

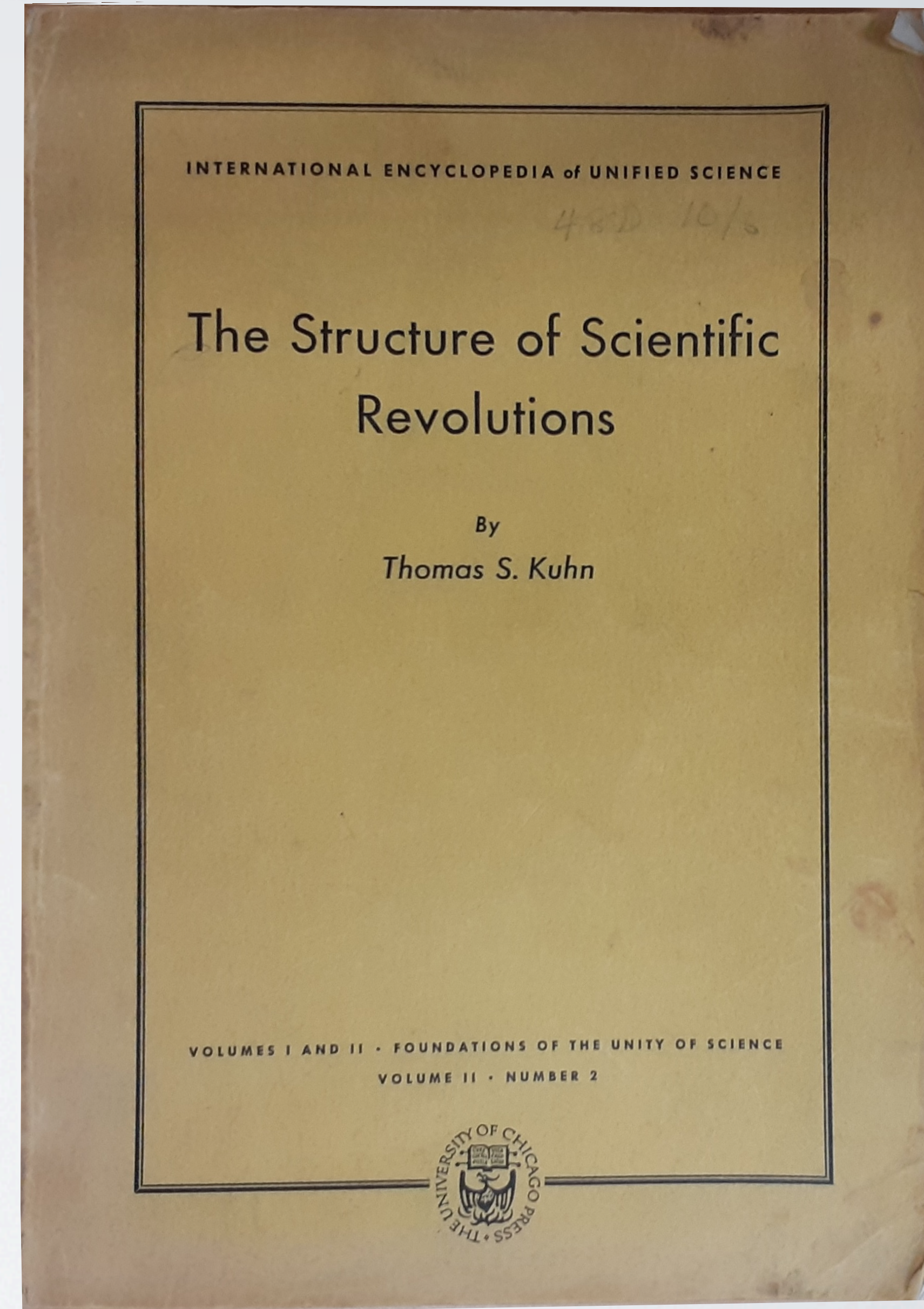
INVISIBLE FRONTLINES— COMBATING HEPATITIS C IN MEN WHO HAVE SEX WITH MEN AND TRANSGENDER COMMUNITIES

Daniel S. Fierer, MD, FIDSA

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ISM at Mount Sinai

REDEFINING THE PARADIGM/DOGMA

- HCV is solely a blood borne pathogen
- Therefore/that is, HCV is not sexually transmitted
- When drug use is present, it is drug use that caused the HCV infection



REDEFINING THE PARADIGM/DOGMA

- The main route of transmission of HCV among MSM and their sex partners (ie including trans women) is sexual
- Therefore/that is, the main transmitting body fluid is semen, not blood
- Drug use is not causally involved in these HCV transmissions
- Sexual transmission among MSM is not so inefficient
- HCV prevalence in sexual networks is heterogeneous

CASE

- 33 yo cisgender MSM with asymptomatic HIV infection on ART. He lives in NYC and has multiple sex partners in NYC and while traveling in Europe. He presents for routine medical visit.
- HIV viral load: <20 (ND) copies/mL [CD4 count: 670/42% cells/uL]
- ALT/AST: 5 | 5/365
- hepatitis C Ab positive

Primary HCV in MSM with HIV: Initial Epidemic Reports



Primary HCV in MSM with HIV: Global Epidemic Reports



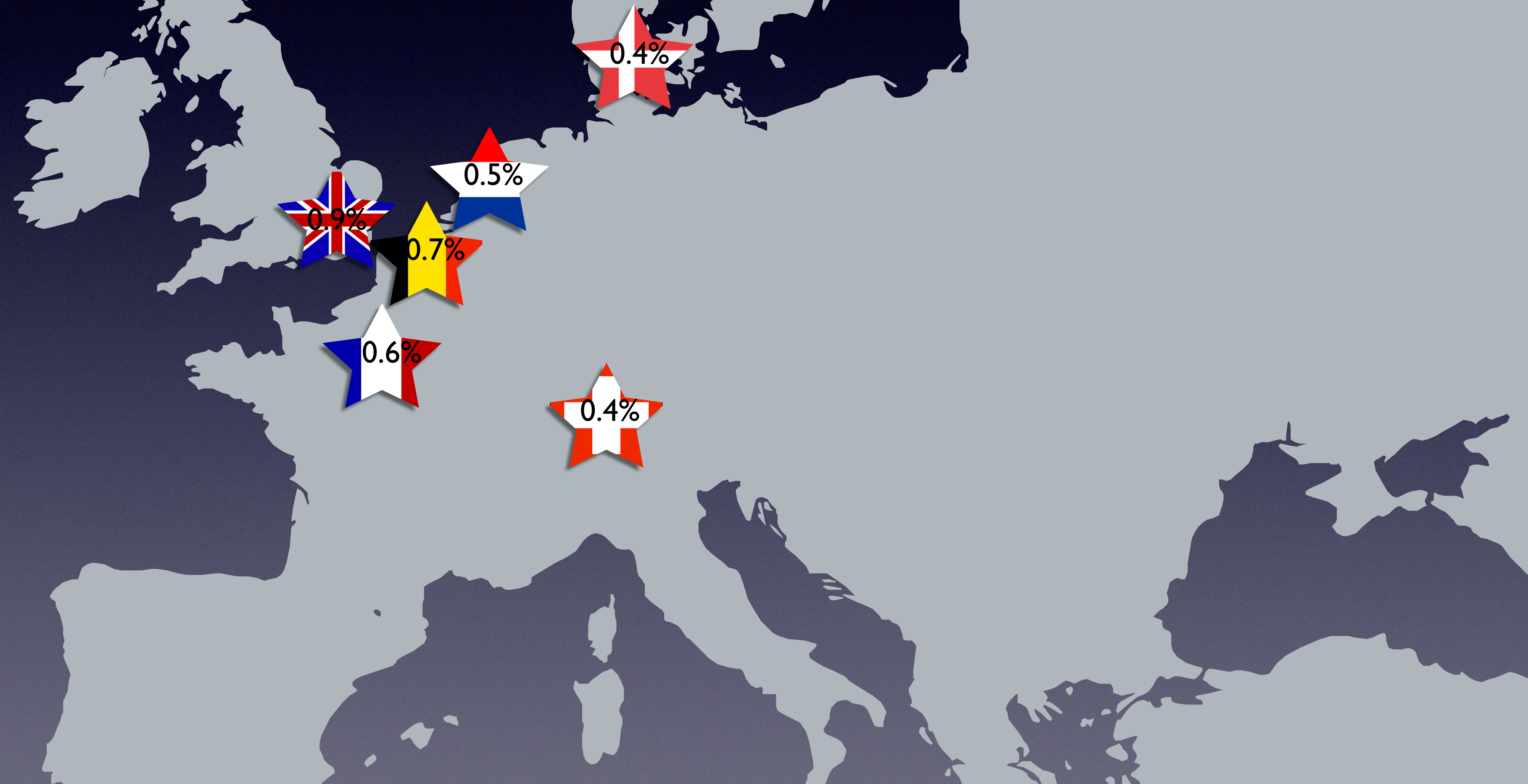
Primary HCV in MSM with HIV: Global Epidemic Incidence



HEPATITIS C PREVALENCE IN TRANS AND GENDER DIVERSE POPULATIONS IN THE US

Study / Location	Population	HCV Prevalence	Notes
Mangla 2017 (NYC)	TGD, gender clinic	1.78% TW; 0% TM	Screening ~27%
Reisner 2014 (Boston)	LGBTQ clinic	3.1% TW; 2.4% TM	Clinic cohort, 12-29 yrs
Wilson 2019 (San Francisco)	Trans women	23% TW	36% reported IDU; high rates of HCV screening
Wolfe 2024 (National claims data)	TGD overall	1.8% TW; 0.73%TM	General pop ≈ 1%

Primary HCV in MSM with HIV: Global Epidemic Incidence



Primary HCV in MSM with HIV: Global Epidemic Incidence

FAST TRACK
AIDS 2011, 25:F21–F27

Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM

Femke A.E. Lambers^a, Maria Prins^{a,b}, Xiomara Thomas^c, Richard Molenkamp^c, David Kwa^d, Kees Brinkman^e, Jan T.M. van der Meer^b, Janke Schinkel^c, on behalf of the

persons were re-infected. The incidence of HCV re-infection in this group was **15.2 per 100 person-years** (95% confidence interval 8.0–26.5). The cumulative incidence was 33% within 2 years.

Background: Hepatitis C virus (HCV) is a well-known blood-borne virus. Infection with HCV is often asymptomatic and can lead to chronic liver disease. In HIV-infected individuals, the risk of HCV re-infection after treatment is high.

who were HCV RNA-negative following HCV treatment of acute primary infection.

Methods: Our study population comprised HIV-infected MSM at two large HIV outpatient clinics in Amsterdam, who were previously diagnosed with a sexually transmitted acute HCV infection and tested HCV RNA-negative at the end of treatment. We defined HCV re-infection as detectable HCV RNA in individuals with an undetectable HCV RNA at the end of treatment accompanied by a switch in HCV genotype or clade. Person-time methods were used to calculate the incidence of re-infection.

Results: Fifty-six persons who became HCV RNA-negative during primary acute HCV treatment were included. Five of the 56 cases relapsed and were not analysed. Eleven persons were re-infected. The incidence of HCV re-infection in this group was 15.2 per 100 person-years (95% confidence interval 8.0–26.5). The cumulative incidence was 33% within 2 years.

Discussion: An alarmingly high incidence of HCV re-infection was found in this group. This high re-infection rate indicates that current prevention measures should be discussed, frequent HCV RNA testing should be continued after successful treatment and, in case of possible relapse, clade typing should be performed to exclude re-infection.

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AIDS 2011, 25:F21–F27

Keywords: hepatitis C virus, HIV, MSM, re-infection

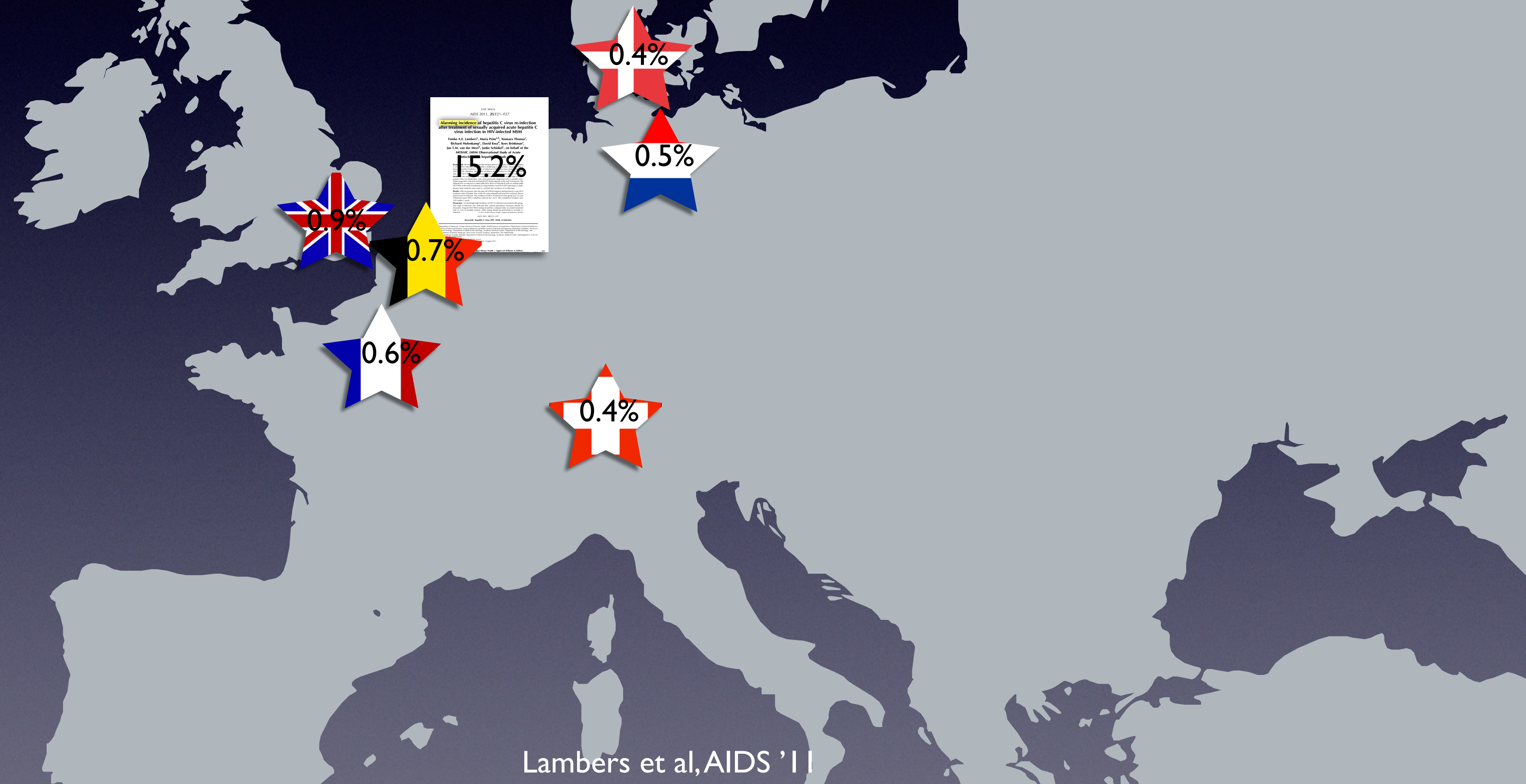
^aDepartment of Research, Cluster Infectious Diseases, Public Health Service of Amsterdam, ^bDepartment of Internal Medicine, Division of Infectious Diseases, Tropical Medicine and AIDS, Center for Infection and Immunity Amsterdam (CINIMA), ^cSection of Clinical Virology, Department of Medical Microbiology, Academic Medical Center, ^dDepartment of Microbiology, and ^eDepartment of Internal Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands.

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HCV in MSM with HIV: Reinfection Incidence



HCV in MSM with HIV: Reinfection Incidence



HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe

Patrick Ingiliz^{1,*}, Thomas C. Martin^{2,1}, Alison Rodger³, Hans-Jürgen Stellbrink⁴, Stefan Mauss⁵, Christoph Boesecke⁶, Mattias Mandorfer⁷, Julie Bottero⁸, Axel Baumgarten¹, Sanjay Bhagani³, Karine Lacombe^{8,9}, Mark Nelson^{2,10}, Jürgen K. Rockstroh⁶, NEAT study group

¹Center for Infectiology (CIB), Berlin, Germany; ²Chelsea and Westminster Hospital, London, United Kingdom; ³The Royal Free Hospital, London, United Kingdom; ⁴Infectiology Center Hamburg (ICH), Hamburg, Germany; ⁵Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; ⁶University of Bonn, Department of Medicine I, Bonn, Germany; ⁷Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; ⁸Service des maladies infectieuses et tropicales, Hôpital Saint-Antoine, AP-HP, France; ⁹Sorbonne Universités, UPMC Univ Paris 06, INSERM, Institut Pierre Louis d'épidémiologie et de Santé Publique (IPLESP UMRS 1136), Paris, France; ¹⁰Imperial College School of Medicine, London, United Kingdom

See Editorial, pages 267–269

Background & Aims: Moderate cure rates of acute hepatitis C virus (HCV) infections with pegylated interferon and ribavirin have been described in the last decade in men who have sex with men (MSM), who are also coinfecting with the human immunodeficiency virus (HIV). However, a subsequent high incidence of HCV reinfections has been reported regionally in men who both clear the infection spontaneously or who respond to treatment. **Methods:** Retrospective analysis of reinfections in HIV infected MSM in eight centers from Austria, France, Germany, and the UK within the NEAT network between May 2002 and June 2014. **Results:** Of 606 individuals who cleared HCV spontaneously or were successfully treated, 149 (24.6%) presented with a subsequent HCV reinfection. Thirty out of 70 (43%) who cleared again or were successfully treated, presented with a second reinfection, 5 with a third, and one with a fourth reinfection. The reinfection incidence was 7.3/100 person-years (95% CI 6.2–8.6). We found a trend for lower incidence among individuals who had spontaneously cleared their incident infection than among individuals who were treated (Hazard ratio 0.62, 95% CI 0.38–1.02, $p = 0.06$). Spontaneous clearance of reinfection was associated with ALT levels >1000 IU/ml and spontaneous clearance of a prior infection. **Conclusions:** HCV reinfection is an issue of major concern in HIV-positive MSM. Prevention strategies are needed for high risk groups to reduce morbidity and treatment costs. HIV-positive MSM with a prior HCV infection should be tested every 3 to 6 months for reinfection. Those who had achieved a reinfection should be tested every 3 months.

Keywords: HCV reinfection; Acute hepatitis C; HIV-HCV coinfection; SVR; Spontaneous clearance; HCV therapy.
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E-mail address: ingiliz@cibp.de (P. Ingiliz).

¹ These authors contributed equally to this work.



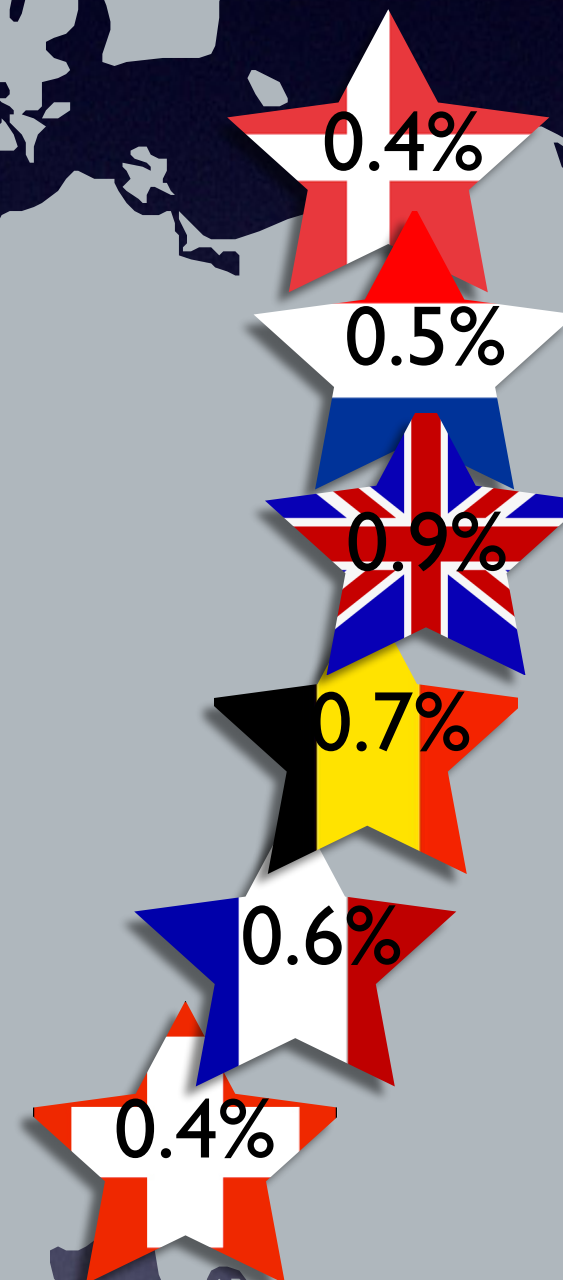
Journal of Hepatology 2017 vol. 66 | 282–287

Lay summary: We evaluated the occurrence of HCV reinfection in HIV-positive men who have sex with men. We found an alarming incidence of 7.3/100 person-years. Prevention measures need to address this specific subgroup of patients at high risk for HCV. © 2016 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

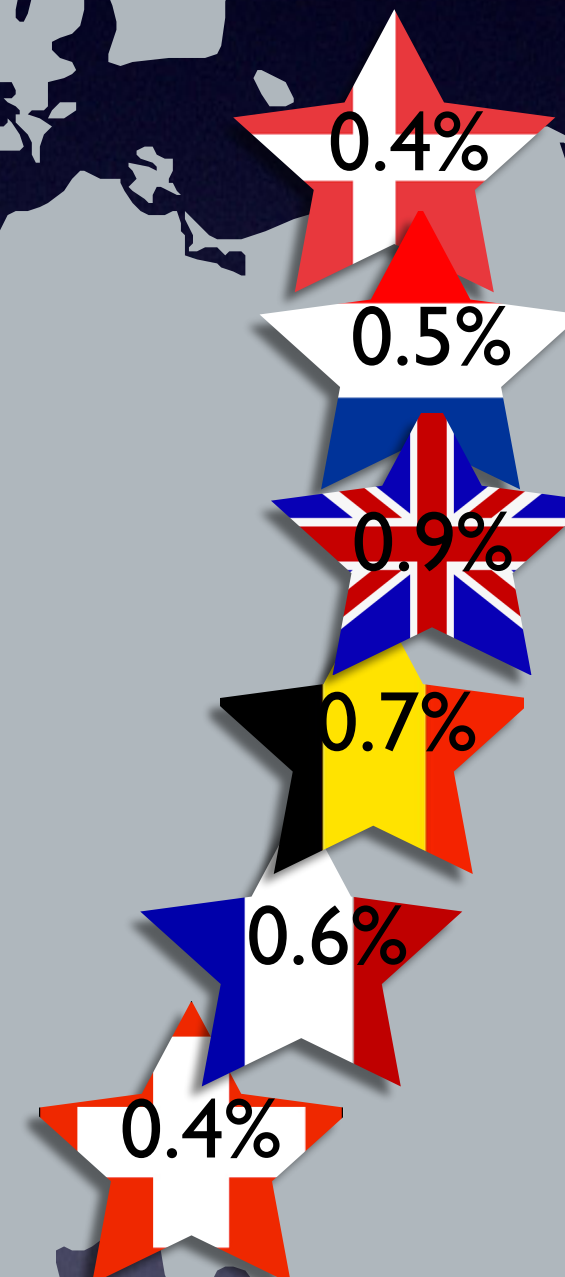
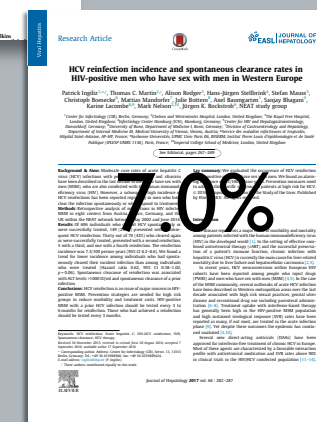
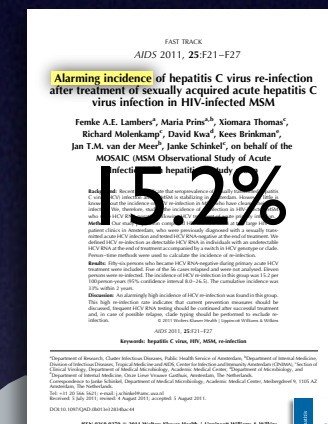
Introduction

Liver disease represents a major cause of morbidity and mortality among patients infected with the human immunodeficiency virus (HIV) in the developed world [1]. In the setting of effective combined antiretroviral therapy (cART) and the successful preservation of a patient's immune function, chronic infection with hepatitis C virus (HCV) is currently the main cause for liver related mortality due to liver failure and hepatocellular carcinoma [2,3]. In recent years, HCV seroconversions within European HIV cohorts have been reported among people who inject drugs (PWID) and men who have sex with men (MSM) [4,5]. In the case of the MSM community, several outbreaks of acute HCV infection have been described in Western metropolitan areas over the last decade associated with high risk sexual practices, genital ulcer disease and recreational drug use including parenteral administration [6–8]. Treatment uptake with interferon-based therapy has generally been high in the HIV-positive MSM population and high sustained virological response (SVR) rates have been reported as many, if not most, are treated in the acute infection phase [9]. Yet despite these outcomes the epidemic has continued unabated [5,10].

Several new direct-acting antivirals (DAAs) have been approved for interferon-free treatment of chronic HCV in Europe. Most of these agents are characterized by a favorable interaction profile with antiretroviral medication and SVR rates above 90% in clinical trials in the HIV/HCV coinfecting population [11–14].



HCV in MSM with HIV: Reinfection Incidence



HCV in MSM with HIV: Reinfection Incidence

CONCISE COMMUNICATION

AIDS 2018, **32**:1077–1082

Incidence of new hepatitis C virus infection is still increasing in French MSM living with HIV

Pierre Pradat^a, Thomas Huleux^b, François Raffi^{c,d}, Pierre Delobel^{e,f,g},
Marc-Antoine Valantin^{h,i,j}, Isabelle Poizot-Martin^{k,l,m},
Pascal Puglieseⁿ, Jacques Reynes^{o,p}, David Rey^q, Bruno Hoen^{r,s,t},
André Cabie^{u,v,w}, Firouzé Bani-Sadr^{x,y}, Antoine Cheret^{z,aa},
Claudine Duvivier^{bb,cc}, Christine Jacomet^{dd}, Anne Fresard^{ee},
Laurent Hustache-Mathieu^{ff}, Laurent Cotte^{gg,hh},
the Dat'AIDS study Group

Objective: High hepatitis C virus (HCV) treatment uptake combined with effective direct-acting antiviral-based regimens resulted in a dramatic decline of HCV infection in French people living with HIV (PLWH). We assessed the yearly incidence of new HCV infection in PLWH enrolled in the large French Dat'AIDS cohort from 2012 to 2016 with a specific focus on MSM.

Methods: The incidence of new HCV infection was determined yearly in HCV-negative PLWH with serological follow-up during 2012–2016. The incidence of HCV reinfection was determined in patients who were cured of a previous infection.

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Correspondence to Laurent Cotte, Department of Infectious Diseases and Tropical Medicine, Croix-Rousse Hospital, 103 grande rue de la Croix-Rousse, 69317 Lyon Cedex 04, France.

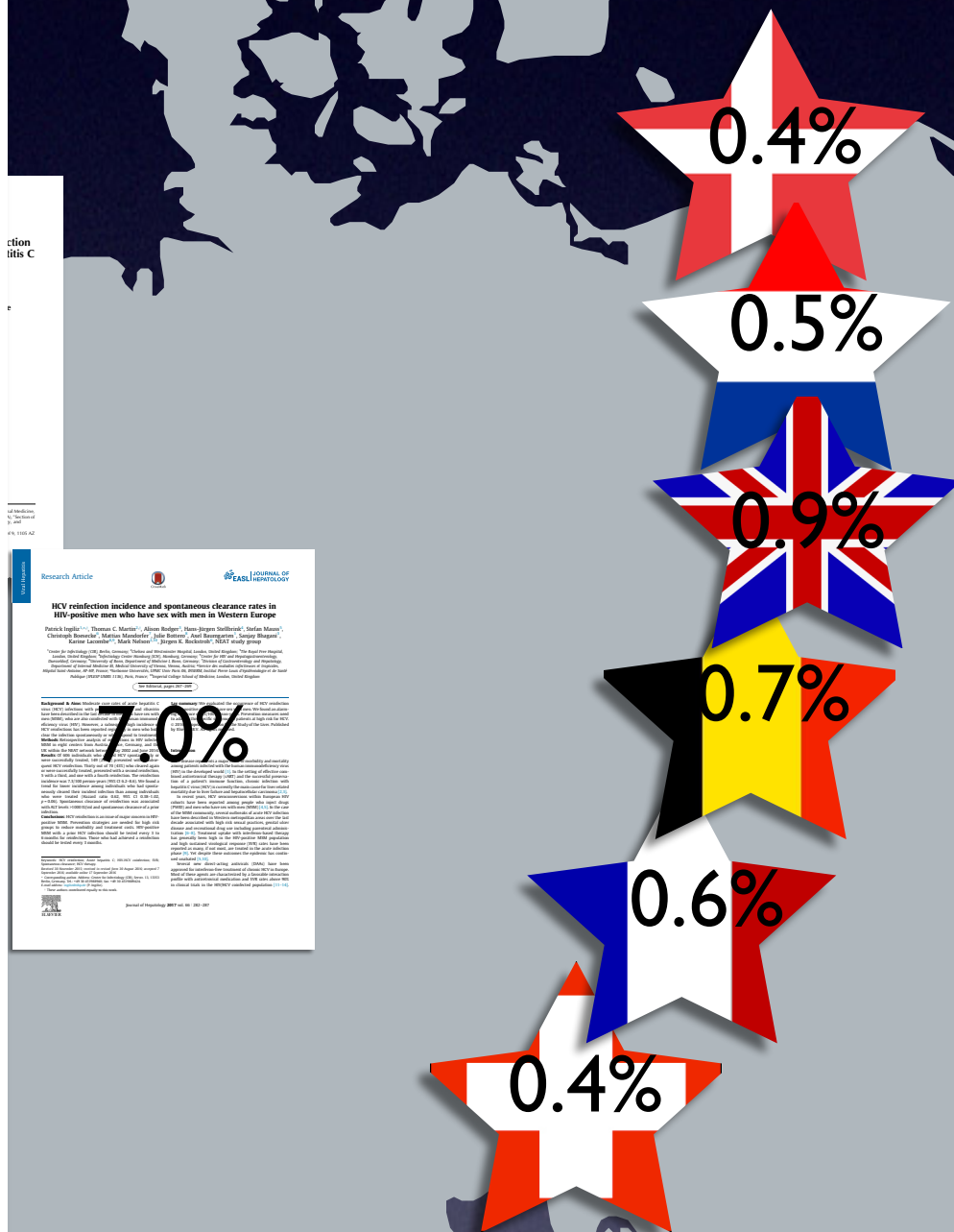
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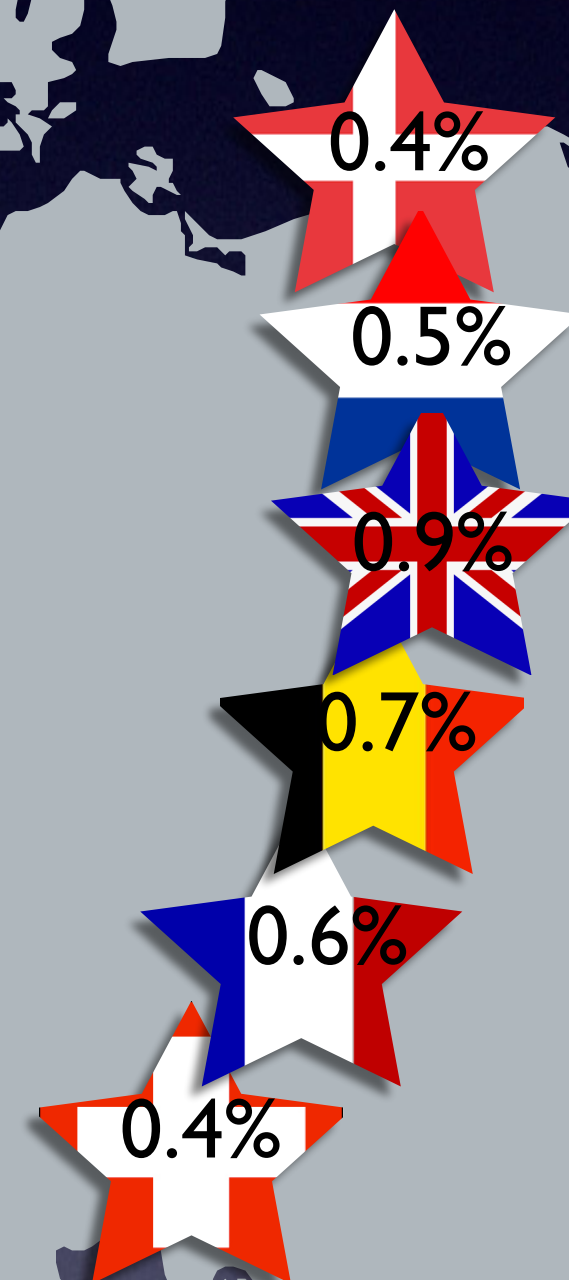
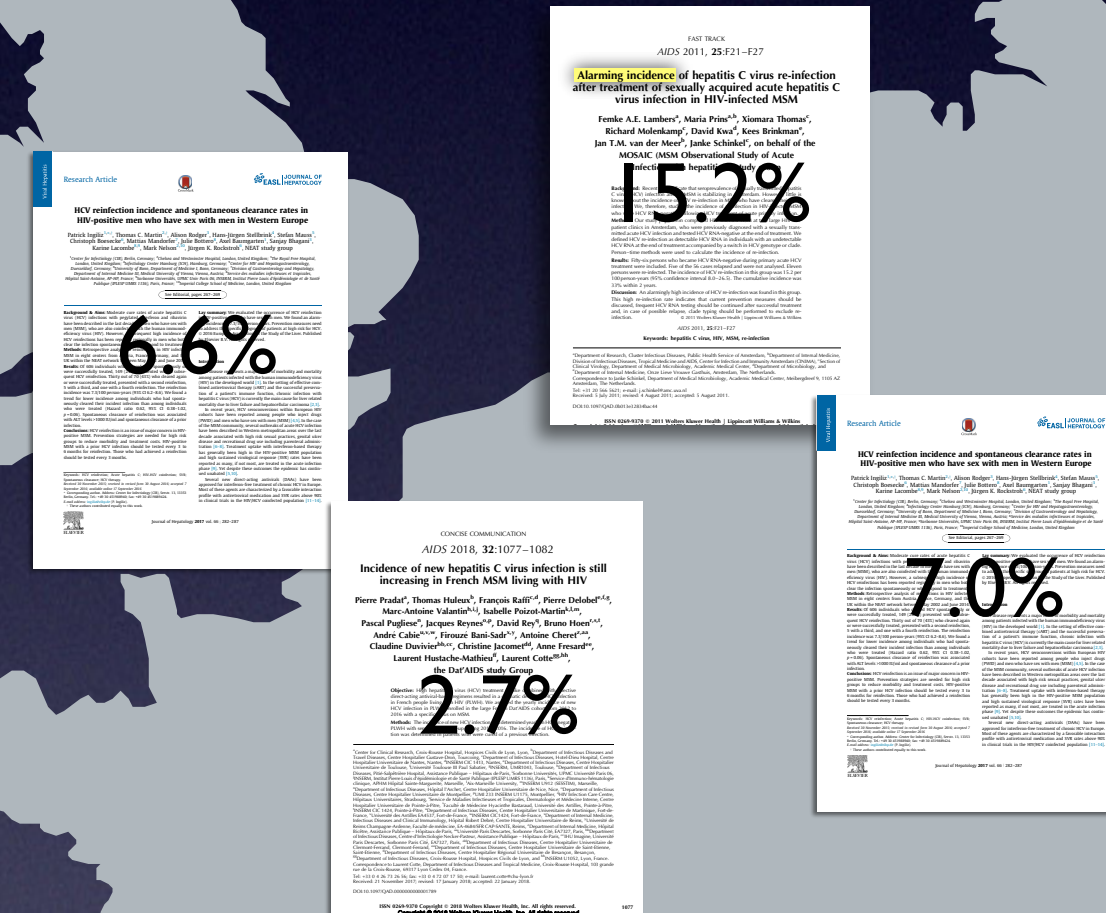
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1077



HCV in MSM with HIV: Reinfection Incidence



PRIMARY HCV: ACQUISITION RISK FACTORS

7 case-control studies with multivariable analyses:

Danta	AIDS 2007	London
Fierer	MMWR 2011	New York
Schmidt	PLoS One 2011	Germany
Wandeler	CID 2012	Switzerland
Witt	CID 2013	Baltimore, Pittsburgh, Los Angeles, Chicago
Apers	JAIDS 2015	Belgium
Vanhommerig	OFID 2015	Netherlands

CONDOMLESS RECEPTIVE ANAL INTERCOURSE (5 OF 7)	
YES	NO
Danta [group sex only] Fierer Wandeler Witt Vanhommerig	Schmidt Apers
DRUGS INJECTED (2 OF 4)	
YES	NO
Witt Vanhommerig	Danta Apers [Fierer, Wandeler, Schmidt excluded injection]
DRUGS SNIFFED (2 OF 5)	
YES	NO
Schmidt Vanhommerig	Danta Fierer Apers
GROUP SEX (3 OF 5)	
YES	NO
Danta Apers Vanhommerig	Fierer Schmidt
FISTING (4 OF 5)	
YES	NO
Danta [group sex only] Schmidt Apers Vanhommerig	Fierer

PRIMARY HCV: ACQUISITION RISK FACTORS

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Witt	
Vanhommerig	
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Vanhommerig	

PRIMARY HCV: ACQUISITION RISK FACTORS

Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Weekly / Vol. 60 / No. 28

July 22, 2011

World Hepatitis Day — July 28, 2011

July 28, 2011, marks the first official World Hepatitis Day established by the World Health Organization (WHO). CDC joins with WHO in calling for a renewed commitment against a largely silent but persistent epidemic. Worldwide, nearly 500 million persons are living with chronic hepatitis B virus or hepatitis C virus (HCV) infections, and these infections cause approximately 1 million deaths annually (*1*); most persons with chronic

Sexual Transmission of Hepatitis C Virus Among HIV-Infected Men Who Have Sex with Men — New York City, 2005–2010

In the United States, an estimated 3.2 million persons are living with hepatitis C virus (HCV) infection (*1*). HCV transmission occurs primarily through percutaneous exposure to blood, and persons who inject drugs are at greatest risk for infection. The role of sexual transmission of HCV has not been well defined. However, reports over the past decade,

Multivariable analysis:

Sex:

- CRAI with ejaculation of semen into rectum:
OR=23

Sexualized drug use:

- CRAI with crystal methamphetamine use
(injection excluded; no route dominant):
OR=29

PRIMARY HCV: ACQUISITION RISK FACTORS

Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

MAJOR ARTICLE

Open Forum Infect Dis Sep 2015

Weekly / Vol. 60 / No. 28

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Risk Factors for Sexual Transmission of Hepatitis C Virus Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men: A Case-Control Study

Joost W. Vanhommerig,^{1,2} Femke A. E. Lambers,¹ Janke Schinkel,² Ronald B. Geskus,^{1,3} Joop E. Arends,⁴ Thijs J. W. van de Laar,⁵ Fanny N. Lauw,⁶ Kees Brinkman,⁷ Luuk Gras,⁸ Bart J. A. Rijnders,⁹ Jan T. M. van der Meer,¹⁰ and Maria Prins^{1,10}; on behalf of the MOSAIC (MSM Observational Study of Acute Infection With Hepatitis C) Study Group

Multivariable analysis:

Sex:

- CRAI: aOR=4.9
- Sharing sex toys: aOR=6.1
- Fisting without gloves: aOR=2.6

Sexualized drug use:

- Sex with drug use, injected: aOR=11.3
- Sex with drug use, straws: aOR=3.8

PRIMARY HCV: ACQUISITION RISK FACTORS

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Multivariable analysis:

Sex:

- CRAI with ejaculation of semen into rectum: OR=23

Sexualized drug use:

- CRAI with crystal methamphetamine use (injection excluded; no route dominant): OR=29

- Incidence NYC: 0.4/100 PY

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Joost W. Vanhommerig,^{1,2} Femke A. E. Lambers,¹ Janke Schinkel,² Ronald B. Geskus,^{1,3} Joop E. Arends,⁴ Thijs J. W. van de Laar,⁵ Fanny N. Lauw,⁶ Kees Brinkman,⁷ Luuk Gras,⁸ Bart J. A. Rijnders,⁹ Jan T. M. van der Meer,¹⁰ and Maria Prins^{1,10}; on behalf of the MOSAIC (MSM Observational Study of Acute Infection With Hepatitis C) Study Group

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- Sex with drug use, straws: aOR=3.8
- Incidence MOSAIC: 0.9/100 PY

HCV REINFECTION: ACQUISITION RISK FACTORS

Clinical Infectious Diseases

MAJOR ARTICLE



Hepatitis C Virus Reinfection Among Men Who Have Sex With Men With HIV in New York City

Daniel S. Fierer,^{1,✉} Jesse R. Carollo,¹ Gabriela Rodriguez-Caprio,^{1,✉} Asa Radix,^{2,✉} Rona Vail,^{2,✉} Robert Chavez,³ Krisczar J. Bungay,⁴ and Stephen M. Dillon⁴; for the New York Acute Hepatitis C Surveillance Network^a

Multivariable analysis:

Sex:

- CRAI with ejaculation of semen into rectum: HR=9.7

Sexualized drug use:

- CRAI with crystal methamphetamine use (injection *included*): HR=NS

- Incidence NYC: 0.4 → 4.7/100 PY

Clinical Infectious Diseases

MAJOR ARTICLE



Incidence of HCV Reinfection Among HIV-Positive MSM and Its Association With Sexual Risk Behavior: A Longitudinal Analysis

Astrid M. Newsum,^{1,2,✉} Amy Matser,¹ Janke Schinkel,³ Marc van der Valk,² Kees Brinkman,⁴ Arne van Eeden,⁵ Fanny N. Lauw,⁶ Bart J. A. Rijnders,⁷ Thijs J. W. van de Laar,^{8,9} Marita van de Kerkhof,^{1,2} Colette Smit,¹⁰ Anders Boyd,^{1,10} Joop E. Arends,¹¹ and Maria Prins^{1,2}; on behalf of the MSM Observational Study of Acute Infection with hepatitis C (MOSAIC) study group

Sensitivity analysis:

Sex:

- CRAI: HR=4.3
- Sharing sex toys: HR=4.9
- Fisting without gloves: HR=NS

Sexualized drug use:

- Sex with drug use, injected: HR=NS
- Sex with drug use, straws: HR=NS
- Incidence MOSAIC: 0.9 → 15.2/100 PY

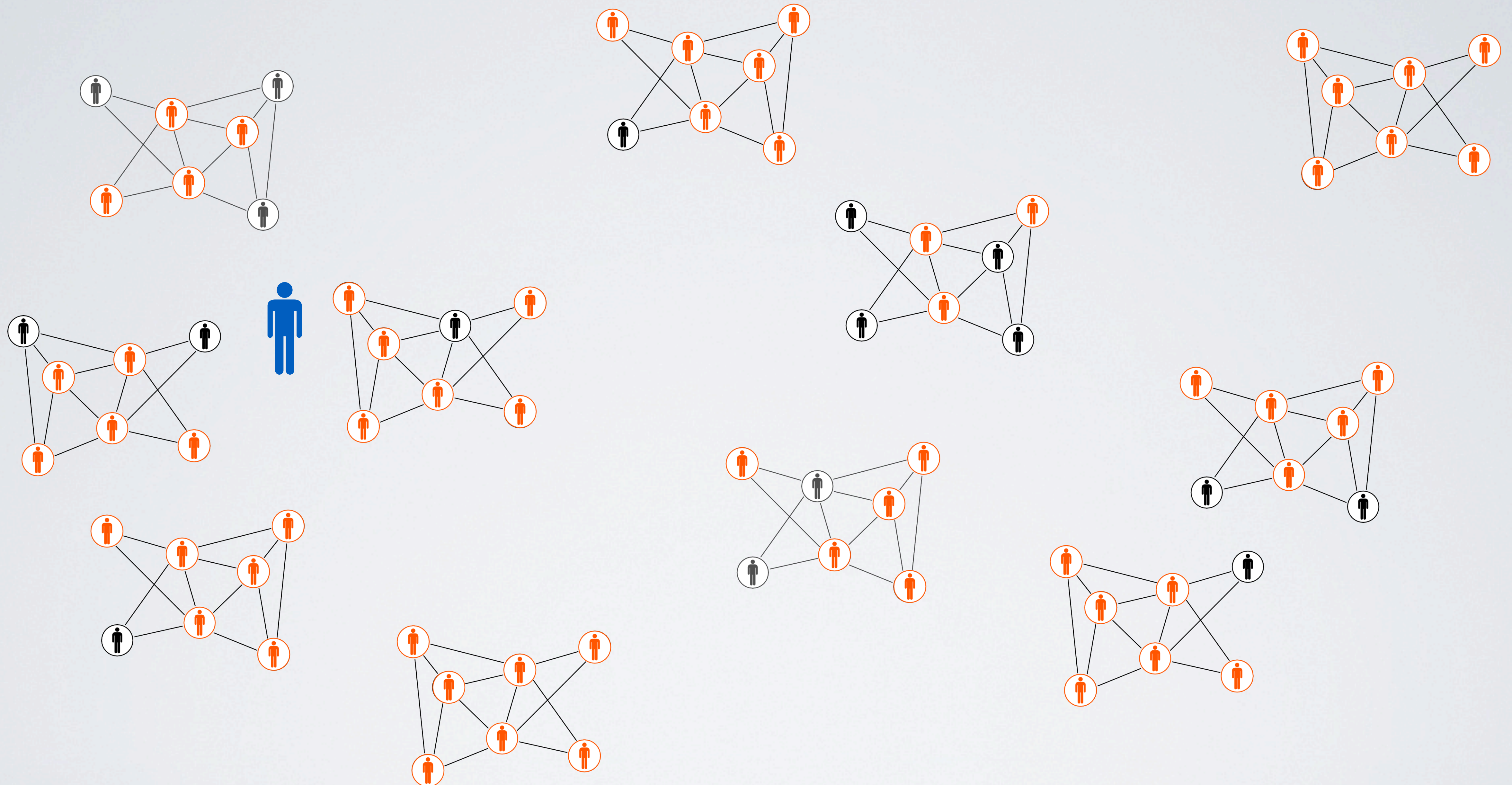
WHAT HCV REINFECTION TELLS US ABOUT HCV IN NETWORKS AND HCV PREVENTION

1. Reinfection rates an order of magnitude higher than primary infection
2. CRAI risk factor for primary and reinfection; sexualized drug use NOT risk factor for reinfection

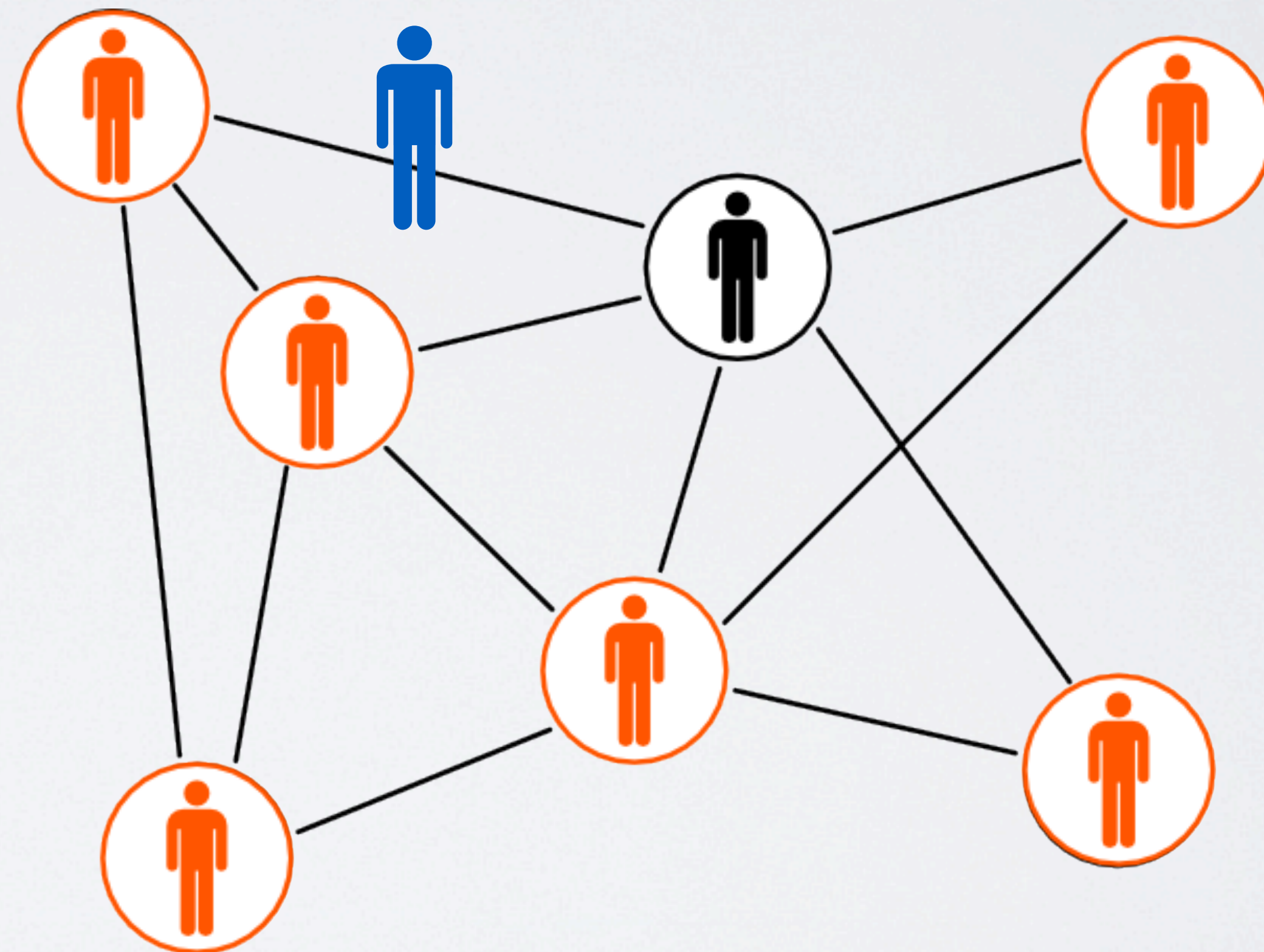
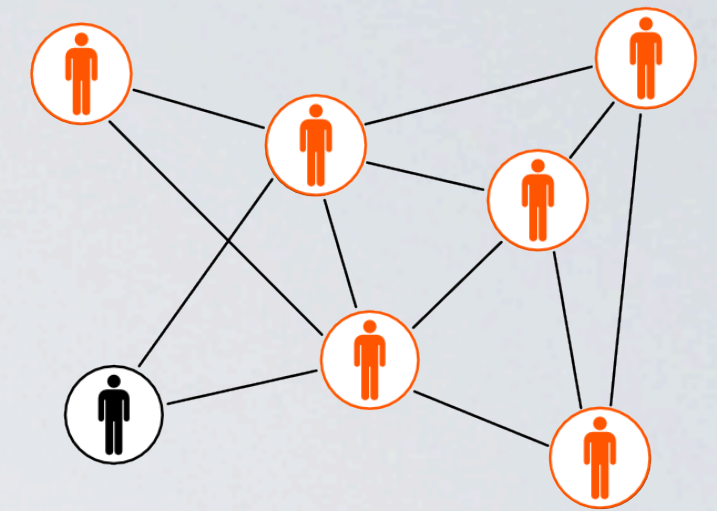
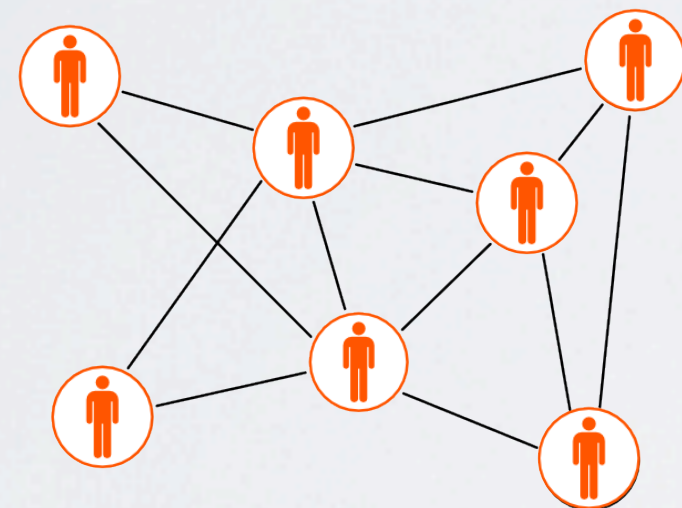
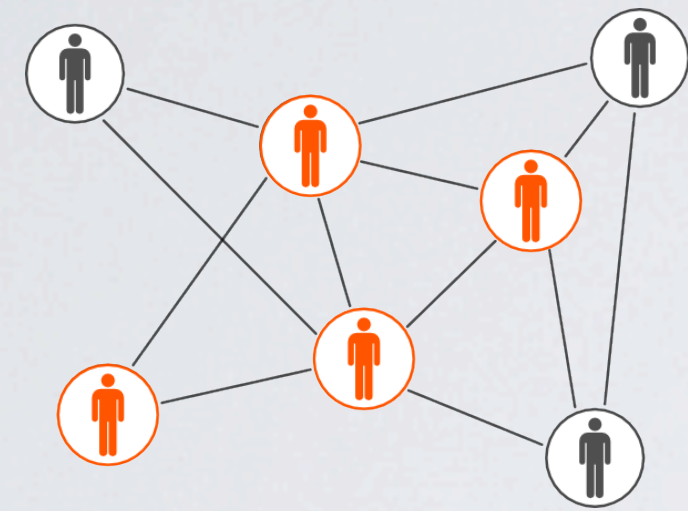
➡ What do these findings tell us about transmission?

1. Heterogenous distribution of HCV among sexual networks of MSM
 - That is, no/low prevalence in most networks, but high prevalence in some ($\sim 1/10^{\text{th}}$) networks
2. Drug use is a surrogate marker for HCV prevalence in a sexual network

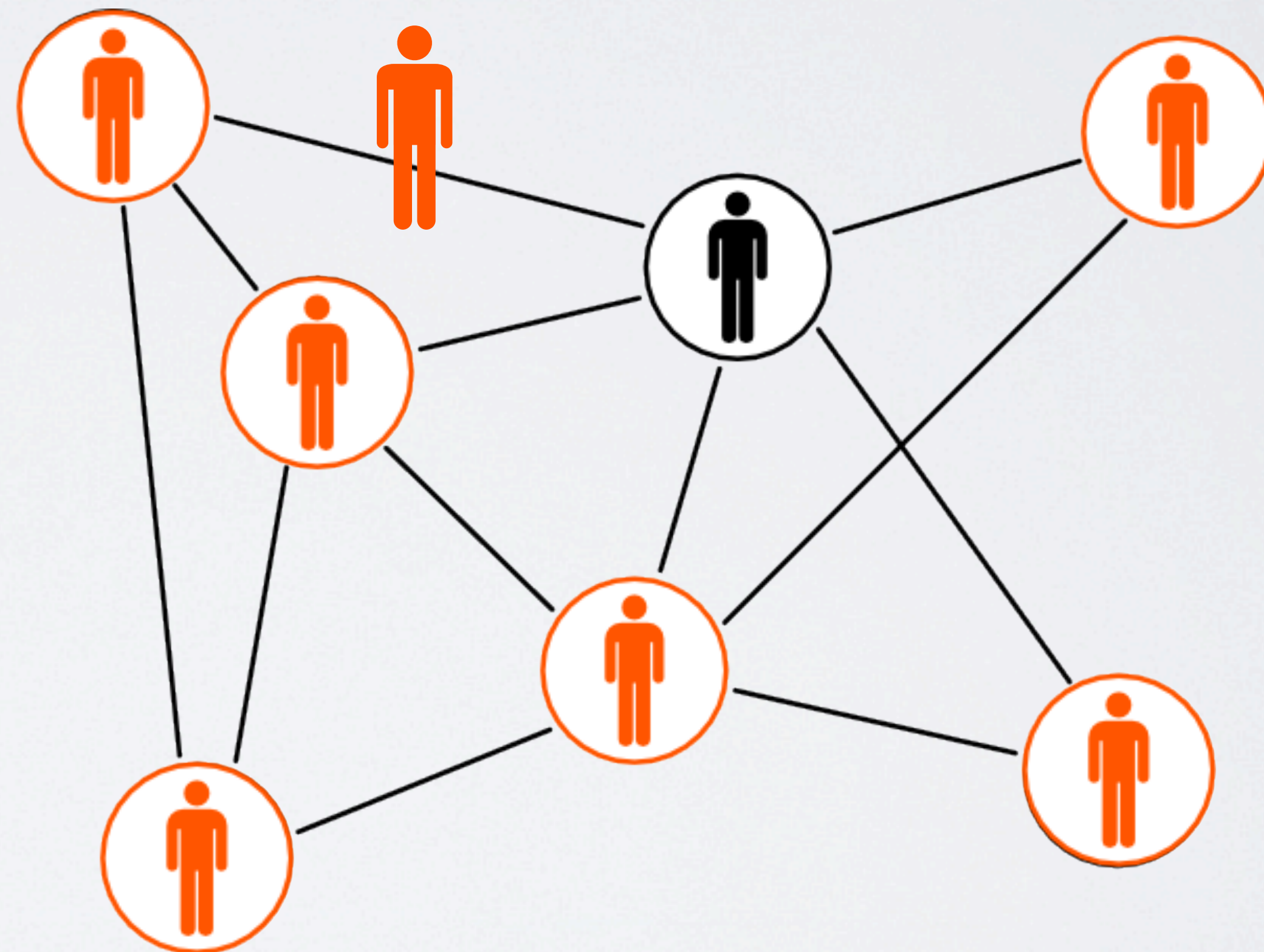
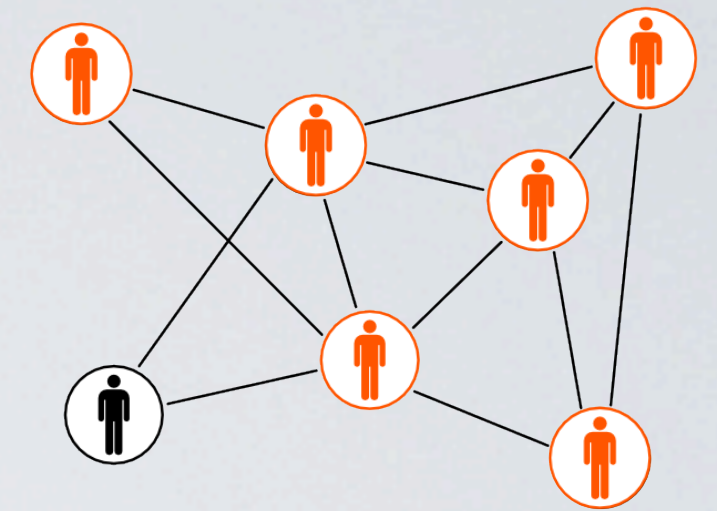
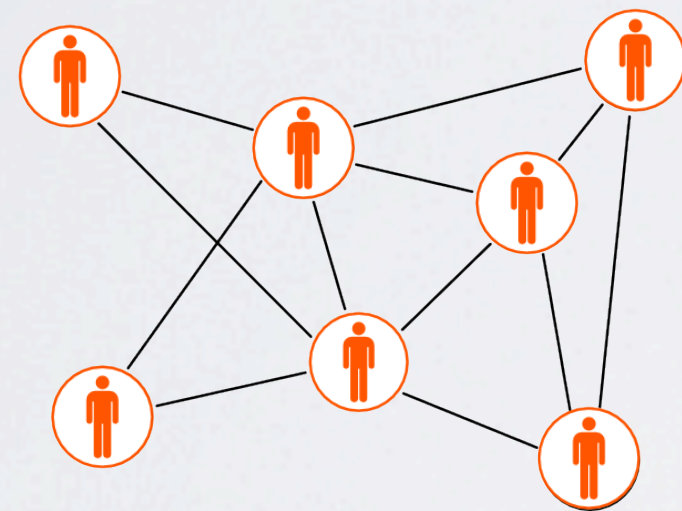
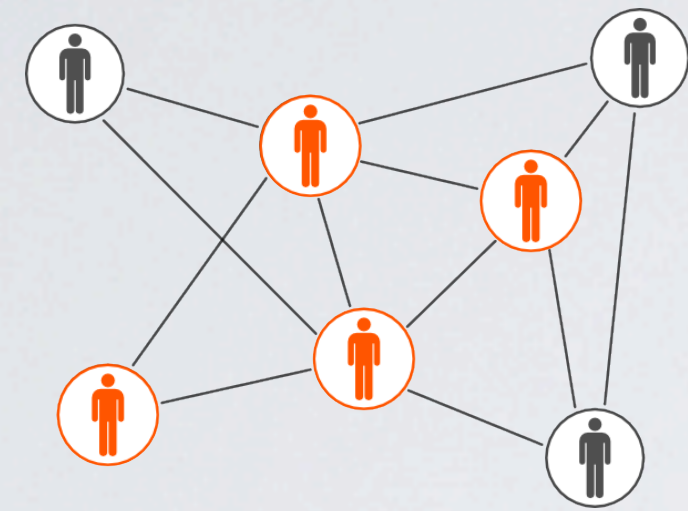
INJECTING NETWORKS IN PWID



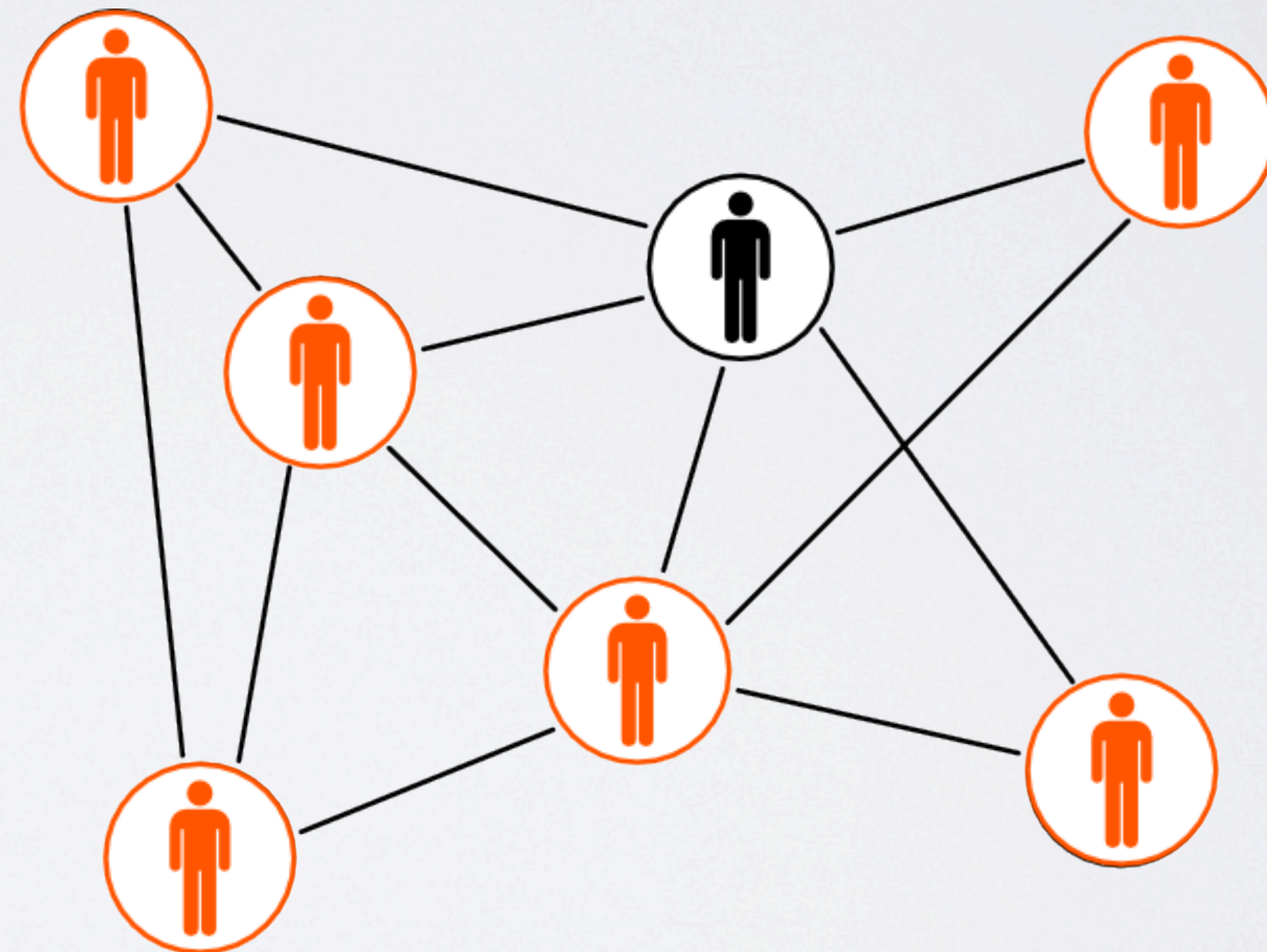
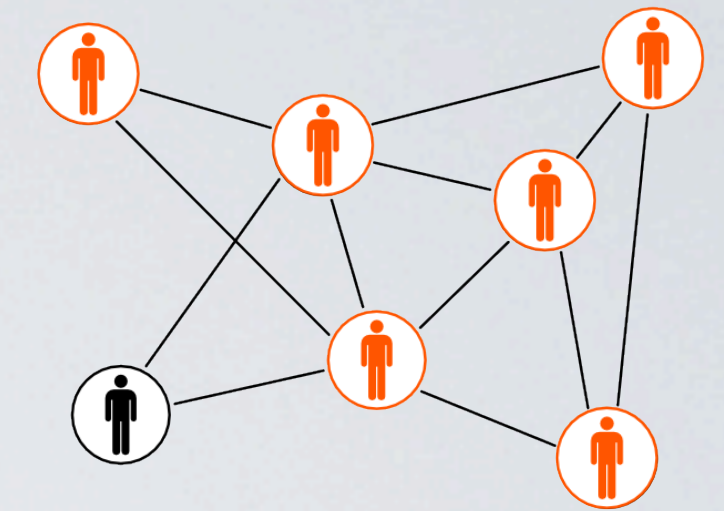
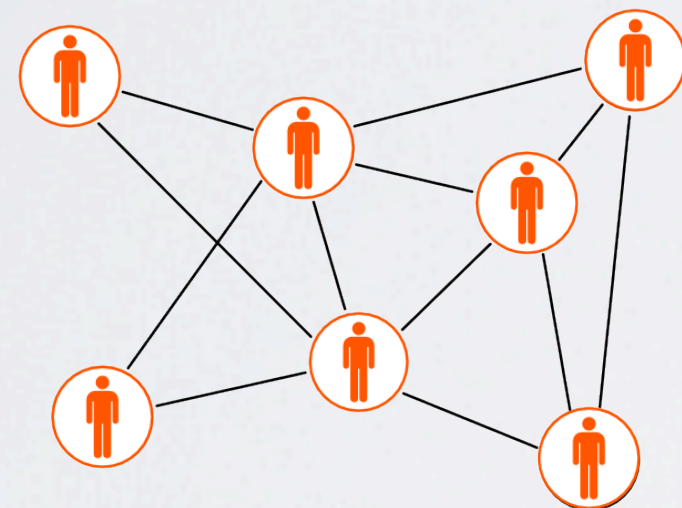
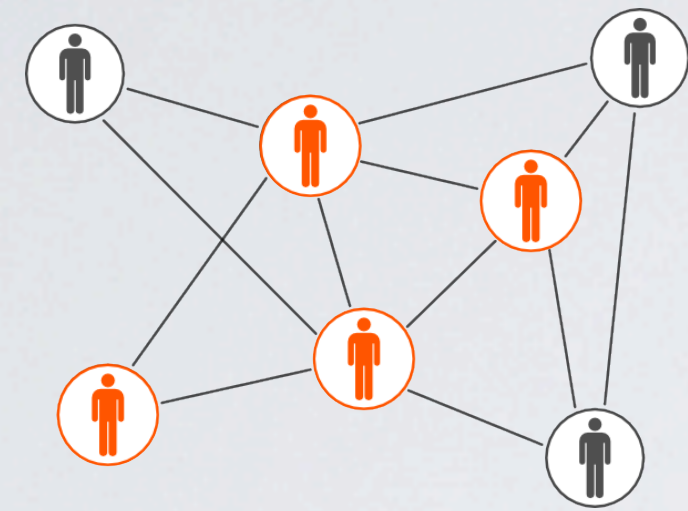
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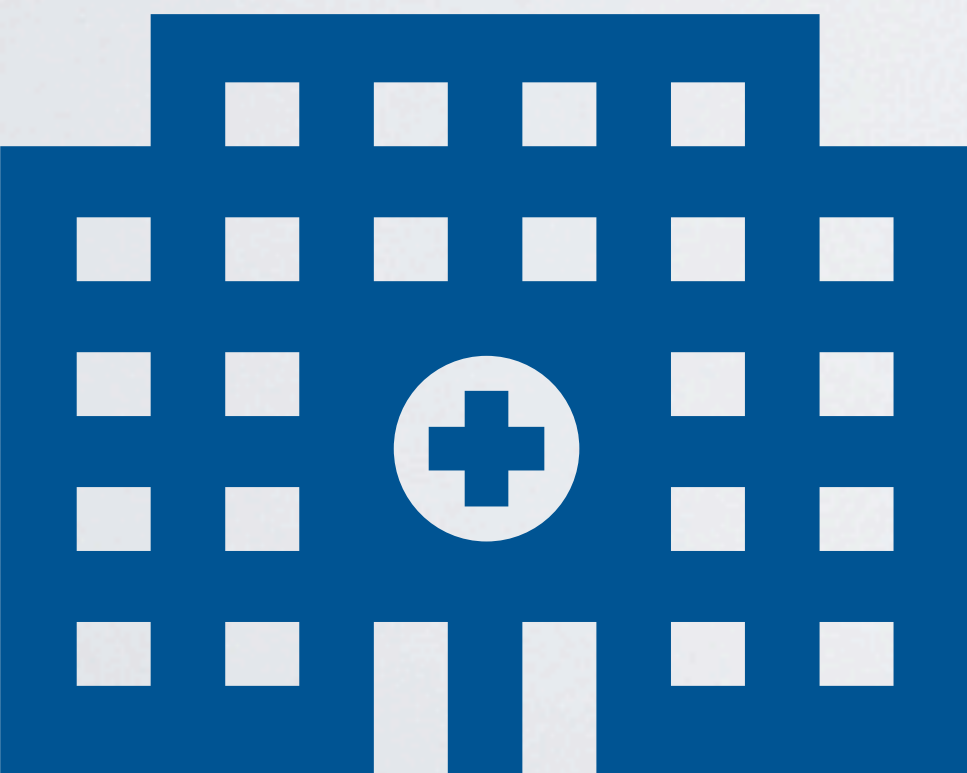
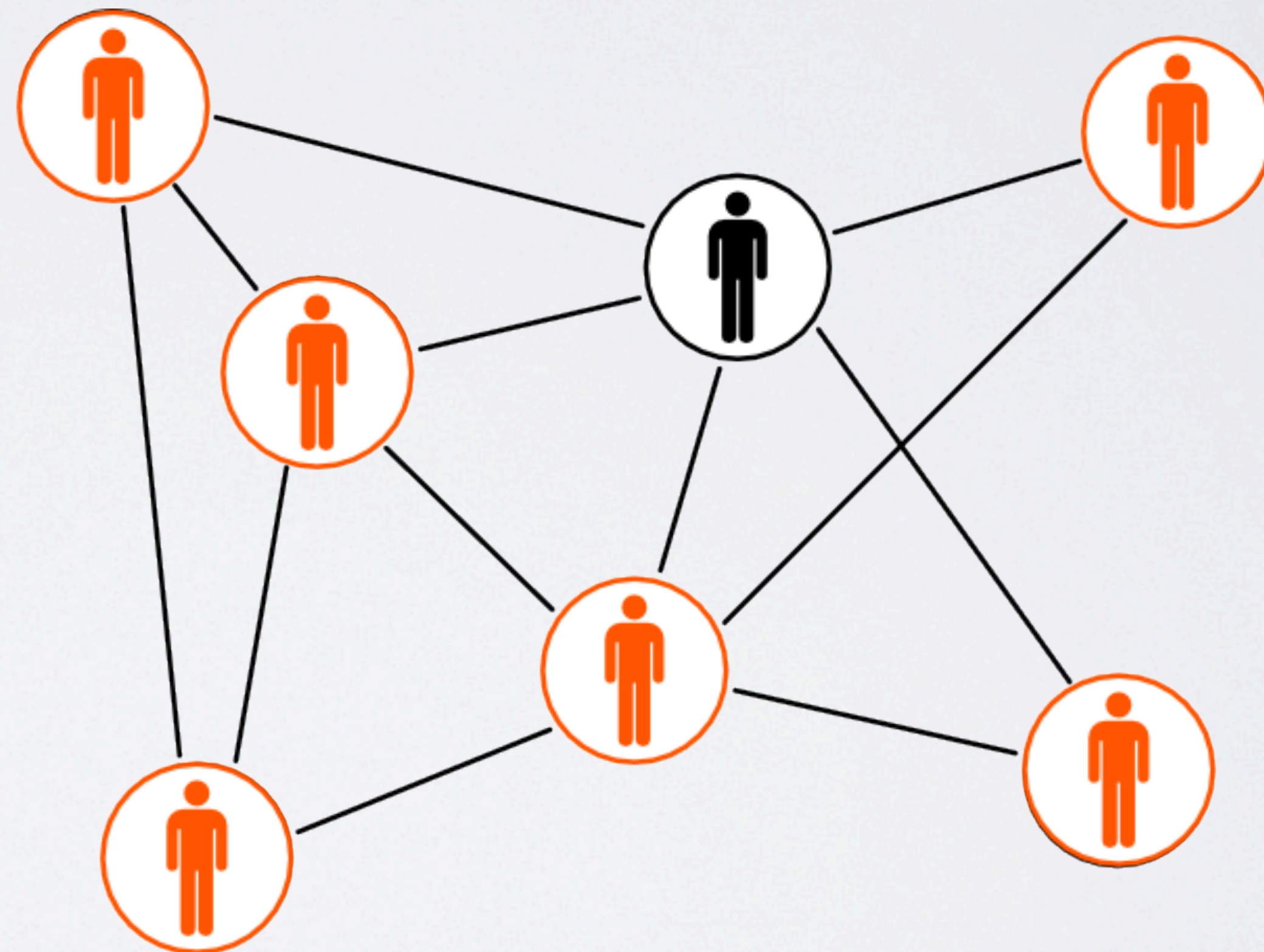
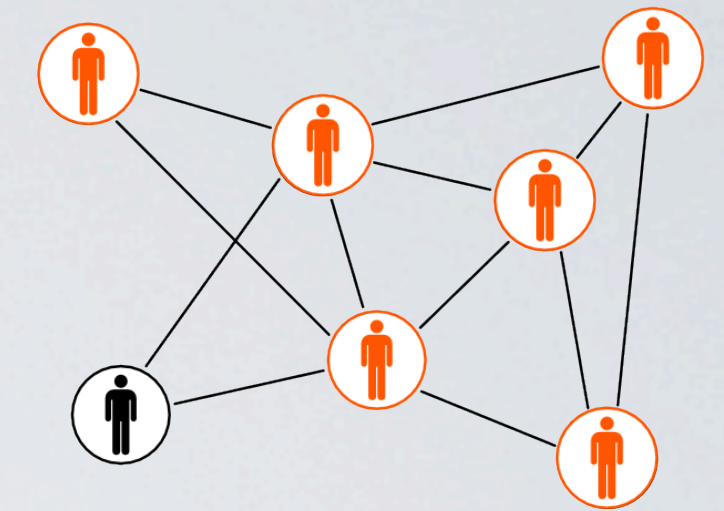
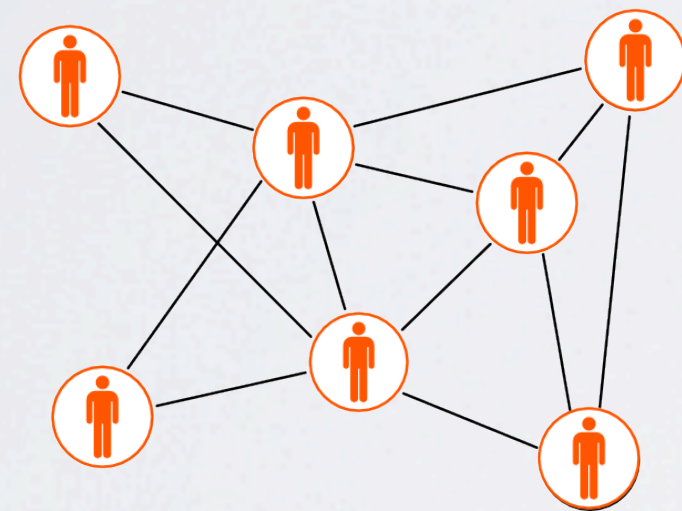
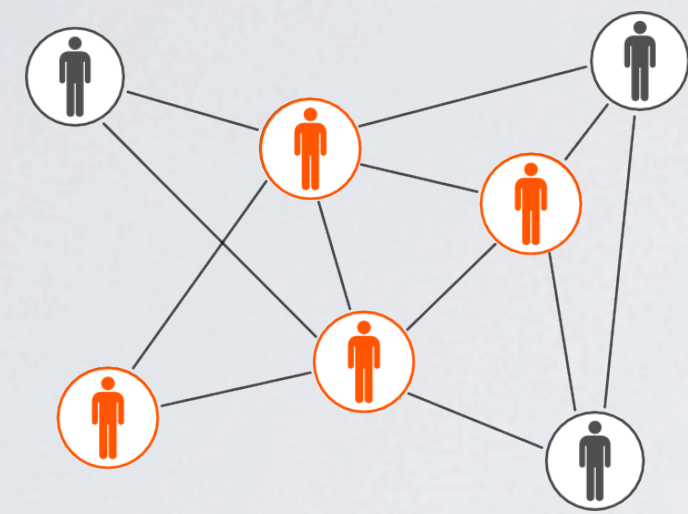
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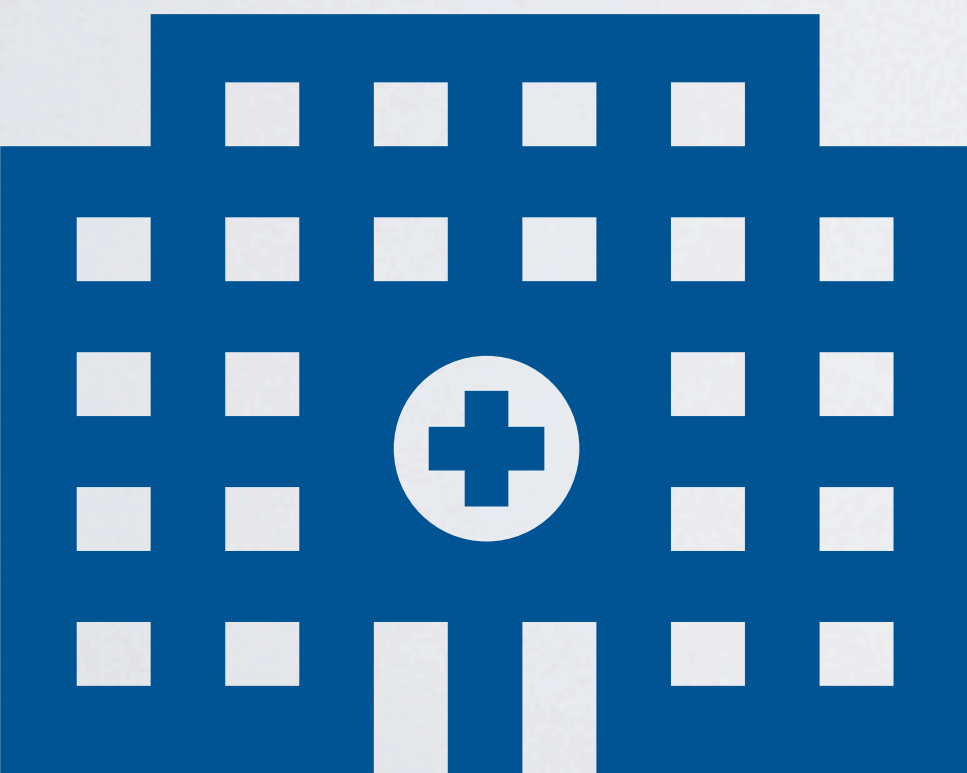
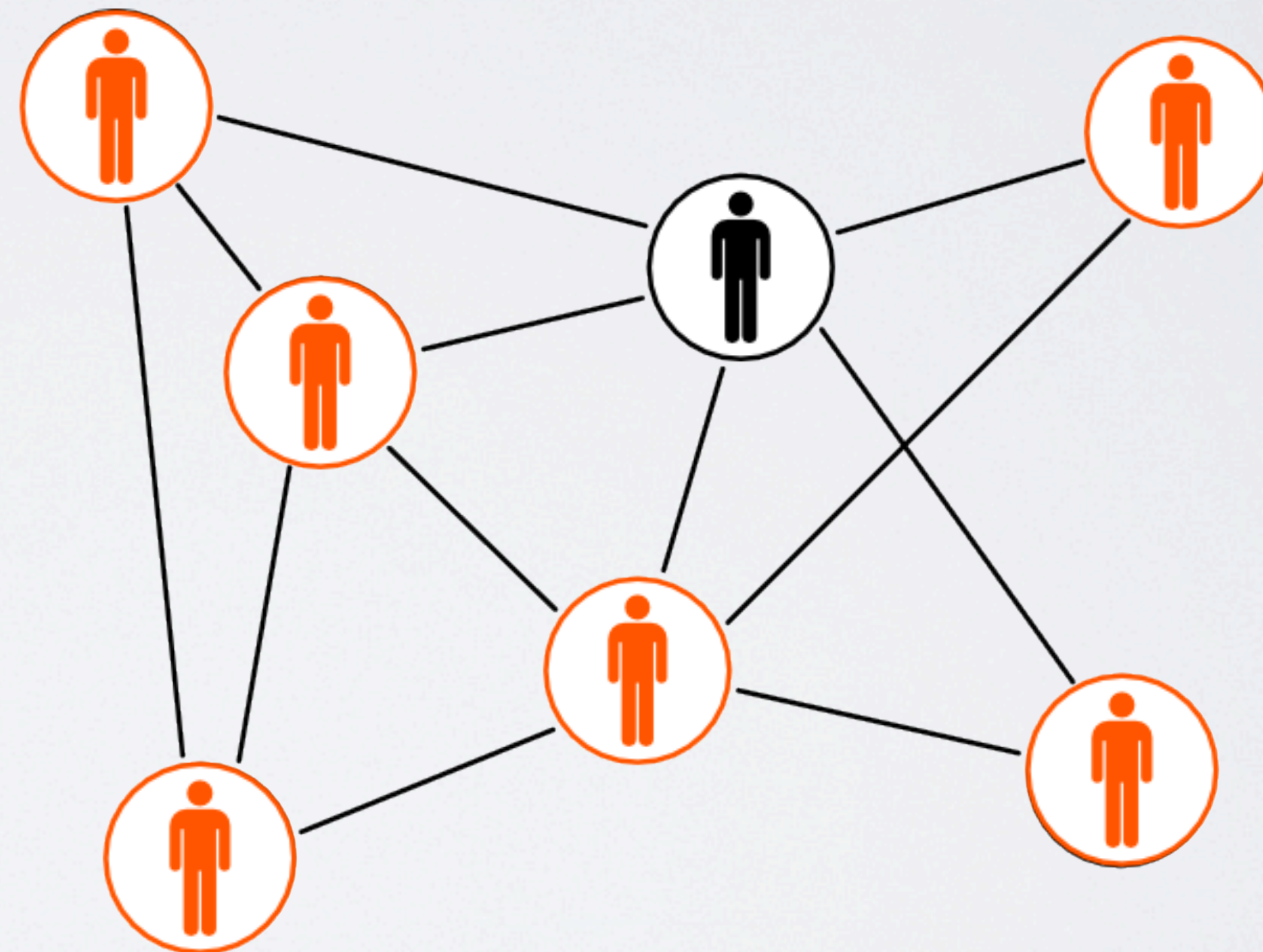
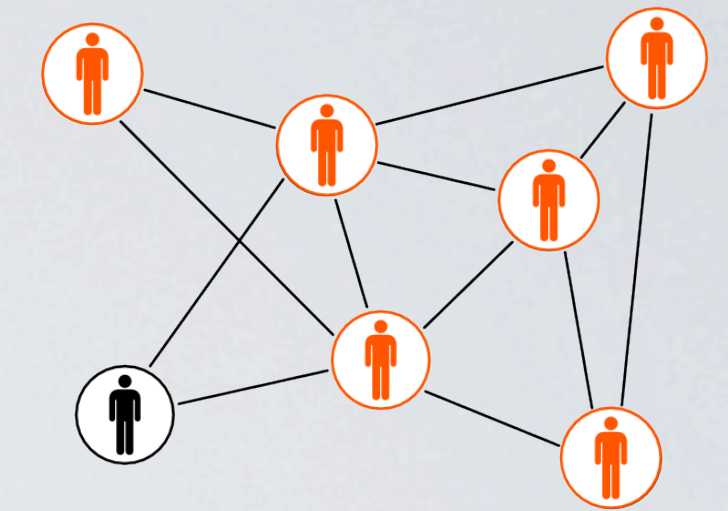
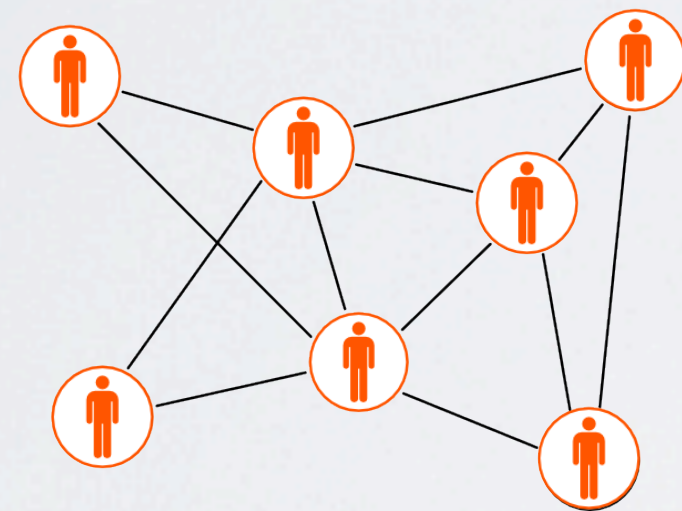
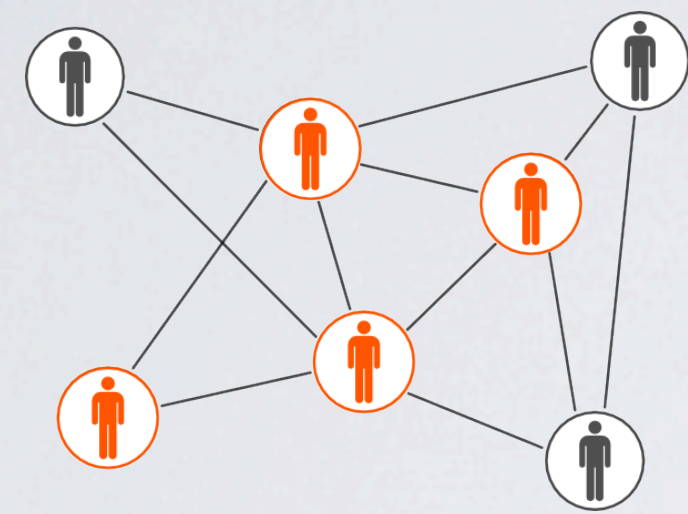
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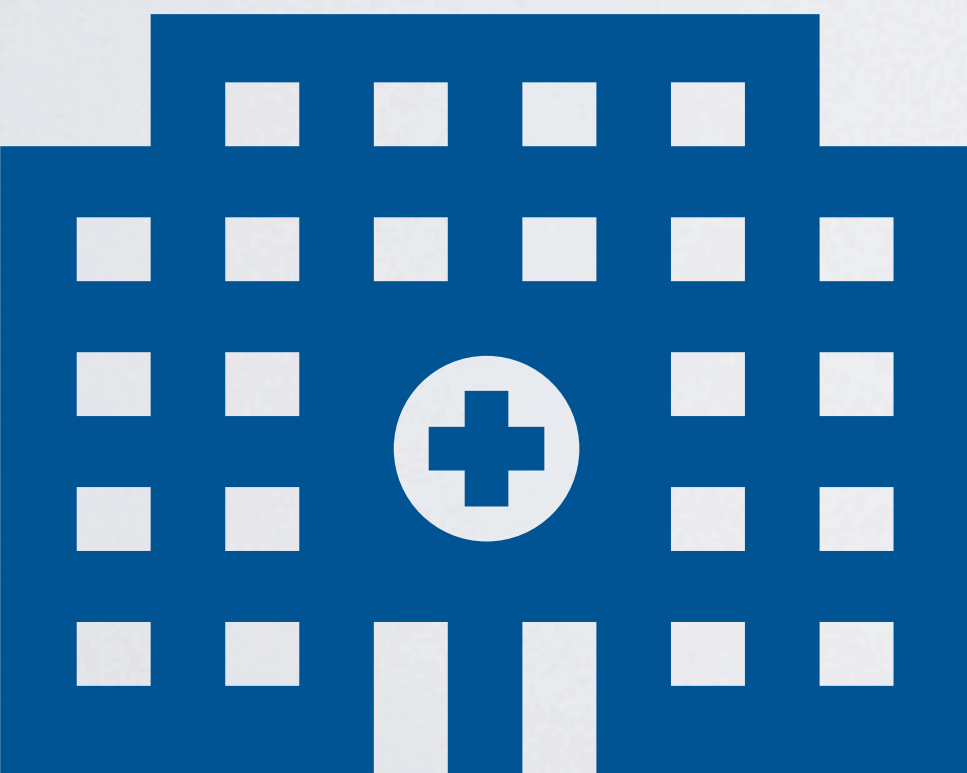
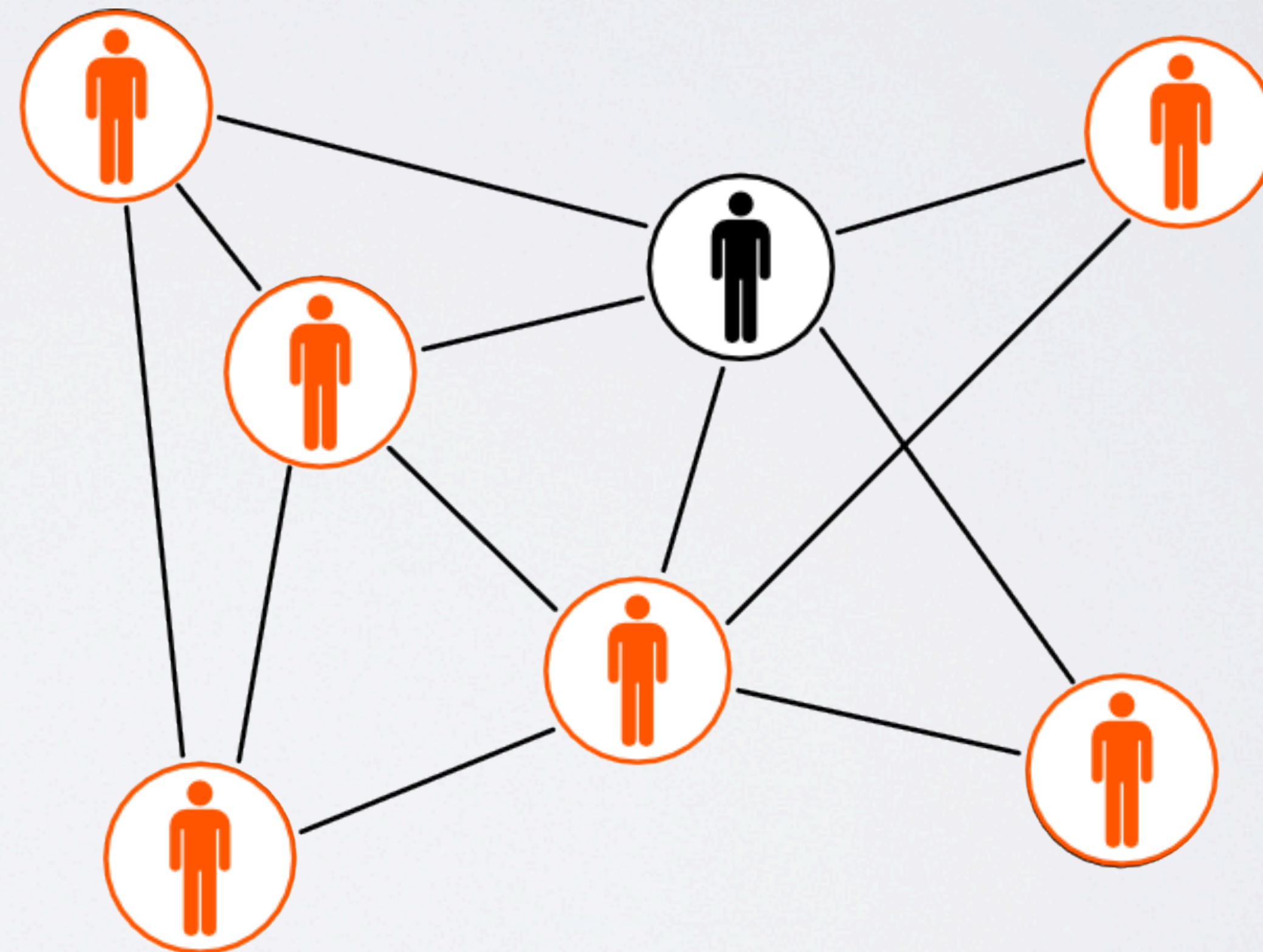
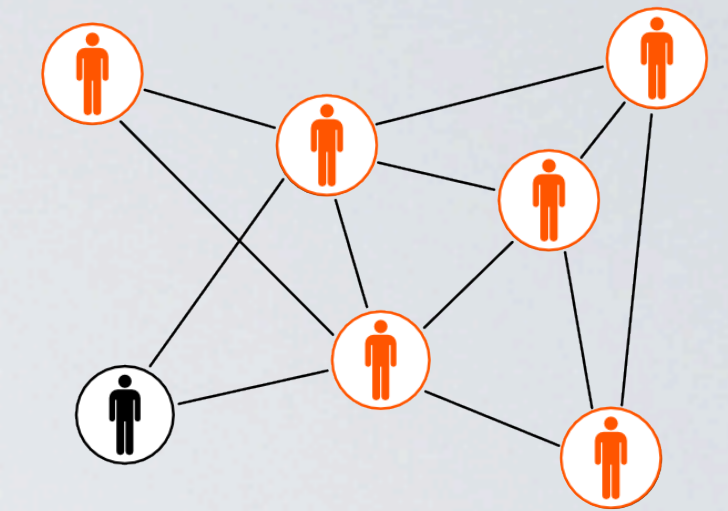
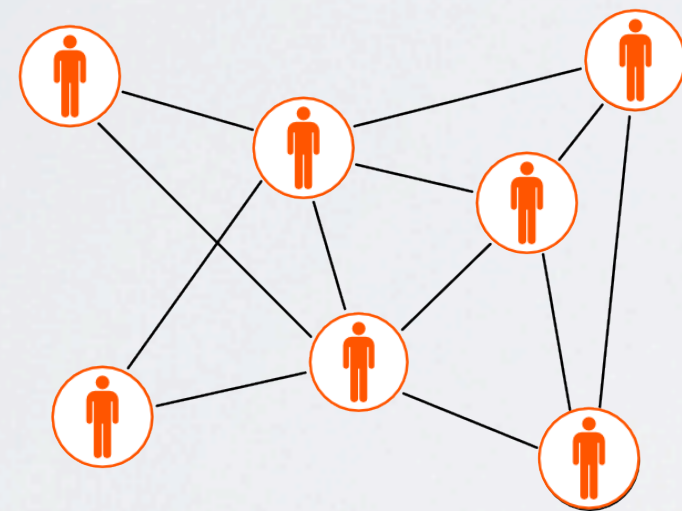
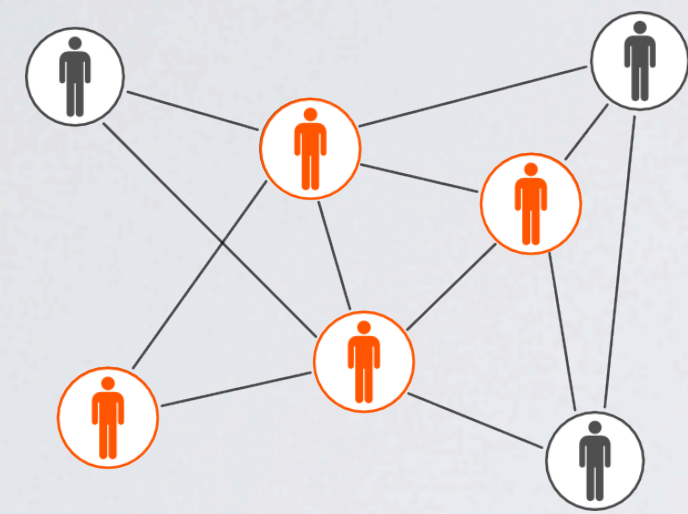
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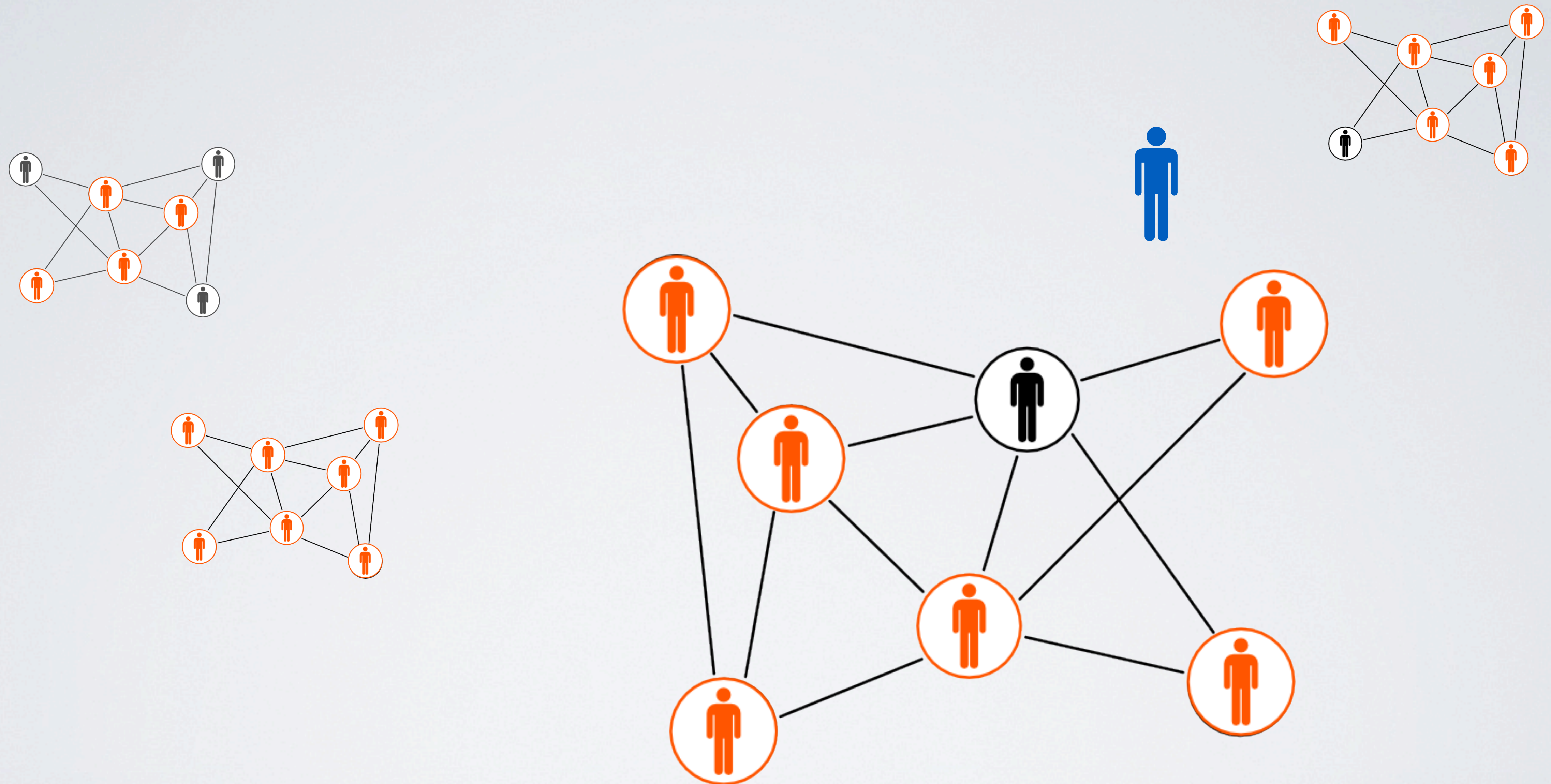
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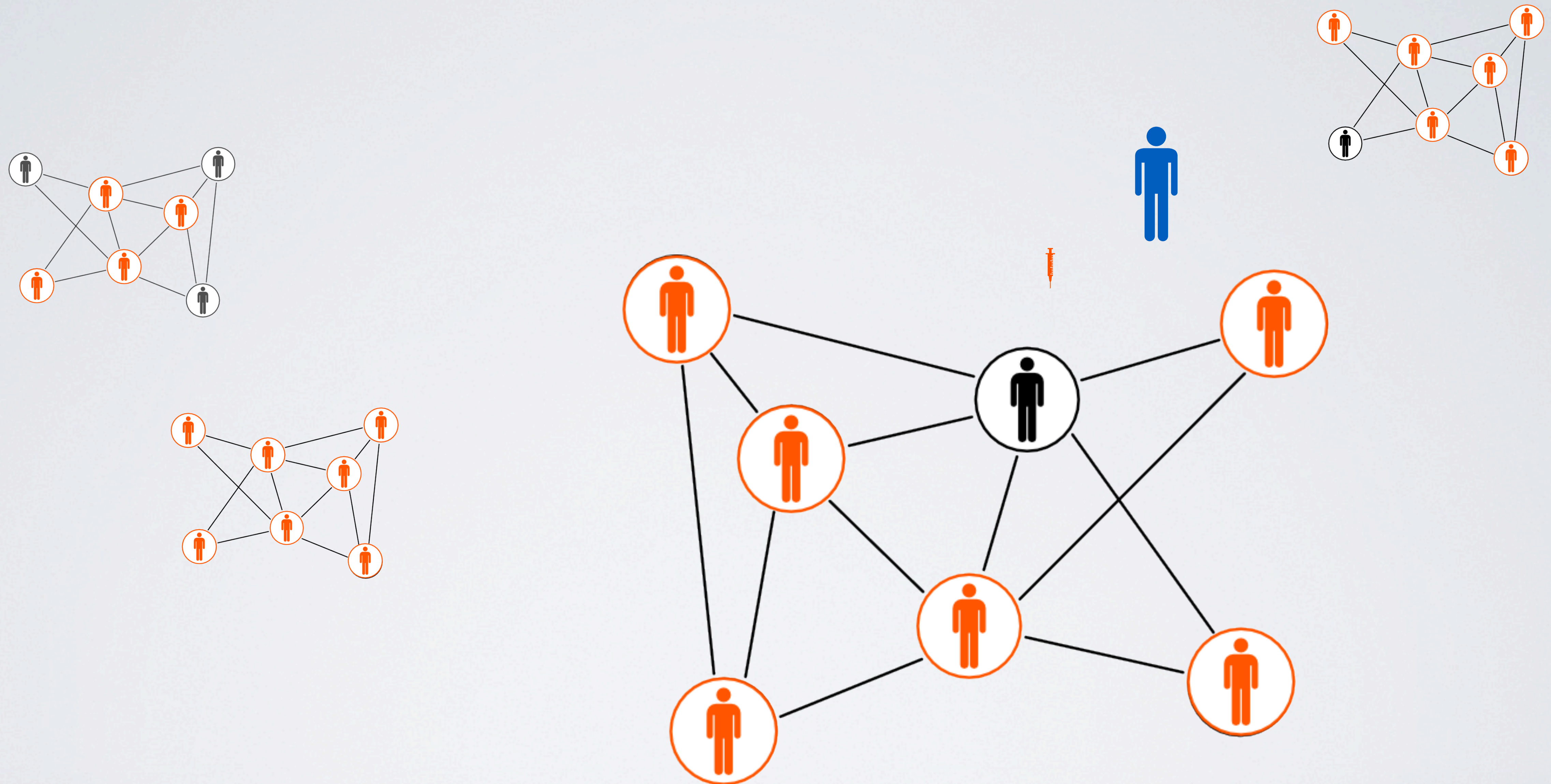
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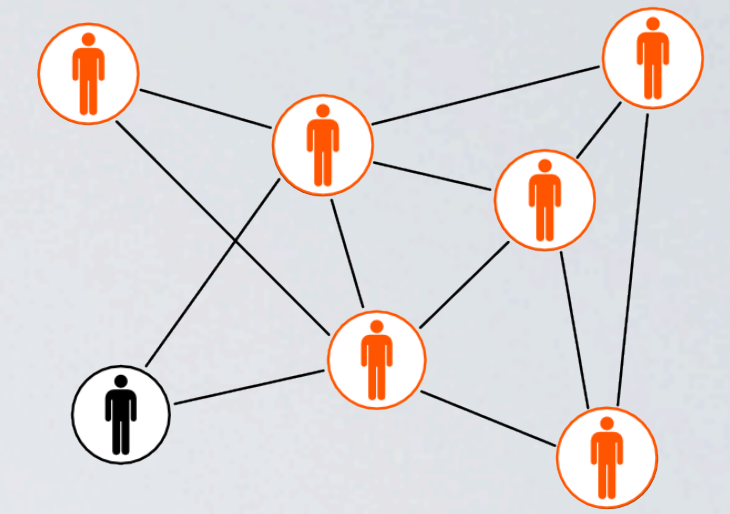
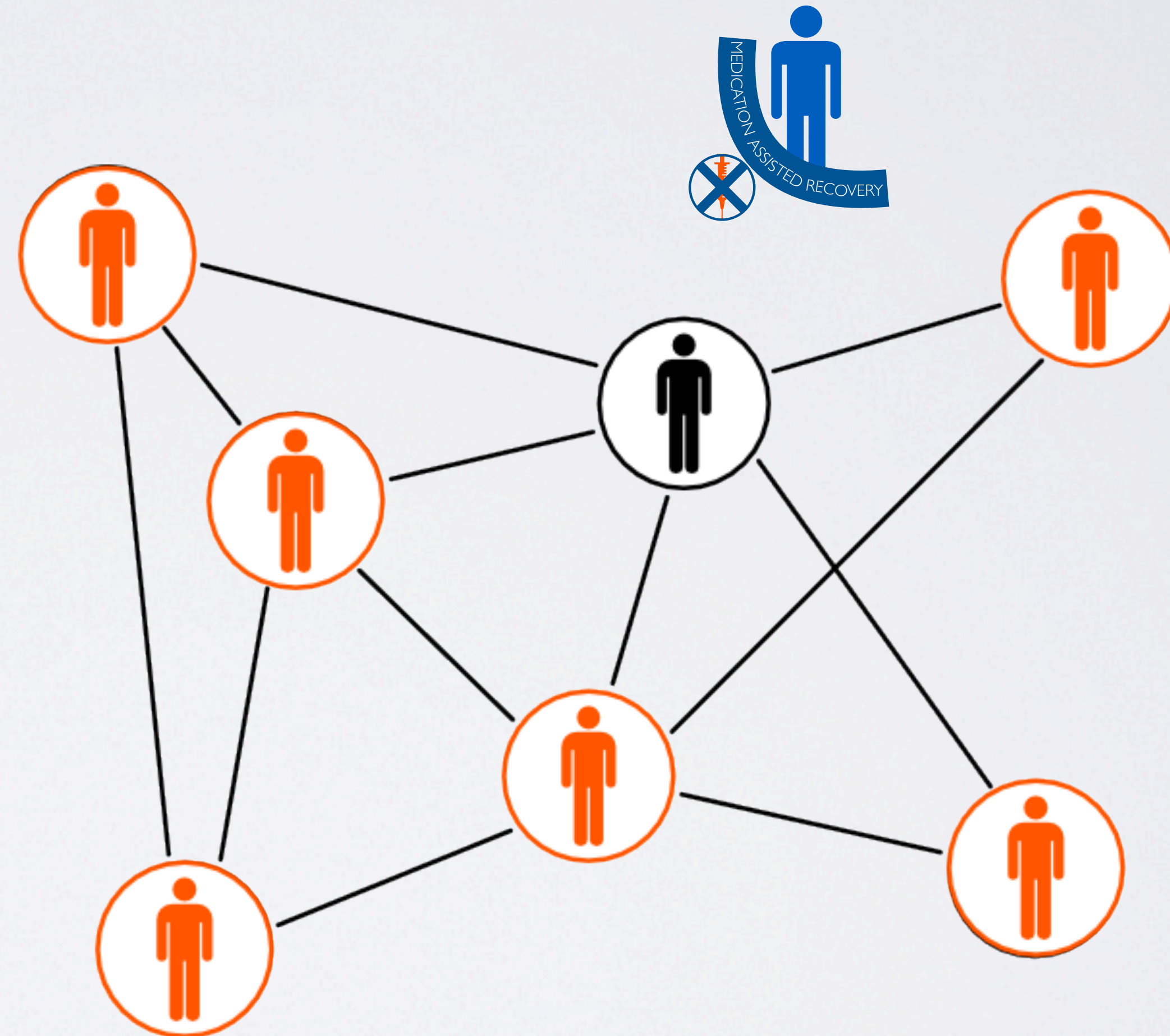
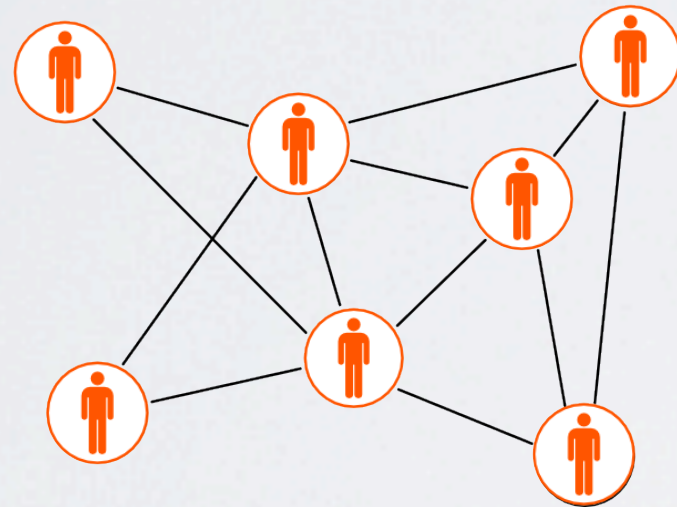
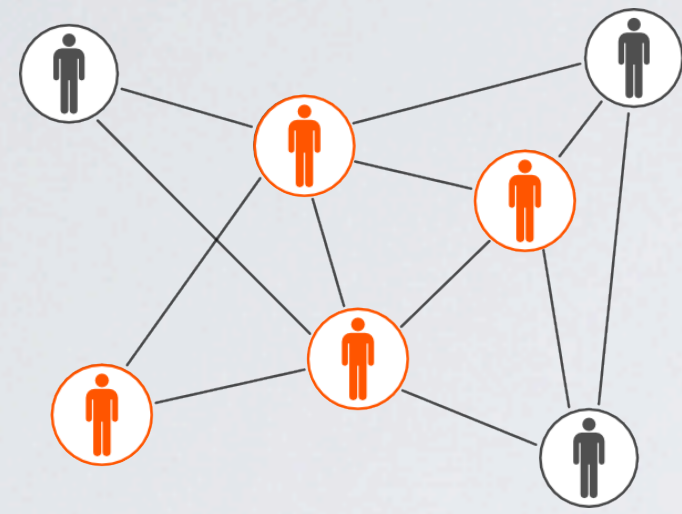
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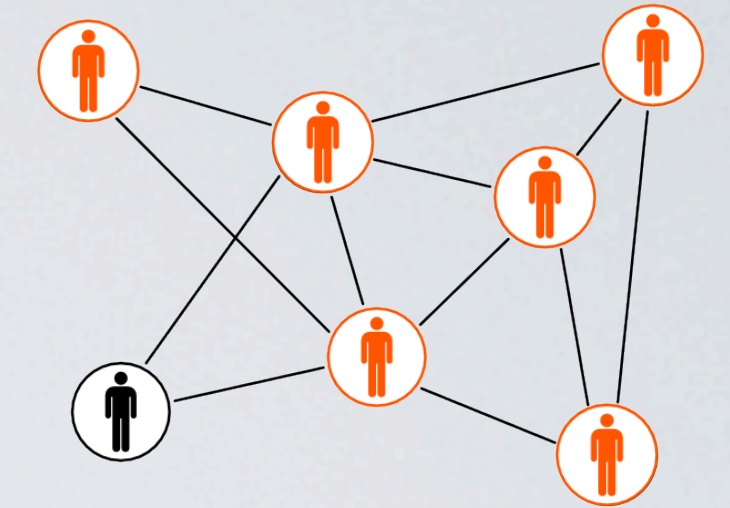
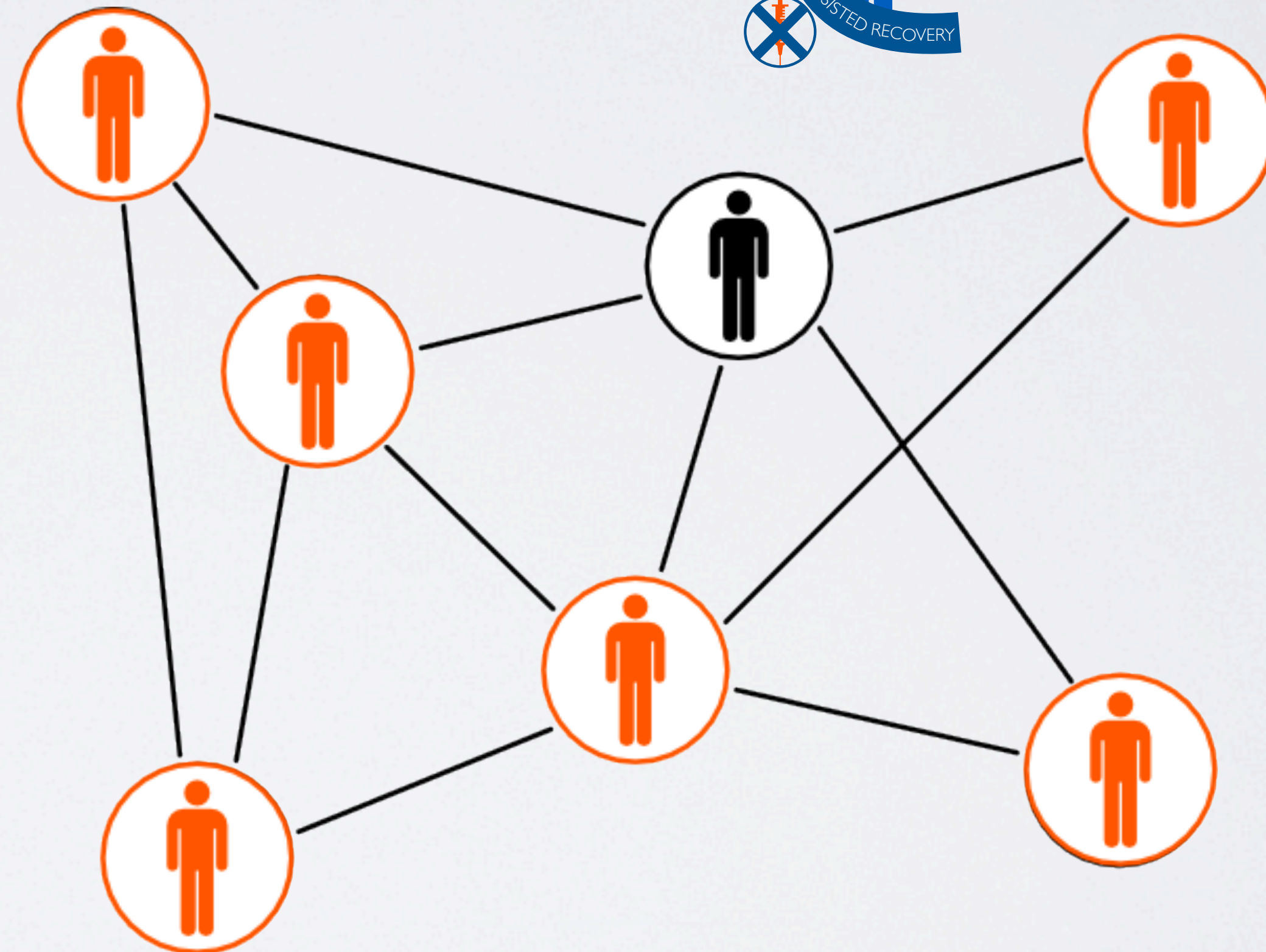
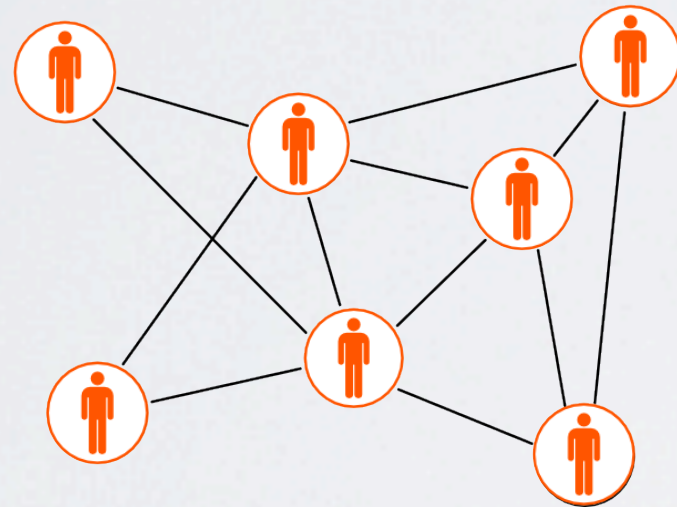
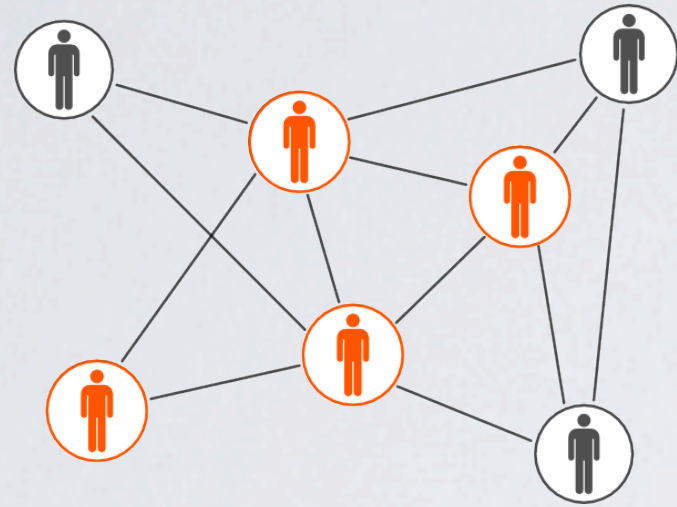


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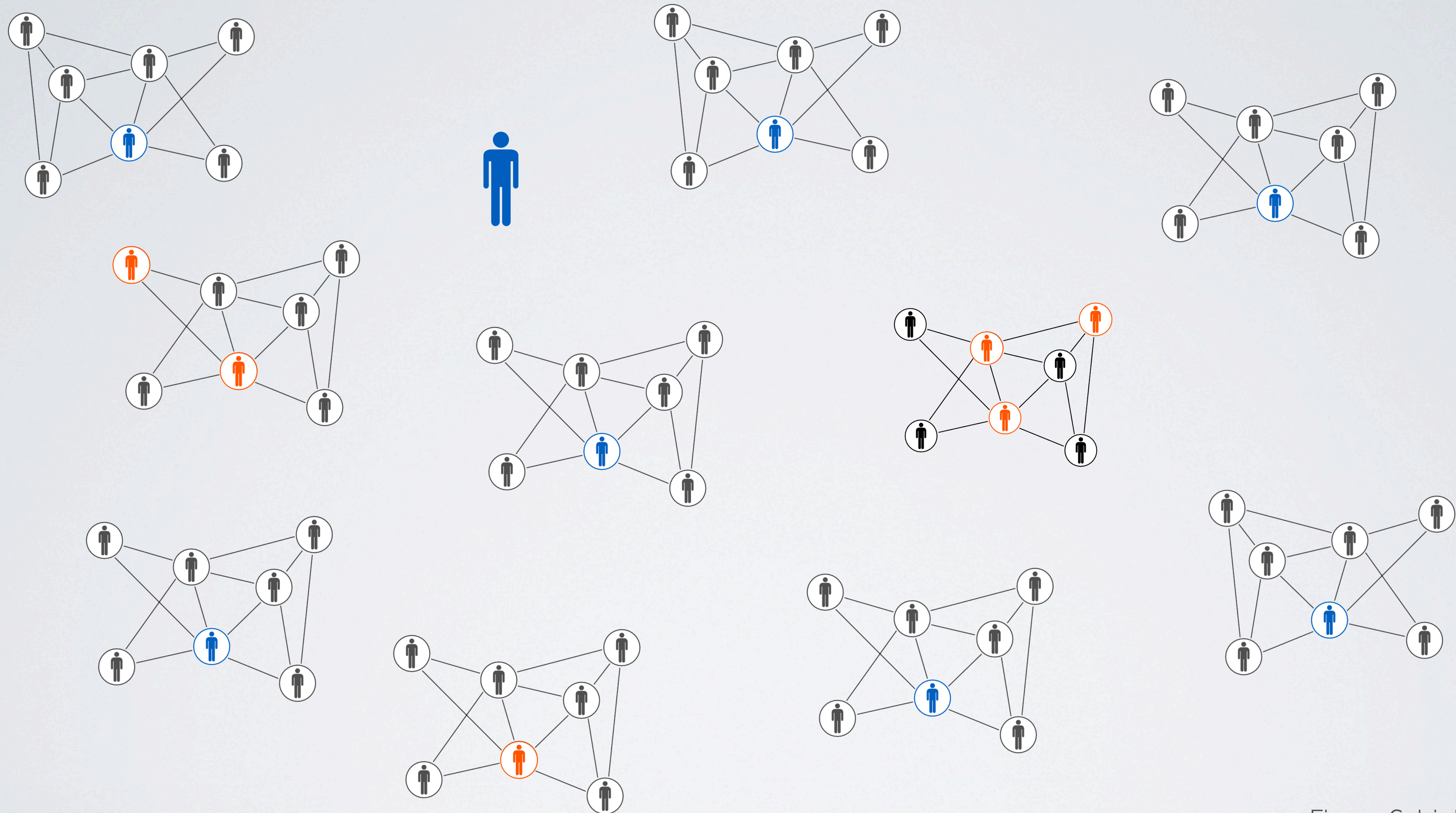


INJECTING NETWORKS IN PWID

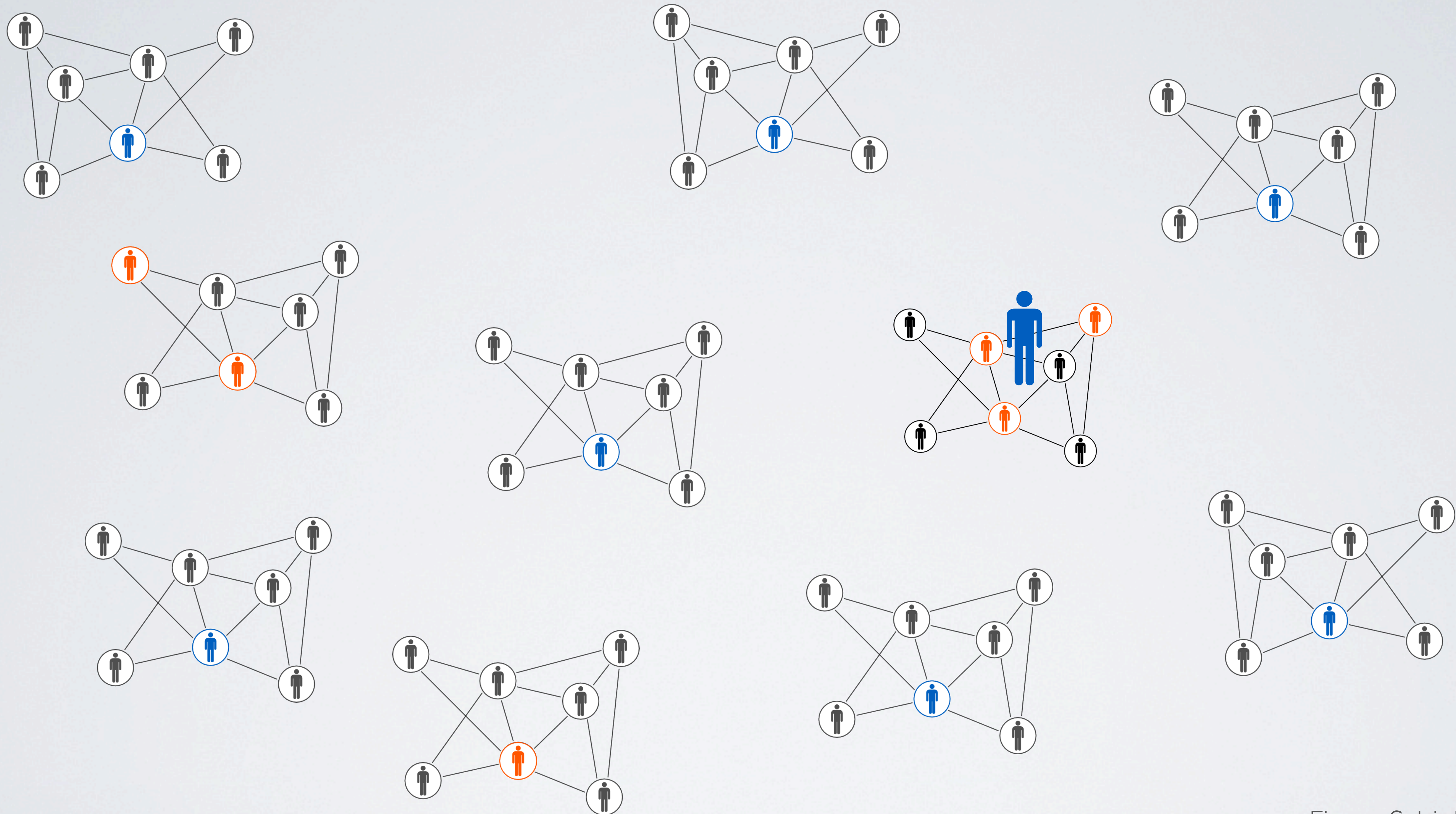
- Key component of MAR that leads to lower HCV reinfection:
 - desire to decrease injection use, leading to:
 - opioid substitution
 - clean injection equipment



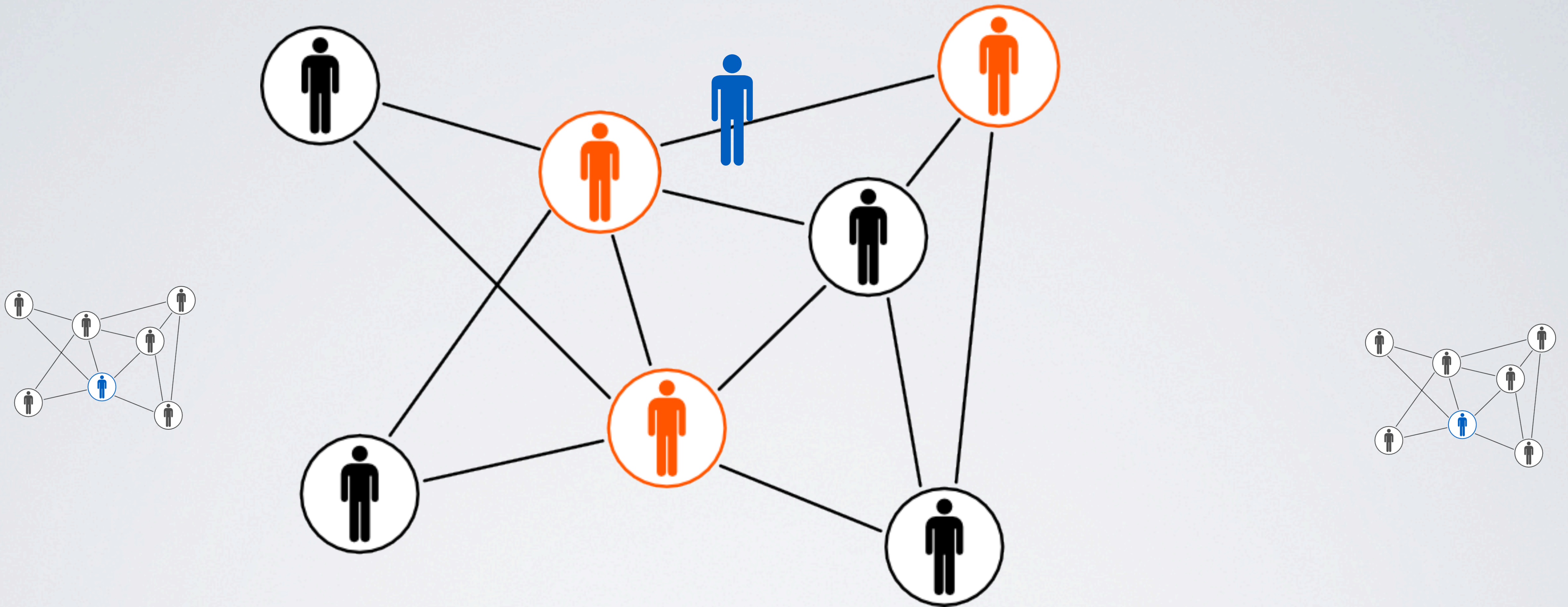
SEXUAL NETWORKS IN MSM



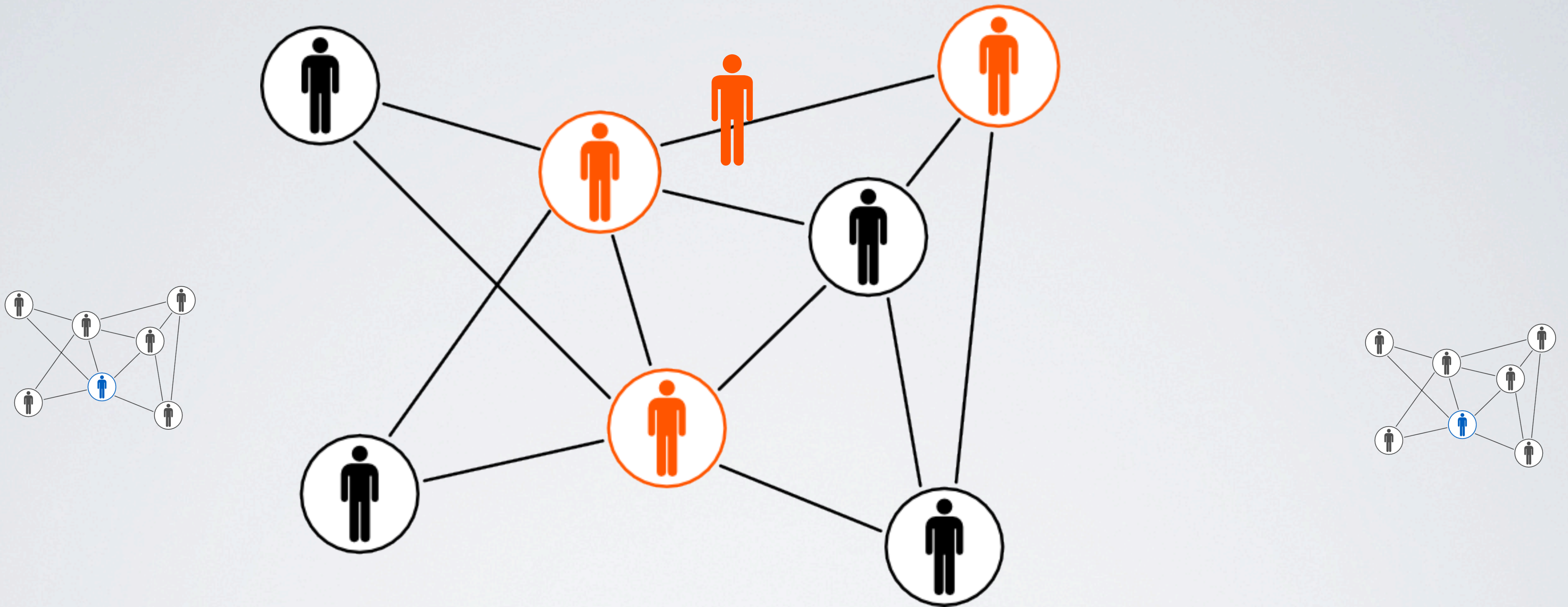
SEXUAL NETWORKS IN MSM



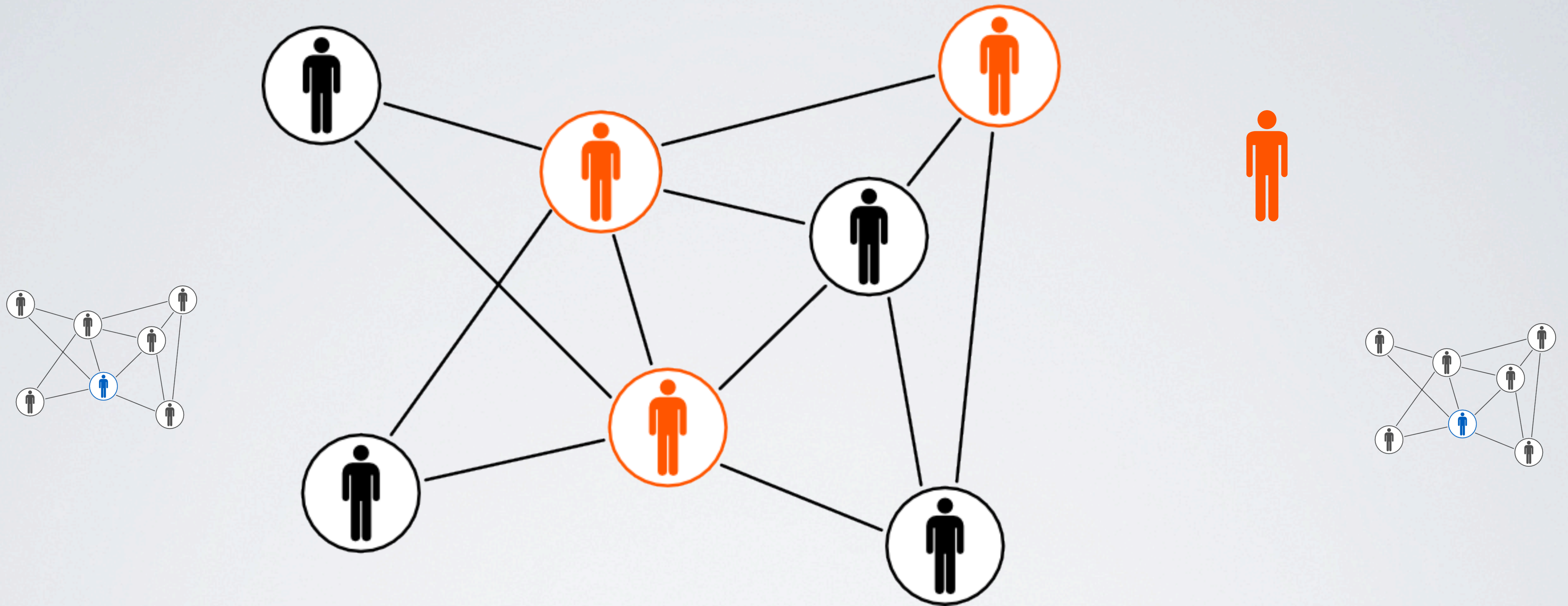
SEXUAL NETWORKS IN MSM



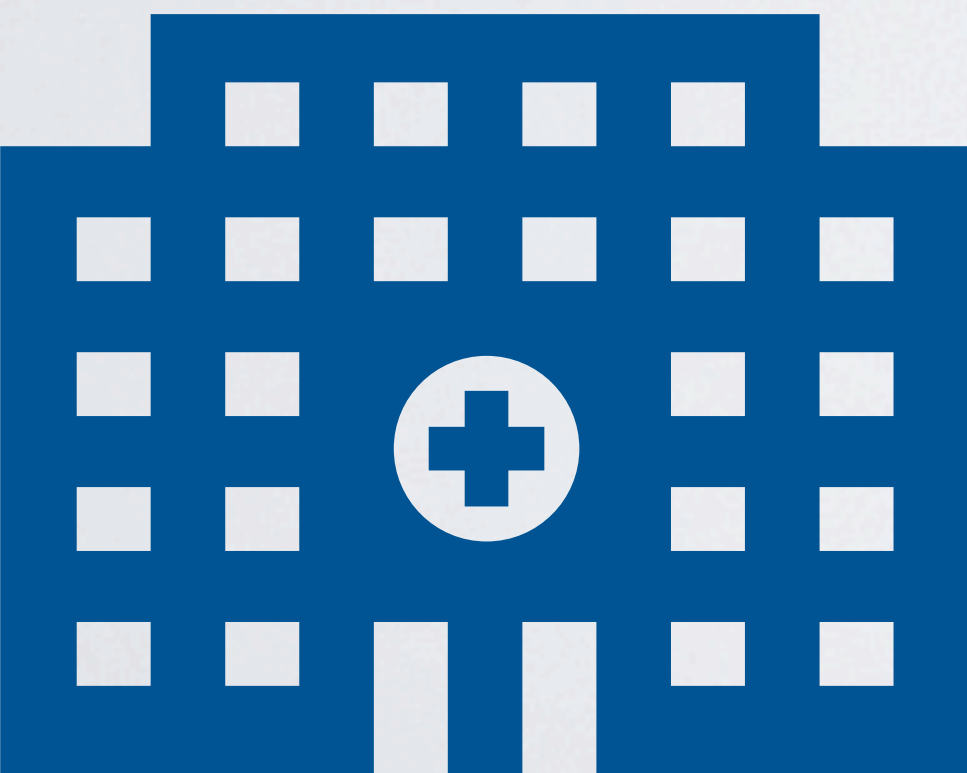
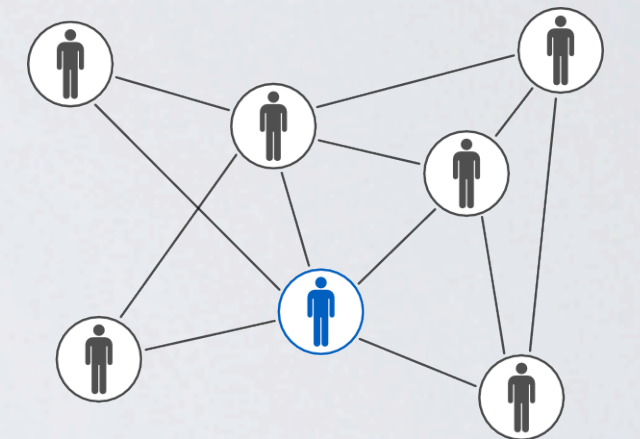
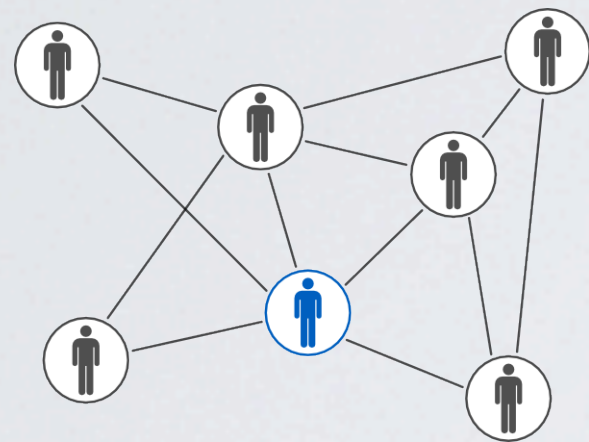
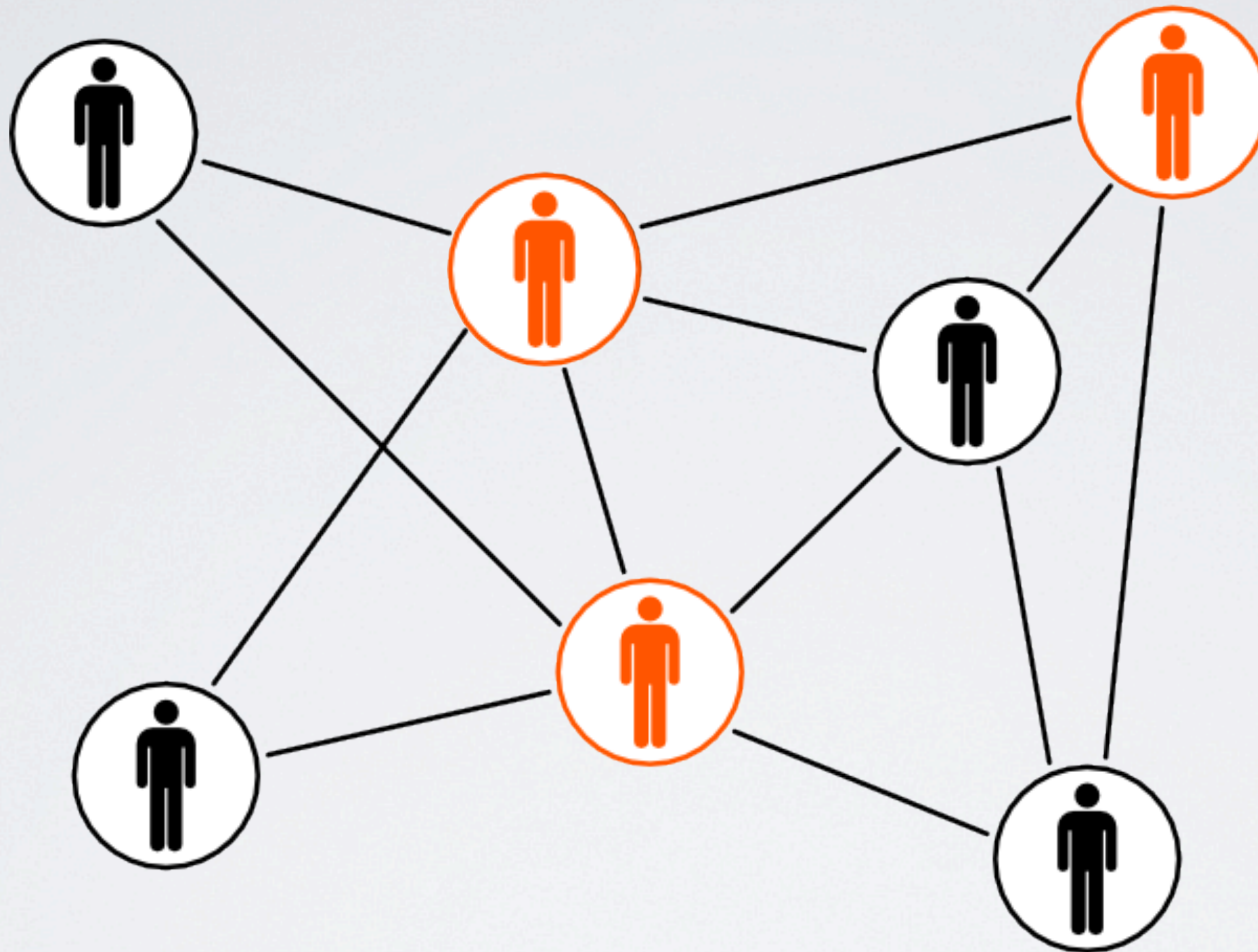
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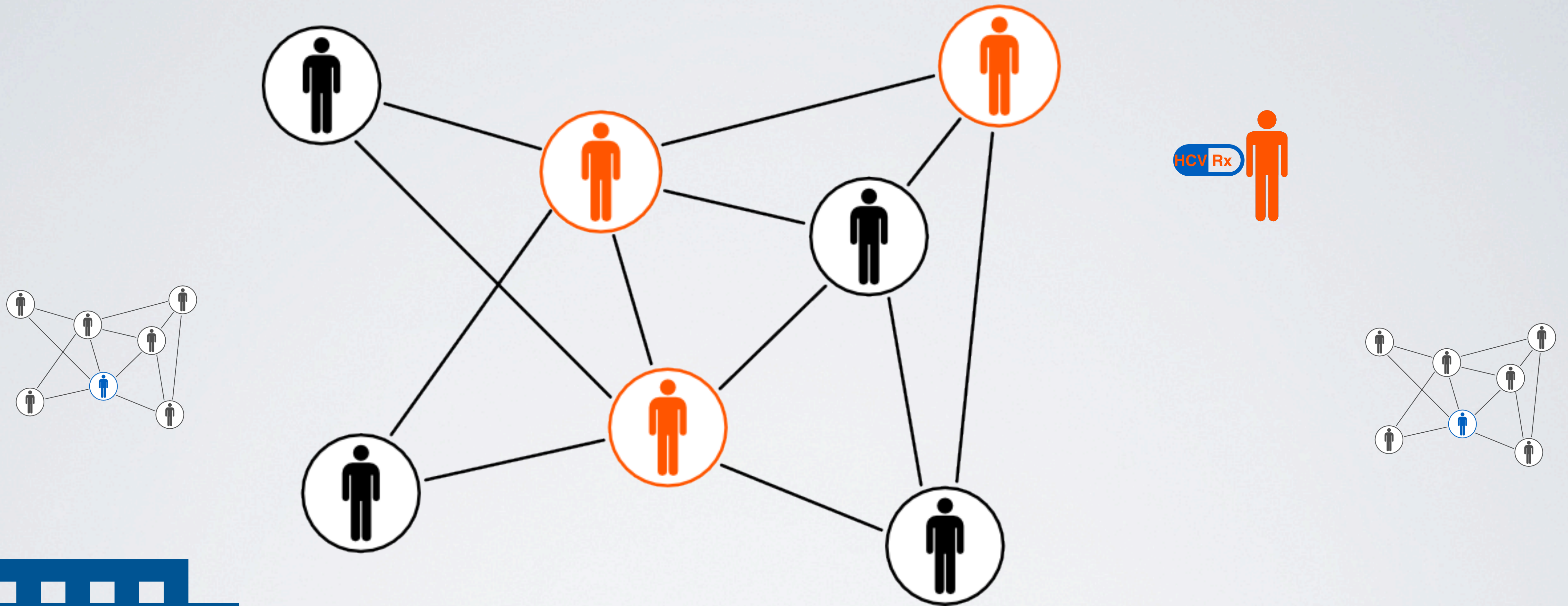
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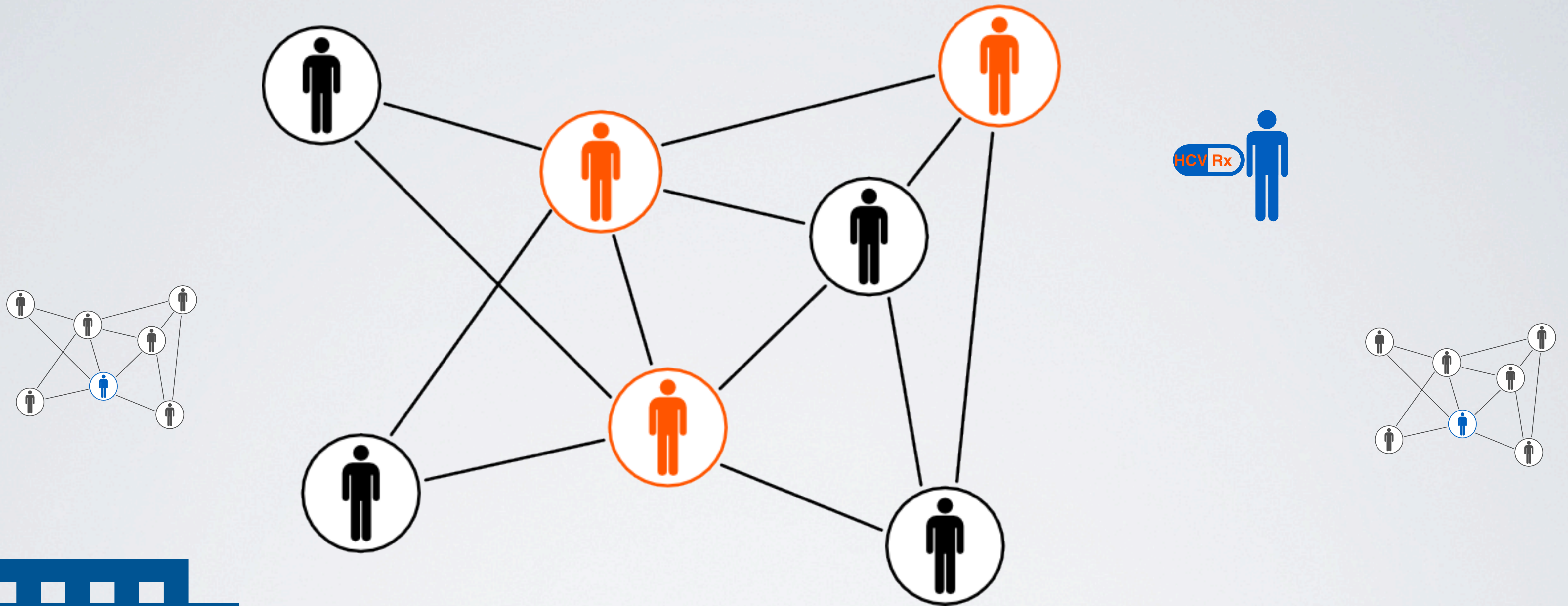
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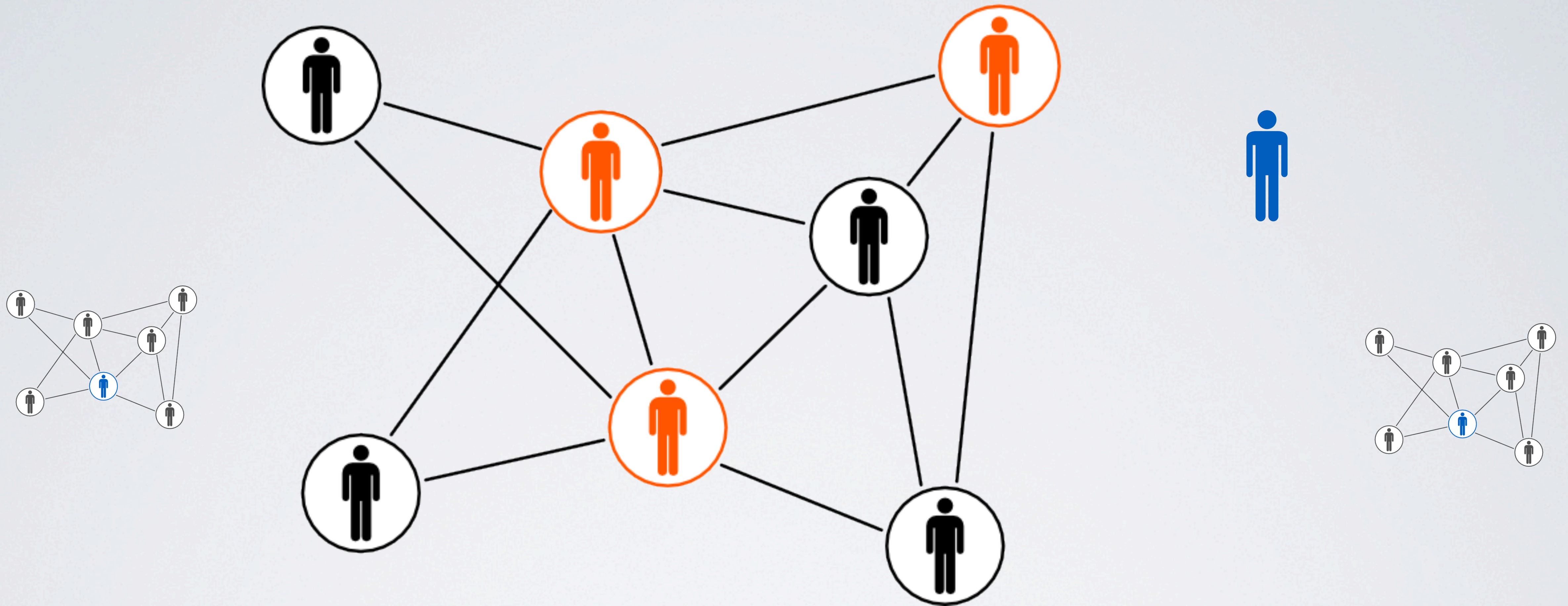
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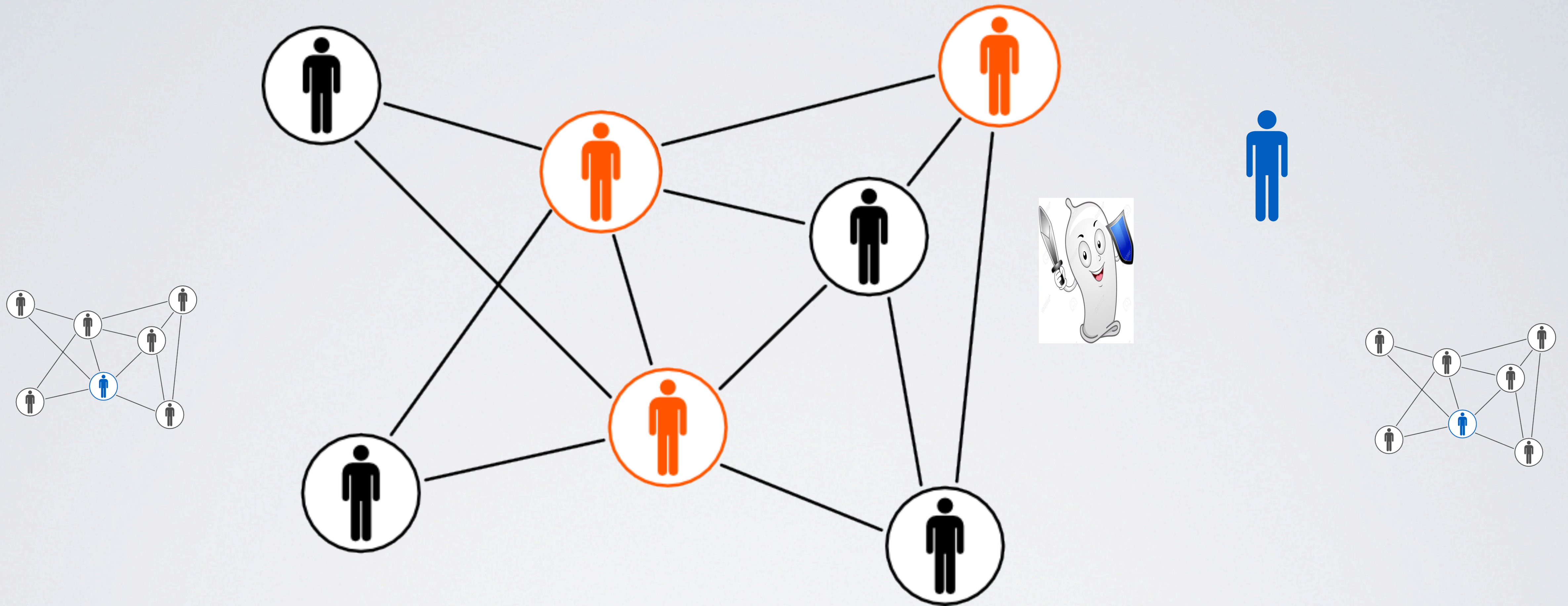
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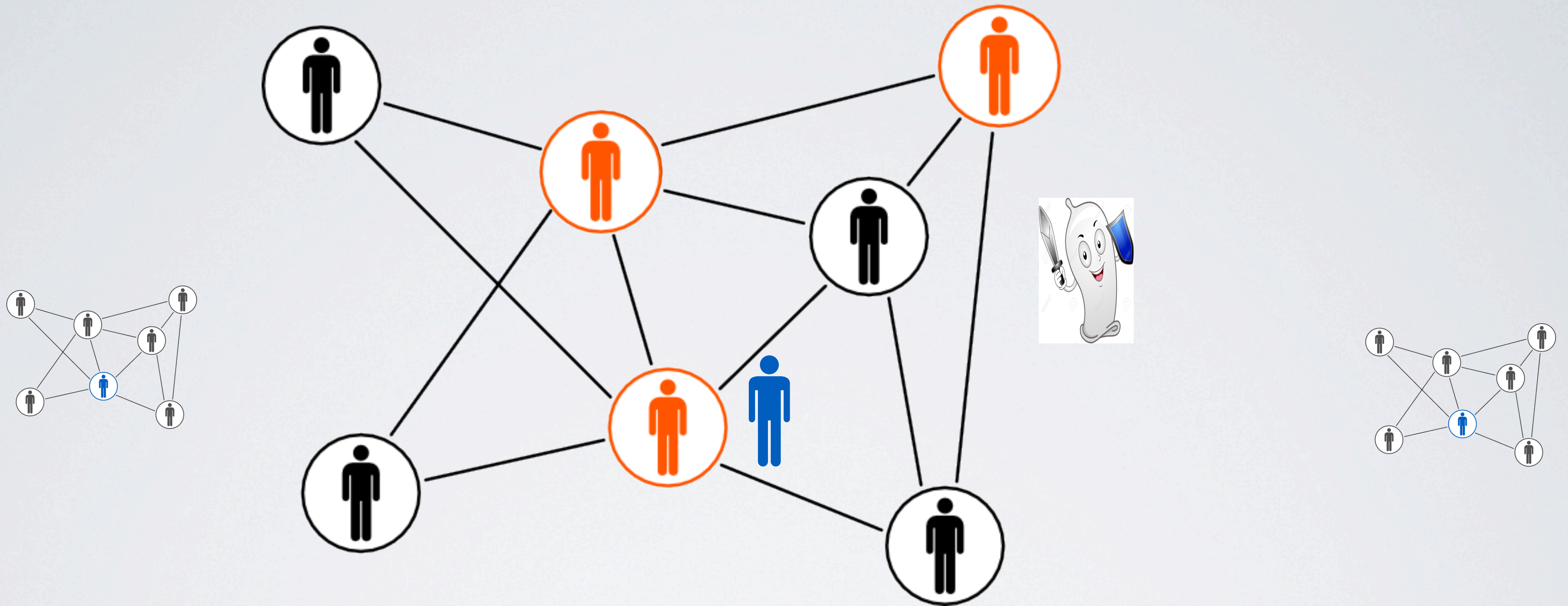
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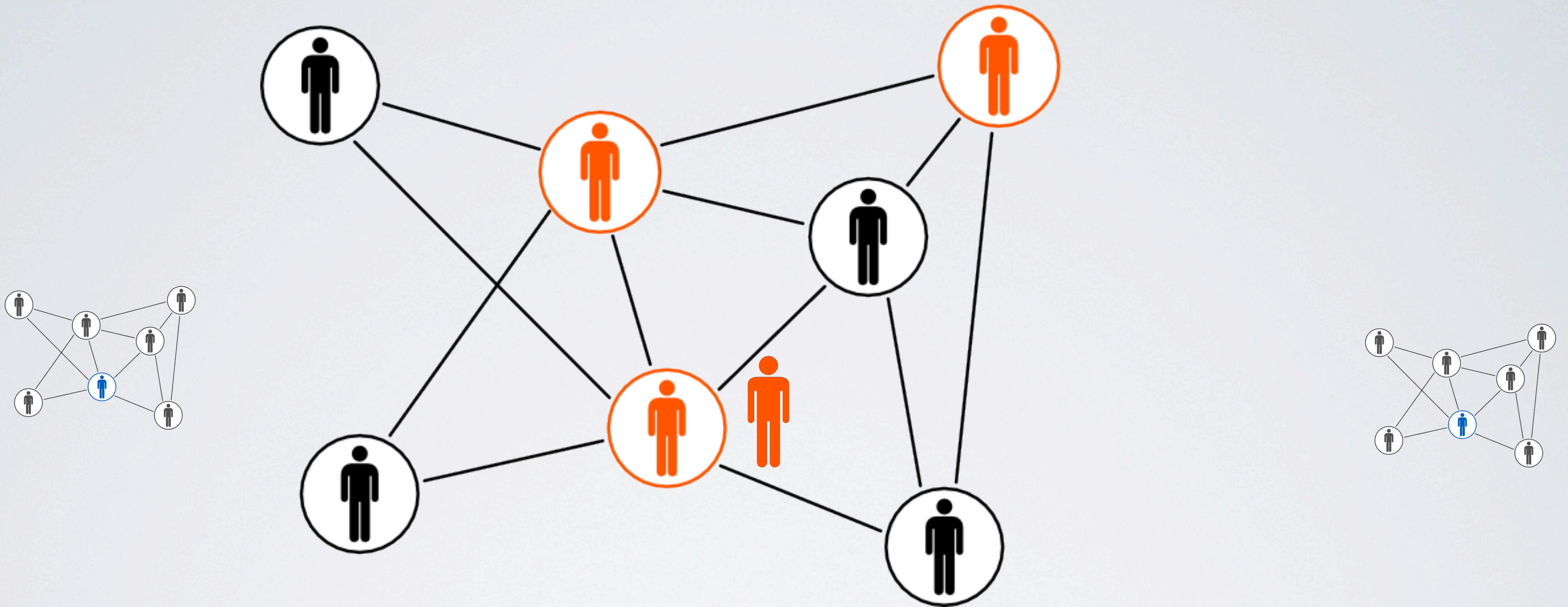
SEXUAL NETWORKS IN MSM



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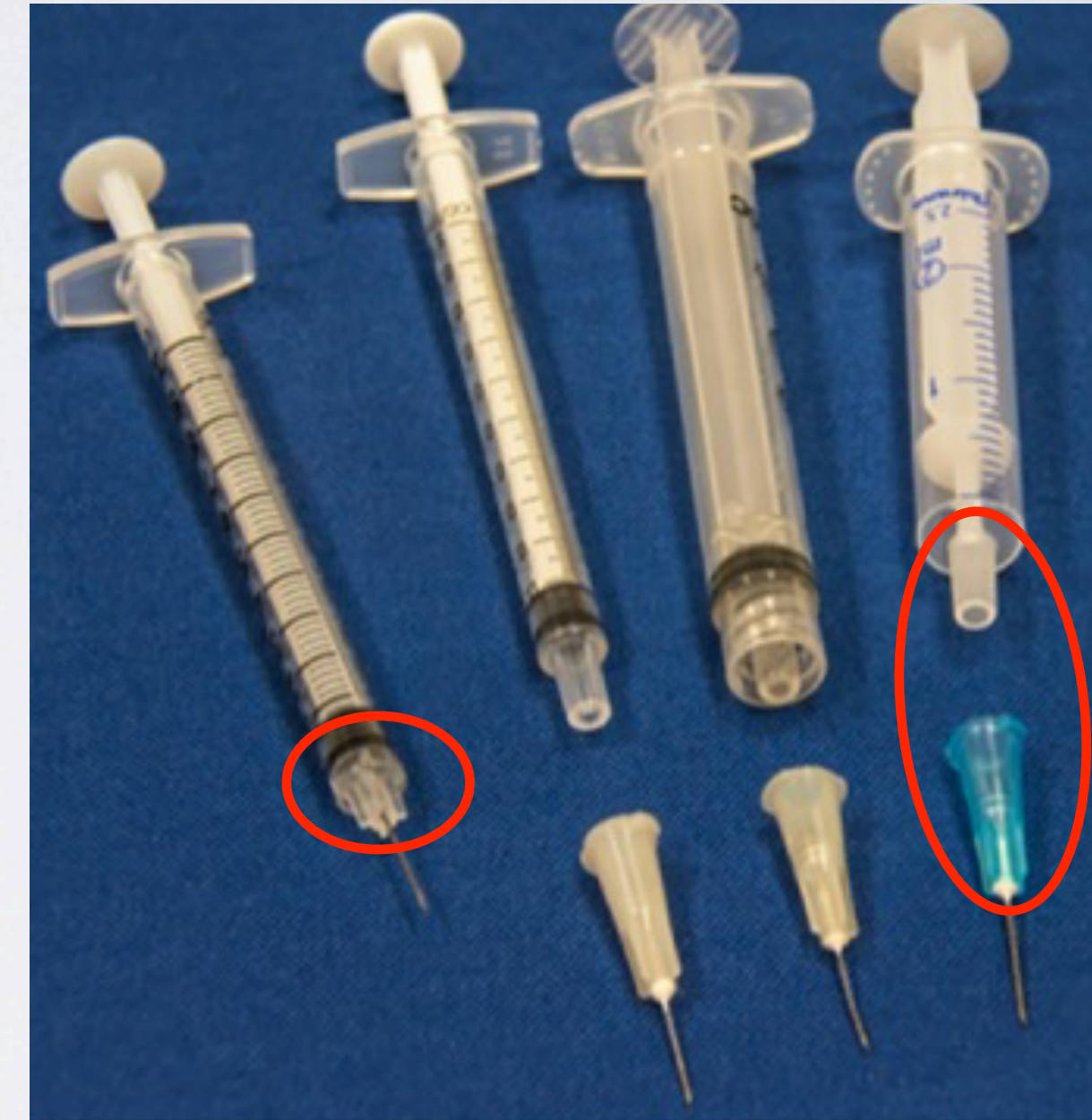


SEXUAL NETWORKS IN MSM



HOW COULD SEMEN REALLY BE THE SOURCE OF HCV (OR: WHY ISN'T IT JUST BLOOD)?

- Hold-back volumes of typically-used syringes: 1.3 uL (non-detachable needles); and 8 uL to 18 uL (detachable needles)
- Assuming blood HCV VL of 10^6 IU/mL, and 10-fold dilution by drug, a used syringe delivers between 130 IU and 1,800 IU HCV
- An average ejaculate (semen) delivers into the rectum of the receptive partner between 50 IU and 6,630 IU of HCV
- Penises don't bleed during insertive anal intercourse



REDEFINING THE PARADIGM, SUMMARY

- The main route of transmission among MSM and their sex partners (ie including trans women) is sexual
- Sexual transmission is just that: the main transmitting body fluid is semen, not blood
- Drug use is not causally involved in these HCV transmissions
- Sexual transmission among MSM is not so inefficient
- Heterogeneity of HCV prevalence in sexual networks explains much of the confusion about route, drugs, and efficiency

SUMMARY: UNDERSTANDING BARRIERS TO HCV ELIMINATION AMONG MSM

Prevention is essential, but we do not currently know how:

- No harm reduction or desire for version of “MAR” for MSM:
 - Parallel to needle exchange is condom use—but not desired
 - No parallel to methadone, suboxone to reduce number of sexual exposures—but not desired
- Role of methamphetamine (sexualized drug) use is secondary:
 - surrogate for high HCV-prevalence networks
 - “trigger” for sex, leading to actual risk, receiving semen into rectum

Acknowledgments

The hundreds of patients who volunteered to become participants in our studies

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