group
n	Average number of injections per PWID per year
s	Proportion of PWID who share injections
q_0	Proportion of the injections that are shared
r	Number of PWID infected in the sharing group
p_0	HIV prevalence among PWID
β	Probability of transmission from a contaminated needle/syringe
ε_c	Effectiveness of needle/syringe cleaning
P_c	Proportion of shared injections that are cleaned
δ_s	Average number of times a shared needle/syringe is used before disposal

The following series of equations describe the Kwon et al model:

- Total number of shared injections per year:

$$S = Nnsq$$

- Average number of sharing events per year:

$$SE = \frac{Nnsq}{m}$$

- Total number of transmissions per year for all PWID (incidence):

$$I = SE * T$$

where T is the average number of transmissions per sharing event

Deriving *T*, the average number of transmissions per sharing event:

- Probability of having r infected people in a sharing group of size m using binomial theory:

$$\mathrm{P}_{r/m} = \binom{m}{r} p_0^{\,r}(1-p_0)^{m-r} = \frac{m!}{r!(m-r)!} p_0^{\,r}(1-p_0)^{m-r}$$

- Average number of uninfected who will inject *before* the first infected in a sharing event:

$$U_b = \frac{m-r}{r+1}$$

- Average number of uninfected who will inject *after* an infected person in a sharing event:

$$U_a = m - r - U_b = \frac{mr - r^2}{r+1}$$

- Average number of needles/syringes used per sharing event:

$$Sy = \frac{m}{\delta_s}$$

- Average number of uninfected who will use the *same needle/syringe after* an infected person in a sharing event:

$$U_s = \frac{U_a}{Sy} = \frac{mr - r^2}{r+1}\frac{\delta_s}{m}$$

- Probability of transmission per shared injection:

$$\beta_c = \beta(1-p_c) + \beta p_c(1-\varepsilon_c) = \beta(1-p_c\varepsilon_c)$$

- Number of transmissions in the sharing group (per sharing event):

$$T = \sum_{r=1}^{m-1} U_s \beta_c \,\mathrm{P}_{r/m} = \sum_{r=1}^{m-1} \frac{mr - r^2}{r+1}\frac{\delta_s}{m} * \beta(1-p_c\varepsilon_c) * \binom{m}{r} p_0^{\,r}(1-p_0)^{m-r}$$

$$T = \frac{\delta_s \beta(1-p_c\varepsilon_c)}{m} \sum_{r=1}^{m-1} \frac{mr - r^2}{r+1} \binom{m}{r} p_0^{\,r}(1-p_0)^{m-r}$$

- Total number of transmissions per year for all PWID (incidence):

$$I = SE * T$$

$$I = \frac{Nnsq\delta_s \beta(1-p_c\varepsilon_c)}{m^2} \sum_{r=1}^{m-1} \frac{mr - r^2}{r+1} \binom{m}{r} p_0^{\,r}(1-p_0)^{m-r}$$

- Incidence rate:

$$\lambda = \frac{I}{N(1-p_0)}$$

B. Modifications to the original Kwon et al model

We further adapted the above model by Kwon et al [1] using the following extensions:

1) Antiretroviral therapy (ART)

We adjusted for the use of antiretroviral therapy (ART) on HIV incidence by incorporating ART effect into the transmission probability per shared injection/coital act:

$$\beta' = \beta(1 - \Omega ART)$$

Where:

β' = ART-adjusted transmission probability per unprotected exposure

β = Original/unadjusted (for ART) transmission probability per unprotected exposure

Ω = Reduction in HIV transmission per exposure due to ART

ART = Proportion of the population on ART (ART coverage)

2) Heterogeneity in risk behavior

The original Kwon et al model [1] uses a fixed level of injecting risk behavior for all PWID. To account for heterogeneity in risk behavior, we accommodated different sizes of the sharing group m. Specifically, we assumed that m follows a gamma distribution with a mean equal to $m_{average}$. The gamma distribution is right skewed, and therefore assumes that the majority of the PWID population shares injections in smaller groups whereas a small fraction shares in larger groups (such as at shooting galleries). Therefore m is gamma distributed with shape (k) and scale (θ) parameters:

$$P(m) = \frac{1}{\Gamma(m)\theta^k} m^{k-1} e^{-\frac{m}{\theta}}$$

In absence of clear data to parameterize the variability in injecting risk behavior in a given PWID population, the structure of the model was informed by data on the variability in sexual risk behavior and networking, where we assumed that the variance of the gamma distribution is equal to its mean [2]. Accordingly, the scale parameter $\theta = 1$ and the shape parameter $k = m_{average}$.

$m_{average}$ was estimated using a deterministic compartmental model [3] to fit the trend in HIV prevalence in two countries with sufficient available trend data (Pakistan and Iran), and then using the estimated incidence rate and the present adapted Kwon et al model to predict using fitting the value of the sharing group size in our model. The fitting was implemented by minimizing the residual sum of squares between all data points and model predictions [4]. Based on the fitting, a value of $m_{average} = 2$ was found for Pakistan and of $m_{average} = 3$ for Iran.

In the remaining countries, we did not have sufficient data to inform a country-specific estimation of $m_{average}$. Based on the range of 2-3 obtained for Iran and Pakistan, and as informed by epidemiological data from Iran [5, 6], we used a value of $m_{average} = 3$ in the remaining countries.

3) Needle/Syringe reuse

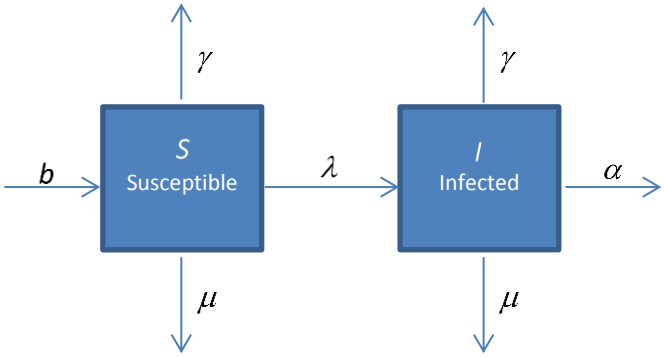
In the original Kwon et al model [1], the number of times a needle/syringe is reused before disposal (δ_s) is fixed and is independent of the size of the sharing group m. Since the model also assumes a fixed total number of injections in the population, fixing δ_s will constrain the transmission system after a certain value of m leading to smaller HIV incidence with larger sharing groups. This was a fair assumption in the study setting of Australia where there are effective needle and syringe exchange programs (NSPs) leading to less needle/syringe reuse, where the size of the sharing group is small ($m = 2$), and where HIV incidence among PWID is low [1].

In the MENA context of emerging HIV epidemics among PWID [7], high levels of needle/syringe reuse, and weak interventions including NSPs among PWIDs, we have modified the above assumption by relating the number of times a needle/syringe is reused before disposal (δ_s) to the size of the sharing group (m). We assumed that if $m < 10$, then $\delta_s = 10$; that is all the PWID in the sharing group will use the same needle/syringe. If $m \geq 10$, then $\delta_s = m$; that is a needle/syringe is reused for a maximum of ten times in any sharing event.

C. Additional analyses

1) Estimating HIV prevalence at endemic equilibrium

To estimate HIV prevalence at endemic equilibrium (P_e) using the estimated HIV incidence rate, the following generic model was used:



The above deterministic compartmental mathematical model describes the parenteral transmission of HIV through sharing unsterile needles/syringes among PWID. Individuals become PWID, and hence enter into the PWID population, at a rate b . . μ . is the natural mortality rate, γ is the leaving injecting career rate, and α is the HIV/AIDS disease mortality rate. λ is the incidence rate (or force of infection) experienced by the susceptible population S . The model is expressed with the below system of coupled differential equations:

$$\frac{dS}{dt} = b - \mu S - \gamma S - \lambda S$$

$$\frac{dI}{dt} = \lambda S - \mu I - \gamma I - \alpha I$$

<u>At endemic equilibrium:</u>

$\frac{dI}{dt} = 0$, and hence $P_e = \frac{\lambda}{\mu + \gamma + \alpha + \lambda}$

2) Past exposures in PWID

To estimate the total number of HIV infections that occurred in PWID since the start of the HIV epidemic among PWID, we retraced the course of the HIV epidemic among PWID at country-level starting from epidemic emergence. The year of epidemic emergence was informed by epidemiological data from each country [7]. We ran, in each country, the model x number of times, where x is the number of years since HIV epidemic emergence. We assumed that at year 0, HIV prevalence is 1% ($p_{y_0} = 0.01$).

The total number of infected PWID in year 1 includes both prevalent infections from the previous year and incident infections in this year, and is given by:

$$Inf_{y_1} = Incident_{y_1} + prevalent_{y_0}$$

$$Inf_{y_1} = I_{y_1} + Np_{y_0}$$

Assuming that the incident infections occur in the middle of the year, the number of HIV infected PWID who will leave the PWID population in year 1 due to leaving injection (γ), natural mortality (μ), or disease mortality (α) is given by:

$$n_{out}^{y_1} = (\frac{I_{y1}}{2} + Np_{y_0}) \times (\mu + \gamma + \alpha)$$

Therefore, HIV prevalence at the end of year 1 will be given by:

$p_{y_1} = \frac{Inf_{y_1} - n_{out}^{y_1}}{N}$ (Note: we assume a fixed total PWID population size ' N ')

The model is then run for year 2 starting with HIV prevalence p_{y_1} . The same calculations and processes are repeated x times.

It bears notice that the number of HIV infected PWID who will leave the PWID population in year 1 due only to leaving injection is given by:

$$n_{past}^{y_1} = (\frac{I_{y1}}{2} + Np_{y_0}) \times \gamma$$

Accordingly, the number of HIV infected PWID who left the PWID population due to leaving injection in each subsequent year is calculated the same way.

Iterating this process until the last (current) year will provide an estimate for HIV prevalence in the last year. However, in the runs for countries, we were not often able to reach observed HIV prevalence, with the last year estimated prevalence being lower than observed prevalence. We therefore increased the level of risk behavior at year 0, to account for higher risk behavior in earlier years of the epidemic, and used linear interpolation for the level of injecting risk behavior from year 0 to the last year, in order to reach observed levels of risk behavior and HIV prevalence at the last (current) year.

In Libya, the measured HIV prevalence (87% [8]) was not consistent with reported levels of current risk behavior. With such levels of risk behavior, the maximum current HIV prevalence the model could reach was 52%; and hence, estimations of past exposures were not possible in Libya.

3) HIV incidence in PWID sexual partners

In a sero-discordant partnership where the PWID is HIV-infected and the sexual partner (opposite sex; only heterosexual transmission was considered) is seronegative, the probability of HIV transmission after one year is given by:

$$z = 1 - (1 - \beta_s)^{y(1-c)}$$

where:

β_s = HIV transmission probability per unprotected coital act

y = Number of coital acts per year

c = Proportion of the coital acts that are protected (condom use at last sex)

The number of sero-discordant partnerships is given by:

$$n_{disc} = Nvp_0(1 - p_p)$$

where:

N = Total number of PWID

v = Proportion of PWID who had a sexual partner in the last year

p_0 = HIV prevalence among PWID

p_p = HIV prevalence among sexual partners of PWID (which was assumed to be equal to one third of HIV prevalence among PWID)

HIV incidence among PWID sexual partners is therefore given by:

$$I_{fsp} = n_{disc} z$$

$$I_{fsp} = Nvp_0(1-p_p)(1-(1-\beta_s)^{y(1-c)})$$

4) Past exposures in PWID sexual partners

HIV incidence in PWID heterosexual sex partners was calculated for each year since start of the HIV PWID epidemic in each MENA country using the year-specific HIV prevalence measures in PWID (P_{y_x}) as estimated in section C2 above (Past exposures in PWID).

References of Additional file 1

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