# TOBACCO SMOKING THE SILENT KILLER

Lene Ryom MD PhD

CHIP, Center of Excellence for Health, Immunity & Infections

Dept of Infectious Diseases, Copenhagen University Hospital, Denmark

# 2018 GLOBAL SMOKING PREVALENCE ESTIMATES

| | Male | Female |
|---|---|---|
| Brazil | 11% | 7% |
| France | 32% | 30% |
| Greece | 38% | 31% |
| Israel | 22% | 12% |
| India | 17% | 1% |
| Japan | 26% | 20% |
| **Lebanon** | **58%** | **48%** |
| Malawi | 15% | 4% |
| **New Zealand** | **8%** | **6%** |
| Russia | 39% | 17% |
| **South Africa** | **49%** | **34%** |
| United Kingdom | 26% | 16% |
| United States | 26% | 11% |

Declining global prevalence:
42% reduction women
25% men since 1980

Ng M et al JAMA. 2014

Smoking prevalence peaks at 45-64 years, most start smoking in their youth

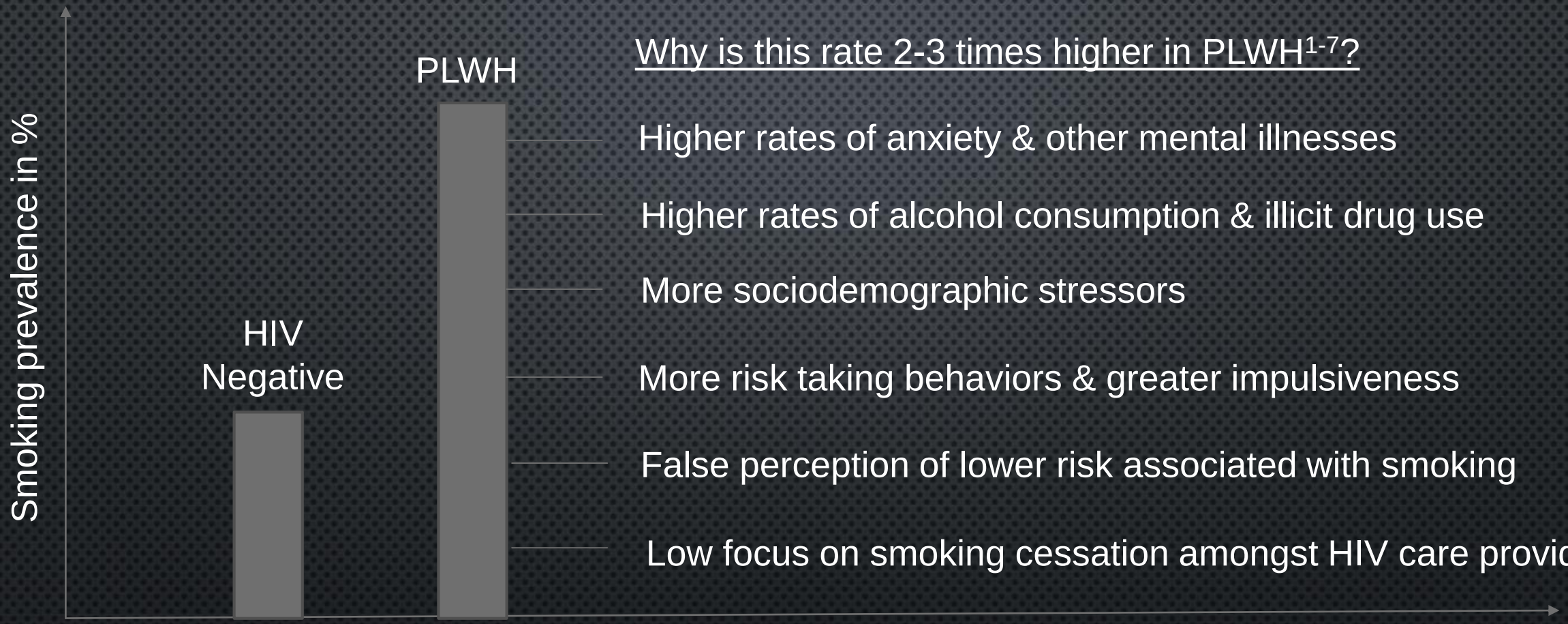
Apelberg BJ et al NEJM 2018
Jamel A et al MMWR 2018

Smoking consumption increase linearly with age

Borland R et al Tobacco Control 2003

State of Smoking 2018 Global Poll https://www.smokefreeworld.org/sites/default/files/uploads/derek-yach-press-conference-presentation.pdf

# SMOKING PREVALENCE IN PEOPLE LIVING WITH HIV (PLWH)

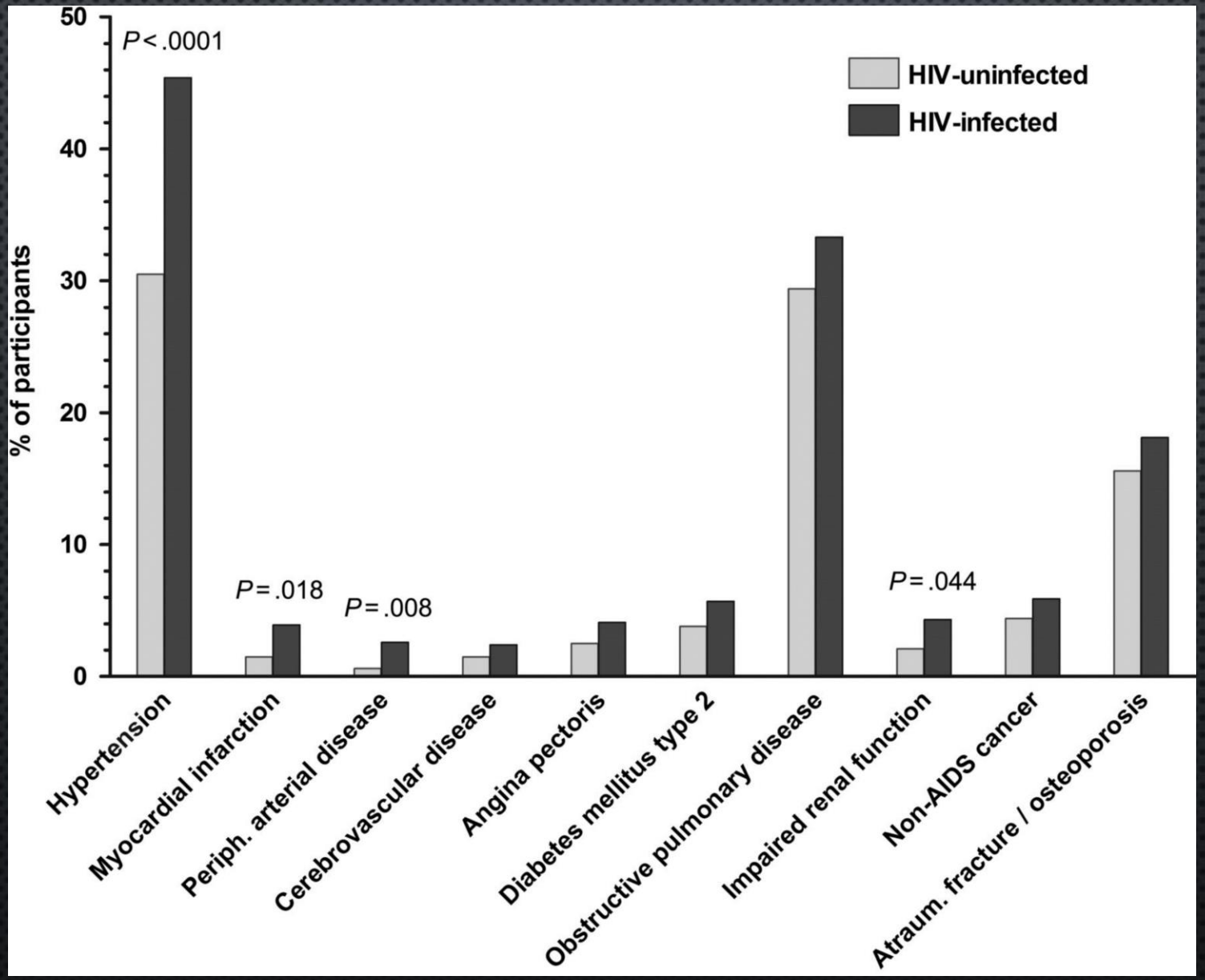



Why is this rate 2-3 times higher in PLWH[1-7]?

- Higher rates of anxiety & other mental illnesses
- Higher rates of alcohol consumption & illicit drug use
- More sociodemographic stressors
- More risk taking behaviors & greater impulsiveness
- False perception of lower risk associated with smoking
- Low focus on smoking cessation amongst HIV care providers

1. Ranjit S et al F1000Res 2018, 2. Mdodo R et al Ann Intern Med 2015 3. Giles ML et al AIDS Res Ther 2018, 4. Fuster M et al HIV Med 2009, 4. Burkhalter JE et al Nicotine Tob Res 2005, 5. Hershberger SL et al Addict Behav 2004 6. Fingeret MC et al Body Image 2007, 7. Frazier EL et al Prev Med 2018

# COMORBIDITIES IN PLWH AND HIV-NEGATIVE INDIVIDUALS




Schouten J et al for AgeHIV CID 2014

# SUBSTANCES IN TOBACCO PRODUCTS

>7000 compounds[1]

- >100 are proven poisonous[1]
- Approx. 70 are carinogenic[1,2]

Smoking may cause disease in nearly every tissue & organ[3,4]

Nicotine[2,3]

- Primary addicting drug, may be as addictive as heroin, cocaine & alcohol
- <10 sec release of dopamine, endorphins & other neurotransmitters
- Levels & speed of delivery are commercially exploited & increasing over time


1. *https://www.cdc.gov/tobacco/data_statistics/sgr/.../general-audience-presentation.pdf,*
*2.* WHO international agency for research of cancer, WHO 2007*, 3*. Bell S InT environ Res Pub Health 2017
4. Calvo M et al AIDS Rev 2015

# RELEVANCE OF HIV-STATUS ON SMOKING IMPACT

- No evidence supporting association between smoking & risk of HIV seroconversion[1,2]

- Some evidence suggesting smoking may impact the health of PLWH more severely than that of the general population[1, 2]

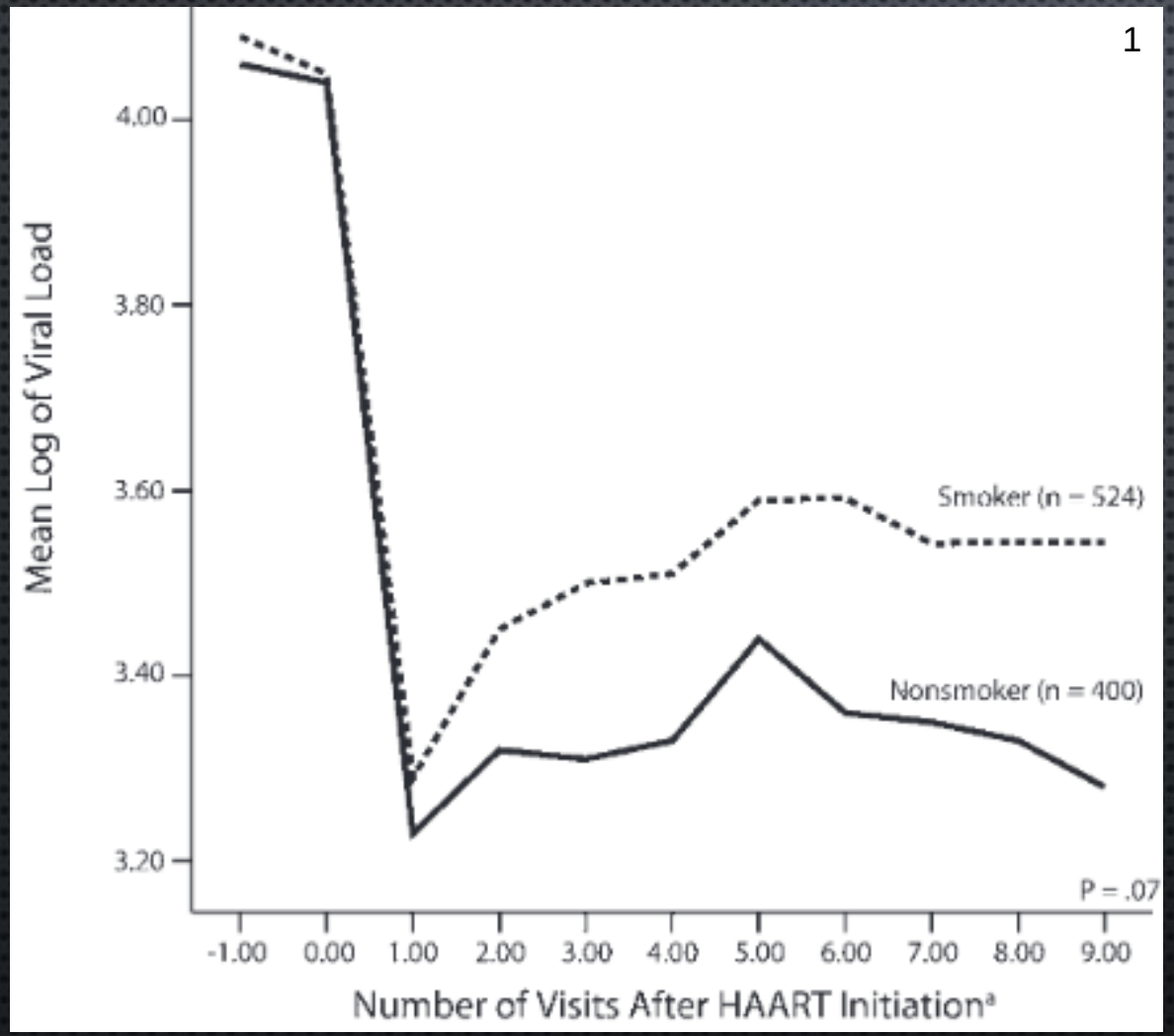
- Smoking may[1,3-9]
  Enhance viral replication
  Increase formation of free radicals -> oxidative stress/mitochondrial dysfunction
  Impair innate/adaptive immune response
  Increase inflammation

  } similar to HIV itself
  double trouble?

- Smoking increases risks of several AIDS-event incl esophageal candidiasis & TB -> directly counteracting effects of ART[10,11]

1. Calvo M et al AIDS Rev 2015, 2. Marshall M et al AIDS Educ Prev 2009, 3. Lee J et al J Dent Res 2012, 4. Valiathan R et al Plos One 2014, 5. Montarroyos U et al PloS One 2014, 6. Zhao L et al Toxicology 2010, 7. MacDonald DM et al for START Pulmonary substudy 2018, 8. Moreno JL et al AIDS Behav 2015, 9. Kooij KW et al for Age$_h$IV JID 2016, 10. Lifson AR for SMART AM J Pub Health 2010, 11. Van Zyl Smit RN Eur Respir J 2010

# RELEVANCE OF HIV-STATUS ON SMOKING IMPACT




In the WIHS study
smoking women with HIV experienced more virologic rebound (HR 1.39 [1.06-1.69]) & reported
<95% ART adherence in
32% of time vs 23% in non-smokers (p=0.01)[1]

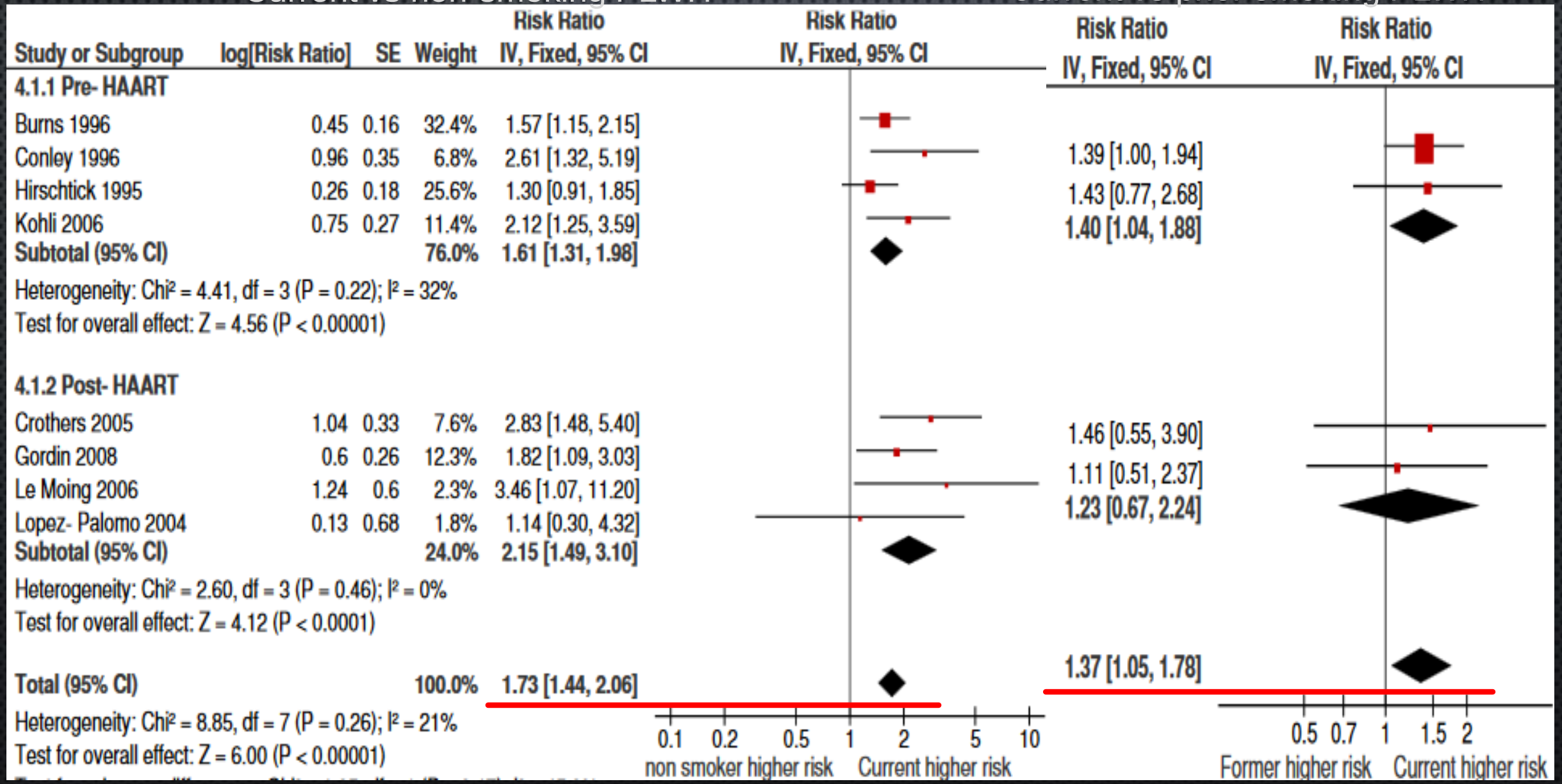
- Causality?
- Smoking as a proxy for other factors impacting adherence/viral suppression[2-4] ?
  - socioeconomic & educational level, substance abuse, mental heath issues etc.

1. Feldman JG et al for WIHS Am J Pub Health 2006, 2. Cropsey KL et al J Addict Med 2016, 3. Lifson AR for SMART AM J Pub Health 2010, 4. Helleberg M et al for the Danish HIV Cohort CID 2013

# SMOKING & PNEUMONIA

## Current vs non-smoking PLWH

## Current vs prior smoking PLWH




De P BMC Med 2013

# SMOKING & CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

- Smoking is the strongest independent risk factor for COPD in the general population[1,3]

- Several studies suggest air way obstruction & COPD is more prevalent in PLWH[1-5]
  - Due to increased risk of pneumonia? Altered local/systemic immune function? Direct viral impact? Higher smoking rates?

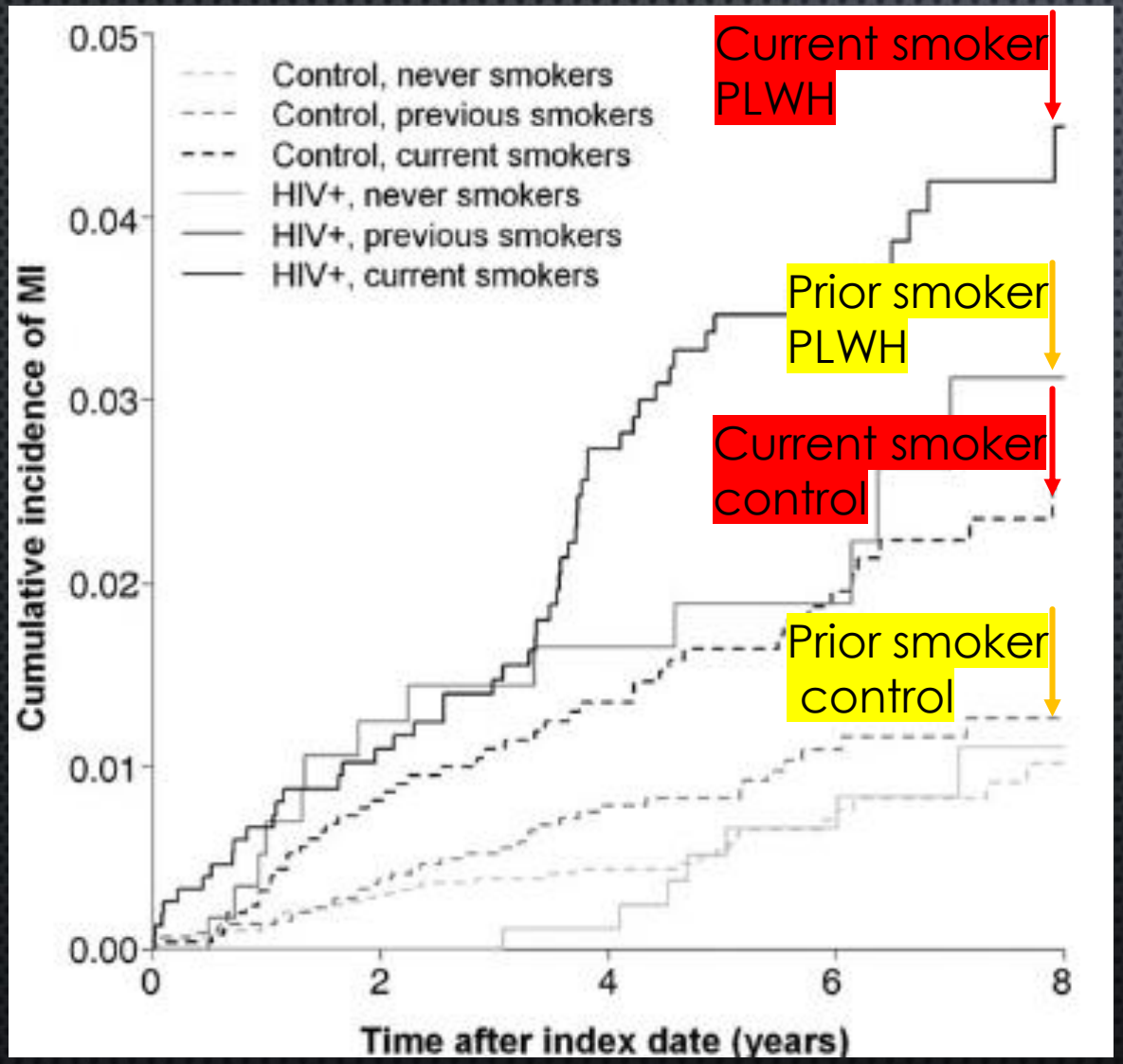
$FEV_1$ slope by smoking status[6]

| | Smoker (n = 247) | Nonsmoker (n = 668) | *P* |
|---|---|---|---|
| Analysis by baseline smoking status | −38.3 mL/yr (−47.1 to −29.4) | −25.1 mL/yr (−30.6 to −19.6) | 0.013 |

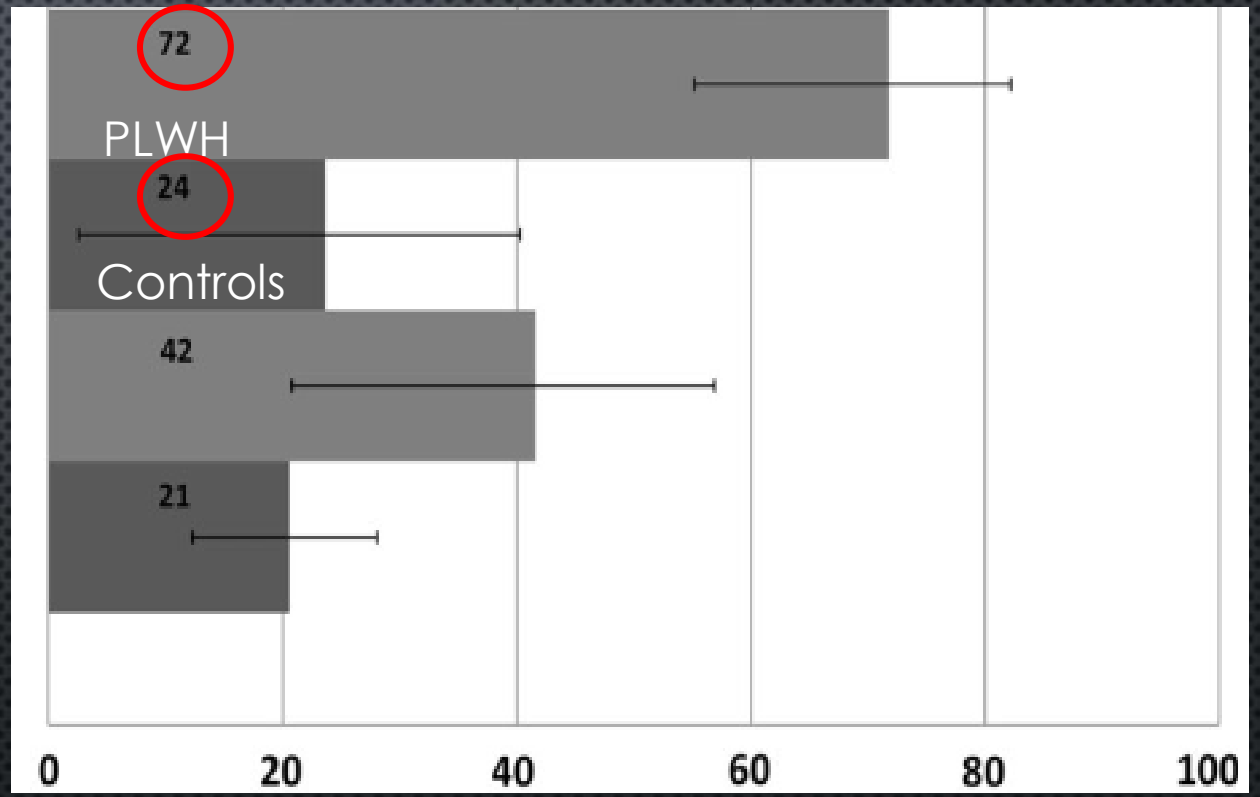
- ART status did not impact $FEV_1$ slopes suggesting an additional role of non-HIV factors (i.e. lifestyle factors) in the COPD pathogenesis[6]

1. Bigna JJ et al Lancet Global Health 2017, 2. Ronit A et al for COCOMO Thorax 2018, 3. Gingo MR et al Am J Respir Crit Care med 2010, 4. Crothers K et al Chest 2006, 5. Shirley DK et al CID 2013, 6. MacDonald DM et al for the INSIGHT START pulmonary substudy, JAIDS 2018

# SMOKING & MYOCARDIAL INFARCTION (MI)



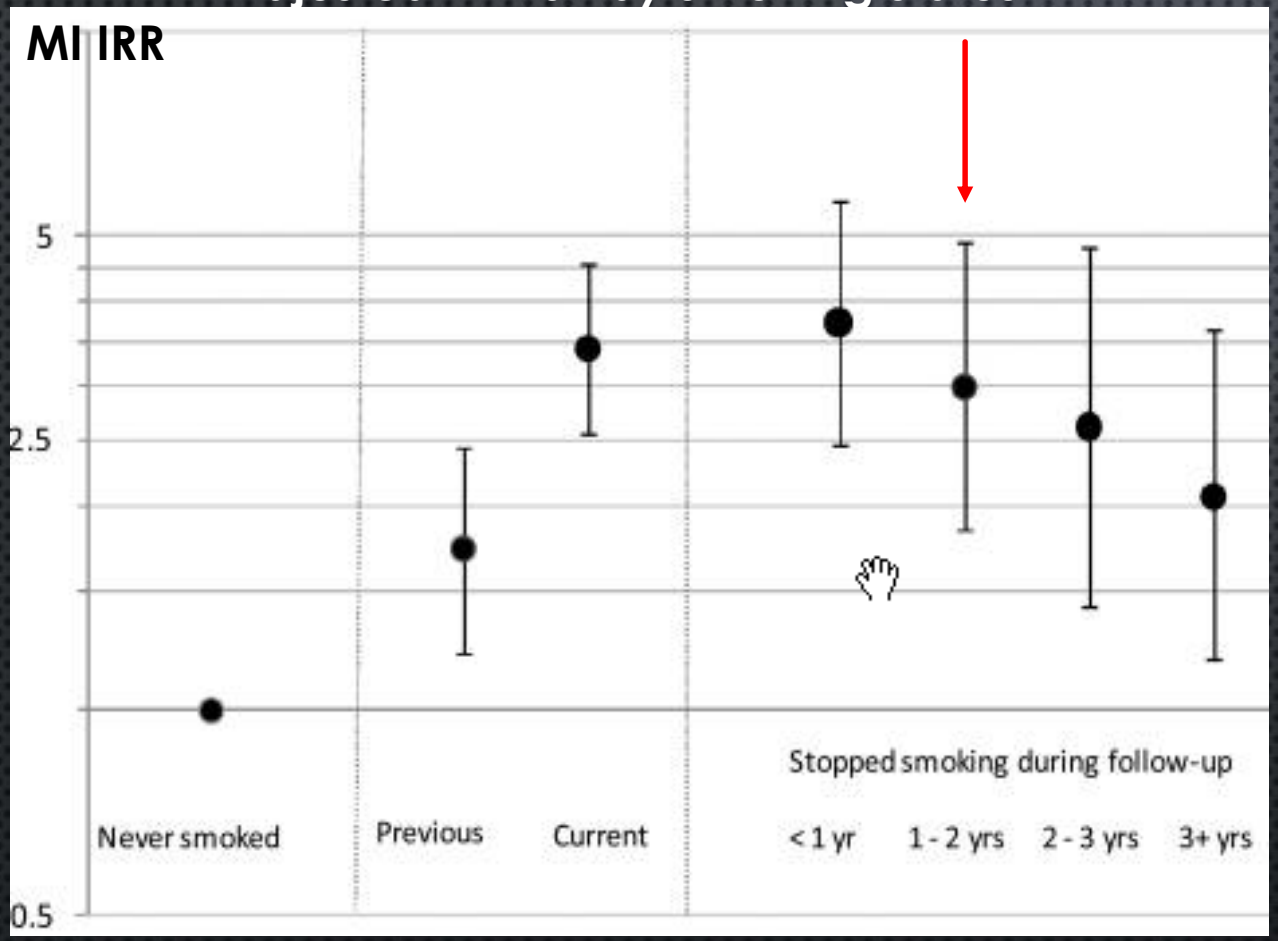

Population-attributable fraction of MI (%) with smoking




Rasmussen LD et al for the Danish HIV Cohort CID 2015

# SMOKING CESSATION & RISK OF MI

## Adjusted MI risk by smoking status




Petoumenos K et al for D:A:D HIV Med 2011

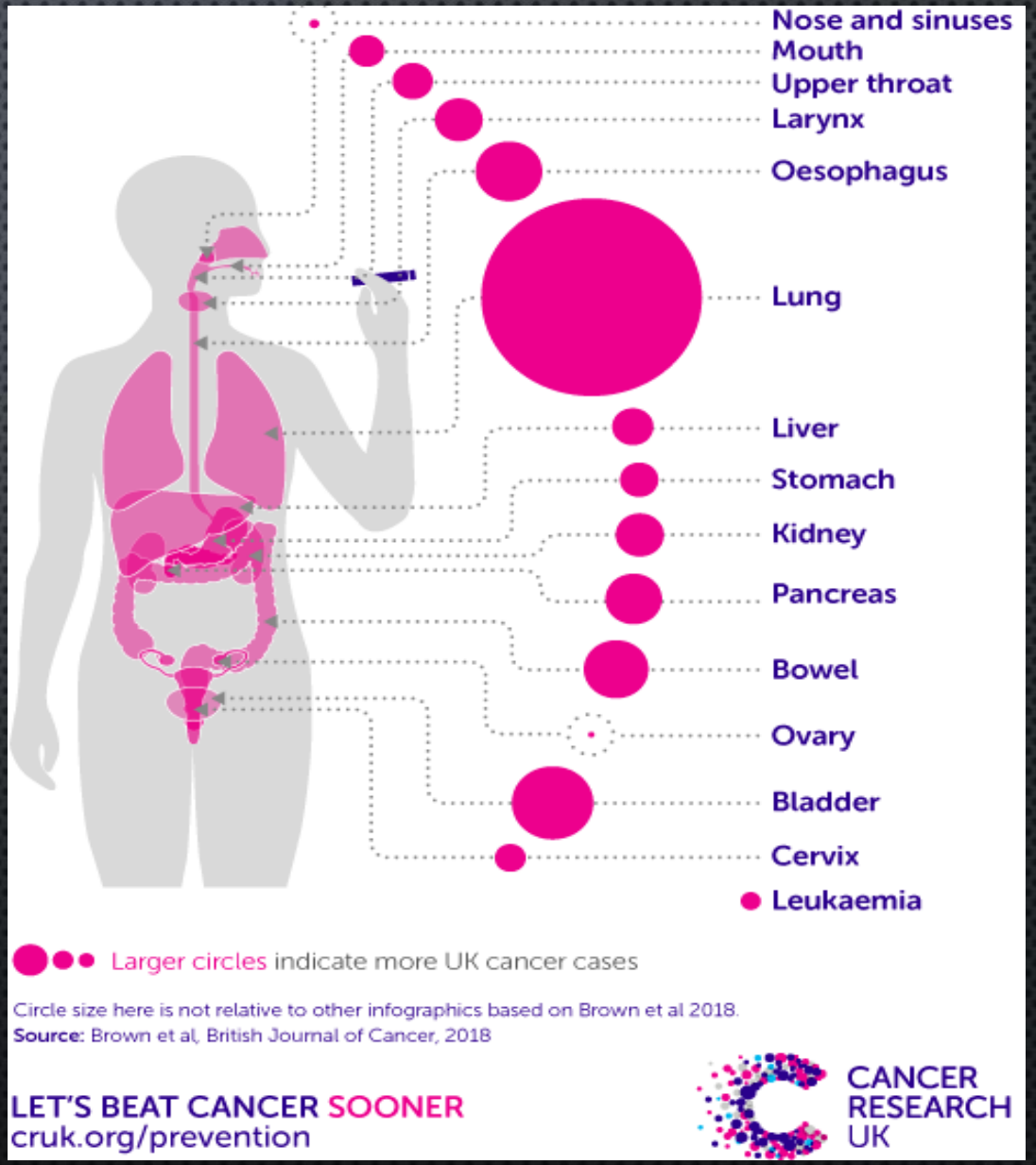
## Impact of improving modifiable risk factors on CVD risk


Petoumenos K et al for D:A:D HIV Med 2014

# SMOKING & CANCER

- PLWH have higher risks of several cancers independently of smoking
  (i.e. lung, anal, HL with SIRs 2-19),
  but smoking increases risks further (HRs 1.4-1.8)[1-3]
  - HIV-related immune impairment & inflammation (i.e. IL6) may increase vulnerability to carcinogenic smoking effects[1,4-7]

- Lung cancer survival in PLWH is shorter than in the general population (median 6 vs 9 months) & related to more advanced stages at diagnosis (87% vs 68%)[5]




1. Lifson AR et al for SMART AM J Public Health 2010, 2 Hernández-Romirez Zu et al Lancet HIV 2017, 3. Altekruse SF et al for NA-ACCORD AIDS 2018, 4. Ranjit S et al F1000Res. 2018, 5. Cheng Z et al thorac cancer 2017, 6. Brock et al. JAIDS 2006 7. Kirk QD et al CID 2007

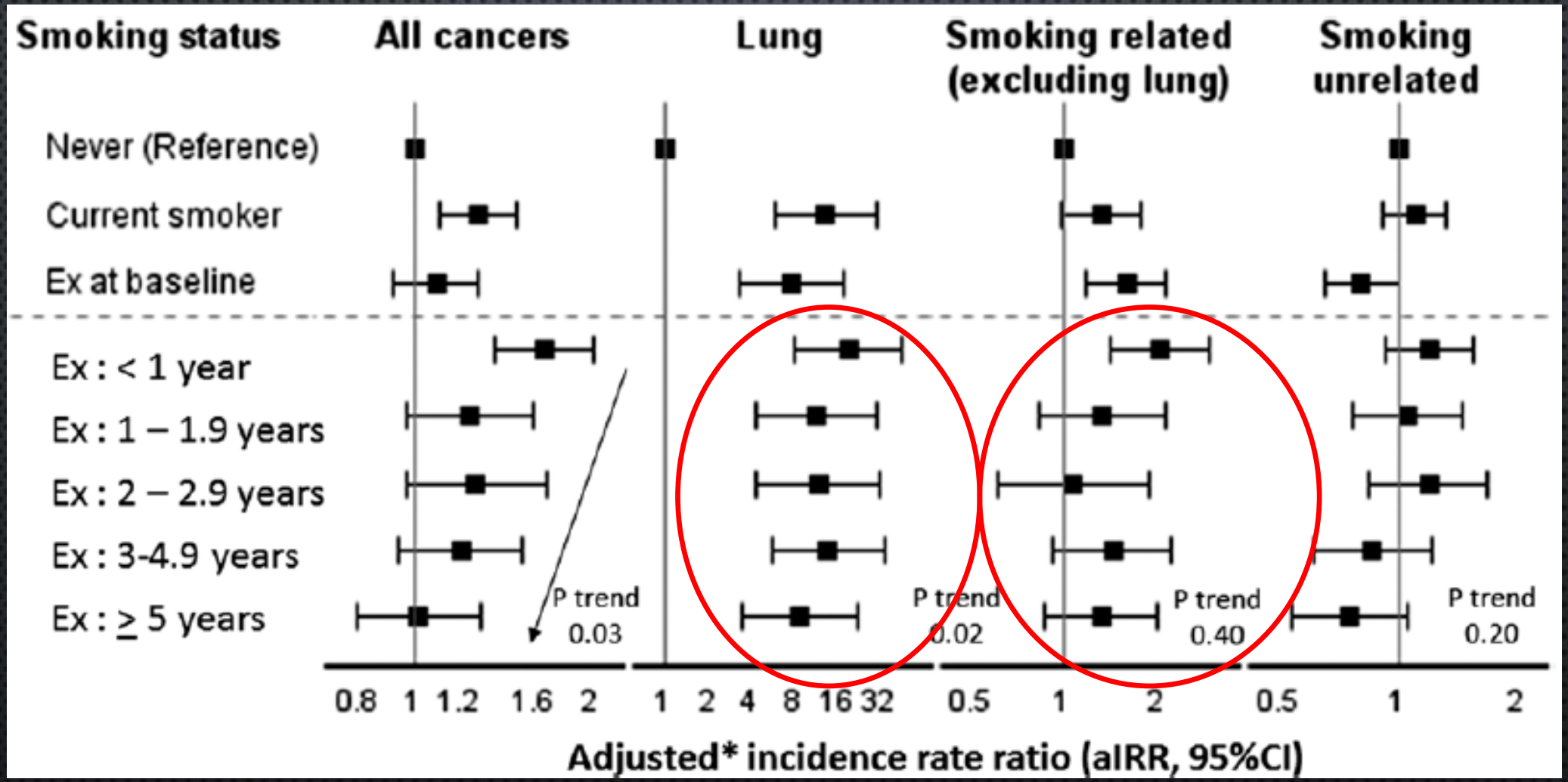
# SMOKING & CANCER

Hazard ratios & population attributable fraction of cancer with smoking

| | Hazard ratios associated with ever smoking cigarettes | | | | Population-attributable fractions associated with ever smoking cigarettes | | | |
|---|---|---|---|---|---|---|---|---|
| Cancer diagnosis | HR | 95% CI | aHR[a] | 95% CI | PAF (%) | 95% CI | aPAF (%)[a] | 95% CI |
| All cancers combined | 1.41 | (1.26, 1.58) | 1.33 | (1.18, 1.49) | 22 | (15, 27%) | 19 | (13, 25%) |
| Smoking-related | 2.65 | (2.07, 3.39) | 2.31 | (1.80, 2.98) | 54 | (43, 62%) | 50 | (39, 59%) |
| Lung cancer | 21.73 | (6.87, 68.71) | 17.80 | (5.60, 56.63) | 95 | (84, 98%) | 94 | (82, 98%) |
| Smoking-related, excluding lung cancer | 1.77 | (1.37, 2.28) | 1.59 | (1.22, 2.06) | 35 | (20, 47%) | 31 | (16, 44%) |

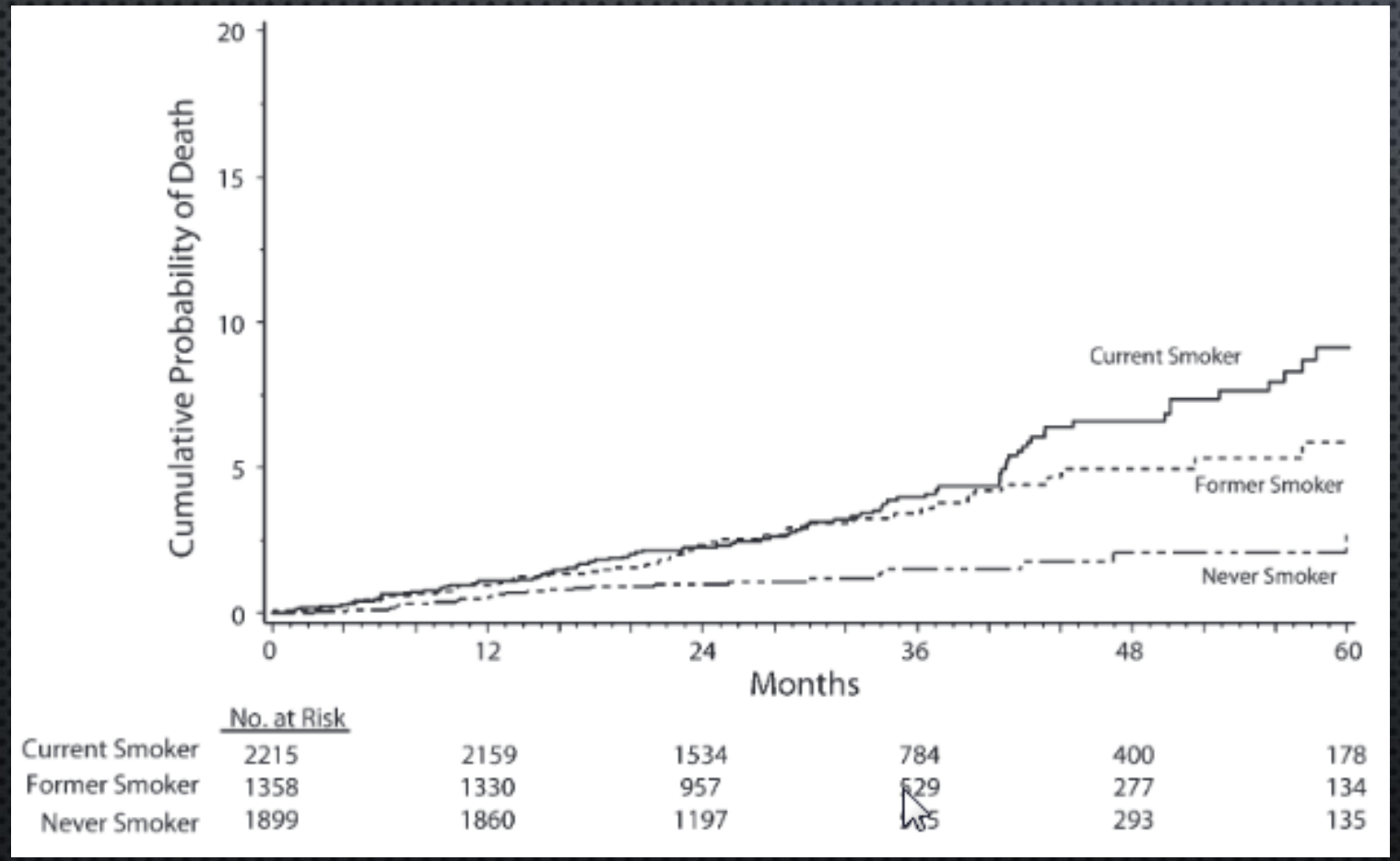
Altekruse SF et al for NA-ACCORD AIDS 2018

# SMOKING CESSATION & CANCER




Shepherd L et al for D:A:D CID 2018

# SMOKING & MORTALITY




| Event | Adjusted HR current vs former smoker |
|---|---|
| All-cause mortality | |
| Unadjusted | 3.0 (1.9, 4.7) |
| Adjusted | 2.4 (1.5, 3.8) |
| AIDS-related disease | |
| Unadjusted | 1.6 (1.1, 2.3) |
| Adjusted | 1.3 (0.9, 1.9) |
| Major CVD | |
| Unadjusted | 1.8 (1.2, 2.8) |
| Adjusted | 2.0 (1.3, 3.1) |
| Expanded CVD[a] | |
| Unadjusted | 1.9 (1.3, 2.6) |
| Adjusted | 1.9 (1.4, 2.7) |
| Non-AIDS cancer | |
| Unadjusted | 1.7 (1.1, 2.5) |
| Adjusted | 1.8 (1.2, 2.8) |
| Major Renal disease | |
| Unadjusted | 6.6 (0.8, 52.4) |
| Adjusted | 6.6 (0.8, 53.9) |
| Major Hepatic disease | |
| Unadjusted | 1.9 (0.7, 5.5) |
| Adjusted | 0.6 (0.2, 1.8) |
| Bacterial pneumonia[b] | |
| Unadjusted | 2.5 (1.7, 3.6) |
| Adjusted | 2.3 (1.6, 3.3) |

Lifson AR et al for SMART AM J Public Health 2010

# SMOKING & MORTALITY

| | Lost life-years [95%CI] | Population attributable fraction (PAF) of death in % |
|---|---|---|
| Smoking vs non-smoking PLWH | 12.3 [11.5-13.0] | 61.5 |
| Smoking vs non-smoking controls | 3.6 [3.1-4.0] | 34.4 |
| Non-smoking PLWH | 5.1 [4.4-5.8] | 0.3 |

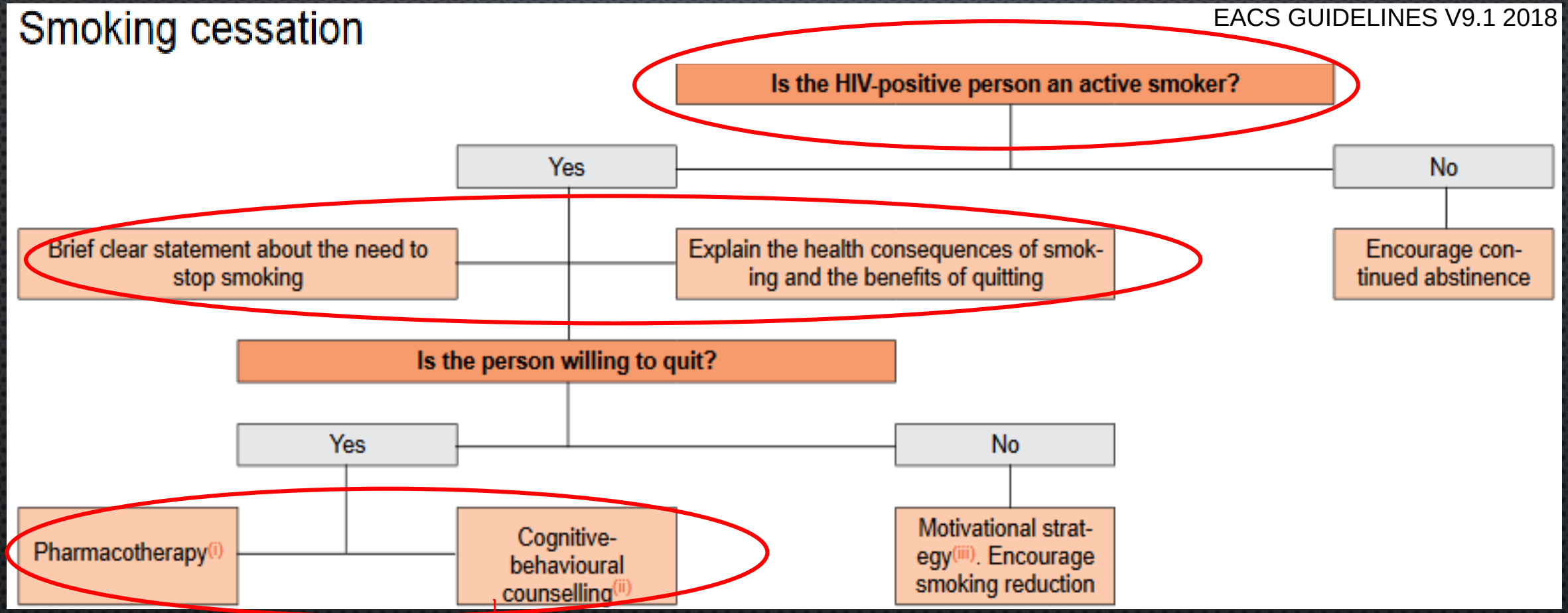
Helleberg M et al for the Danish HIV Cohort CID 2013

# SMOKING CESSATION


- Reduces the risk of excess morbidity & mortality[1,2]
- Health benefits are greater if stopping at earlier ages, but beneficial at all age[1,2]
- Success rates for smokers trying to quit on their own is low (<5-10%)[6]
- PLWH less likely to quit smoking than the general HIV-negative population (quit ratios 32-37% vs 52-57%)[3,4,5,10]
  - Multifactorial, but likely related to greater sociodemographic challenges & enhanced nicotine metabolism[7-9]
- Often require repeated attempts (median 4 in a 2009 US study of PLWH[4])

1. US Dept of Health & Human Services, Surgeon General 1990, 2. US Dept of Health and Human Services Surgeon General 2014, 3. CDC MMWR 2017, 4. Humfleet et al AIDS Educ Prev 2009,
5. Mdodo R et al Ann Intern Med 2015, 6. Hughes JR et al Addiction.2004, 7. Fuster M et al. HIV Med 2009, 8. Earla R et al. Drug Metab Disoos 2014,
9. Regan S et al, PloS One 2011, 10. Frazier EL et al Prev Med 111 2018

# GUIDELINES RECOMMENDATIONS IN PLWH




Group therapy/self help groups/online courses/mobile support etc[1-3]

- Changing habits/routines
- Alternatives for inducing pleasure/calming/relaxation
- Bounderies; co-abuse, mental illness, educational level

To control physical withdrawal cravings/insomnia/concentrations problems/irritability/weight gain[1-3]

1. Lindson-Hawley N et al. Cochrane Database Syst Rev. 2016, 2. McRobbie H et al Respir Med 2005, 3. Frishman WH Prev Cardiol 2017

# RECOMMENDED PHARMACOTHERAPY

| Agent | Mode of action | Treatment (weeks) | Efficacy |
|---|---|---|---|
| **Nicotine**<br>Patches, gum, lozenges inhalers & nasal sprays[1,2] | Binds nicotine receptor | 6-12 (max 28) | Patchy data & low adherence in PLWH[3-6]<br>General population;<br>RR 1.6 vs placebo at 6 months[1,7-8] |
| **Varenicline** | Binds nicotine receptor | 12 (+12) | PLWH; varenicline/counselling 15% vs placebo/counselling 6% at 48 weeks[9-10]<br>Risk of Depression/CVD?[9] |
| **Bupropion** | Inhibits noradrenalin/ dopamine reupdate | 7-12 (max 56) | Limited data in PLWH[11]<br>General population;<br><15% at 12 months[9,12-13]<br>Risks of interactions PIs/NNRTIs |

Smoking cessation studies in PLWH are small with limited follow-up & focus mostly on behavioural approaches with conflicting results, especially after the intervention ends[3-6]
-> calls for better powered intervention studies

1. Stead LF et al Cochrane Database Syst Rev 2012, 2. Gilles ML et al AIDS Res Ther 2018, 3. Wewers ME et al J Assoc Nurses AIDS Care 2000, 4. Lloyd-Richardson EE et al Addiction 2009, 5. Ingersoll KS et al AIDS Behav 2009, 6. Elzi L et al Antivir Ther. 2006, 7. Lindson-Hawley N et al Cochrane Database Syst Rev, 8. Pool ER et al Cochrane Database Syst Rev 2016, 9. Mercie P et al Lancet HIV 2018, 10. Ferketich AK et al Nic Tob Res 2013, 11. Pedrol-Clotet E, Enferm Infec Microbiol Clin 2006, 12. Gonzales D et al Jama 2006, 13. Jorenby D et al Jama 2006

# SECONDARY PROPHYLAXIS INITIATIVES

The WHO recommends promoting public awareness on tobacco risks[1]

- Increased pricing
  - 5% prevalence reduction in Australia, & 45% cutting down/attempt quitting in French PLWH (especially adolescents), similar results in the general population[2-4]
- Legislative smoking ban in public buildings/areas
  - Inconsistent impact[5,8]
- Health warnings on packages
  - Inconsistent longer-term outcomes, but some evidence suggesting higher impact of pictorial than text warning on cessation attempts & short term abstinence 29-53%[6,7]
- National mass media campaigns
  - 12% increased quit attempts in the US & Australia[9-11]. 0,5% increased quitting success in the UK[5]; but rapid decrease after campaigns ended[9,12]

Large regional differences in implementation & uncertainties on effectiveness in PLWH,
-> calls for adequately powered high quality studies in PLWH

1. WHO 2003, 2. Diethelm P et al Tob Prev Cessation 2011, 3. Peretti-Watel P et al Curr HIV Res 2009, 4. Dunlop SM et al Addiction 2011, 5. Frazer K et al Cochrane Database Syst Review 2016, 6 Brewer NT et al Jama Int Med 2016, 7.Evan AT et al Plos One, 2015, 8. Wakefield MA et al Am J Pub Health 2008 9. McAfee T et al Lancet 2013, 10. Wakefield MA et al Am J Pub Health 2008, 11. Borland R et al Tob Control 2003, 12. Xiao D et al Lancet 2013

# CONCLUSIONS & PERSPECTIVES

- The smoking epidemic in PLWH & in the general HIV-negative population differs significantly
  - Smoking rates disproportionally high in PLWH
  - Smoking may induce a state of double trouble in PLWH & impact morbidity/mortality more severely
  - Smoking cessation is particularly challenging in PLWH

- Smoking is a leading cause of preventable morbidity -> imperative to design studies to clarify the complex needs of different groups of smoking PLWH
  - Effectiveness of different cessation interventions & safety profiles of pharmaceutical therapies
  - Challenges in resource limited settings

- Guidelines provide cessation recommendations including addressing motivation to quit & combined behavioral counselling & pharmaceutical substitution therapy
  - Time for smoking cessation to become a top priority in the clinical management of PLWH

- It is never too late to quit!

## Thanks to

Jens Lundgren, Ole Kirk, matthew Law, Kathy Petomenos, Wafaa El-Sadr & the session moderators for their help reviewing the presentation