

Web Appendix 1: Characteristics of earlier cohorts and analyses overlapping with COHERE evaluating KS incidence in PLWH according to drug use

| COHORT, author (year) | Location | Primary data source | Study period | Mean follow-up (years) | PLWH (N) | Incident KS cases (n) | Crude incidence rate (per 1000 person-years) | |
|---------------------------|---------------------------|---|--------------|----------------------------|----------|-----------------------|--|----------------------|
| | | | | | | | No anti-retroviral | ART-treated |
| FHDH, Grabar (2006) | France | FHDH | 1993-2003 | 3.3 [†] | 54 999 | 1634 | 32 | 3 |
| CASCADE, Lodi (2010) | Europe/ Canada/ Australia | CASCADE (25 cohorts including FHDH, SHCS) | 1986-2006 | 4.7 [†] | 9473 | 555 | 8.2 | 2.5-6.7 [‡] |
| KAISER, Chao (2012) | US | Kaiser | 1996-2008 | 4.5 | 12 872 | 313 | NA | 32 |
| FHDH-ANRS, Lacombe (2013) | France/French territories | FHDH-ANRS | 1992-2009 | 4.7 [†] | 66 369 | 1811 | 30 | 2.4-4.5 [¶] |
| DAD, Bruyand (2015) | Europe/Canada/ Australia | D.A.D. (11 cohorts, including ATHENA, SHCS) | 2004-2012 | 5.8 | 41 762 | 341 | NA | 1.4 |
| COHERE29, COHERE (2016) | 10 European countries | 29 European cohorts (see original paper) | 1996-2014 | Median= 4.6 (IQR: 2.0-8.0) | 109 461 | 916 | NA | 1.8 |

aHR=adjusted hazard ratio. aIRR=adjusted incident rate ratio. ART=combination antiretroviral therapy. ATHENA=AIDS Therapy Evaluation in the Netherlands. BMI=body mass index. CASCADE=Concerted Action on Seroconversion to AIDS and Death in Europe. COHERE=Collaboration of Observational HIV Epidemiological Research in Europe. FHDH-ANRS=French Hospital Database on HIV-Agence Nationale, de Recherches sur le SIDA. HBV=hepatitis B virus. HCV=hepatitis C virus. KS=Kaposi sarcoma. NNRTI=non-nucleotide reverse

| Adjusted relative risk (95% CI) [Referent group]* | | Factors adjusted for |
|--|---|---|
| PI-based ART | NNRTI-based ART | |
| aHR 0.68 (0.61-0.75) [all other drug users and non-drug users] | aHR 0.62 (0.54-0.71) [all other drug users and non drug users] | Age, CD4 nadir, exposure group, sub-Saharan origin, occurrence of AIDS |
| aIRR 0.80 (0.46-1.41) [NNRTI-based ART] | aIRR 1.25 (0.71-2.17) [PI-based ART]§ | Age, current CD4, HIV duration, HIV VL, time since ART initiation, type of ART, any prior antiretroviral |
| aIRR 0.84 (0.75-0.94) [for every additional year of PI-based ART] | aIRR 0.81 (0.67-0.99) [for every additional year of NNRTI-based ART] | Age, CD4, sex, year, years of HIV infection, HIV VL, ART duration, race, year, smoking, overweight ICD-9, substance abuse, exposure group, any prior antiretroviral |
| aIRR 1.15 (NR) [NNRTI-based ART] | aIRR 0.87 (NR) [PI-based ART]§ | Age, CD4, sex, exposure group, HIV VL, migration for sub-Saharan Africa, AIDS stage |
| aIRR 0.93 [0.87-1.00] (for every additional year of PI-based ART) | aIRR 0.81 (0.74-0.90) [for every additional year of NNRTI-based ART] | Age, sex, cohort, exposure group, race, year, BMI, prior cancer/AIDS, smoking, HBV/HCV status |
| aHR 1.22 (1.03-1.45) [NNRTI-based ART for boosted PI only | aHR 0.82 (0.69-0.97) [boosted PI-based ART] | Age, CD4, exposure group, HIV VL, origin, year |

***Bold** indicates statistical significance at $p < 0.05$. †Calculated (total person-years divided by number of patients). ‡2.5 if excluding KS diagnoses within first year of ART initiation; 6.7 if including the first year. §Calculated as invert of PI-based results. ¶Two time periods: 4.5 (1996-1999) and 2.4 (2000-2009). ||Calculated as invert of NNRTI-based results. See original article and Web Appendix 5 for nonboosted PI results.

Web Appendix 2: Factors significantly associated with overall PLWH KS incidence in multivariable analysis

| COHORT, author (year) | Variables in model | ART duration effect | Excluded IRIS† |
|---------------------------|--|--|-----------------|
| UK, Portsmouth (2003) | Age (for every 1 year decrease), nadir CD4 (<150 vs. ≥200), ART (PI or NNRTI or NRTI only) vs. no ARV, ethnic origin‡, gender‡, CD8 count‡ | NR | No |
| VA, Kowalkowski (2015) | Age (≥40y or <60), nadir CD4 <200 vs. 200-350, CD4 at event/censor >200, HIV VL <500, Black ethnicity, year of HIV diagnosis ≥2003, ART initiated ≥3 vs. <1y earlier, ≥80% time on ART, cumulative boosted PI 12-23 or ≥36 vs. < 6 months, every additional 10% time of cumulative boosted PI ≥24 months (year 3), Deyo comorbidity score=1 (vs. 0), clinic visits per year | Magnitude of effect reported per unit time | Within 6 months |
| COHERE42, COHERE (2017) | Age‡, current CD4‡, CD4*region‡, female sex vs. male in all regions, women in Europe vs. women in South Africa, men in Europe vs. men in South Africa or North America, younger age in Europe and North America, older age in Latin America and South Africa, first-line NNRTI-based vs. PI-based ART, year ART initiated‡ | No | Within 30 days |
| FHDH, Grabar (2006) | Age (per 10-year decrement), nadir CD4, female sex vs. heterosexual male, heterosexual male vs. MSM, no AIDS-defining criteria, ART (PI or NNRTI or NRTI only) vs. no ARV | NS (ART >1 vs. ≤1 year) | No |
| CASCADE, Lodi (2010) | Age (per 10-year increment), current CD4 (<500 vs. ≥500), undetectable HIV VL for ≥2 years , time from initiating ART >1 year vs. ≤1 year, HIV infection duration (per year increment), PI vs. non-PI ART, pre-ART ARV experience vs. no experience | NR | Unclear |
| KAISER, Chao (2012) | Age‡, baseline CD4‡, HIV VL‡, race‡, sex‡, every additional year of PI-based or NNRTI-based ART (vs. no ARV) , year‡, years of HIV‡, exposure group‡, pre-ART ARV experience‡, smoking‡, overweight‡, alcohol/drug abuse‡, AIDS stage | Magnitude of effect reported per unit time | No |
| FHDH-ANRS, Lacombe (2013) | Age‡, current CD4, current HIV VL , subsaharan Africa origin‡, ART duration >6 months , exposure group‡, AIDS stage‡ | NR by ART type§ | No |
| DAD, Bruyand (2015) | Age‡, gender‡, cohort‡, exposure group‡, ethnicity‡, year‡, BMI‡, previous cancer or AIDS dx‡, smoking‡, HBV or HCV status‡, longer duration of overall ART, PI, or NNRTI | Magnitude of effect reported per unit time | No |
| COHERE29, COHERE (2016) | Age 16-30 vs. >50y, CD4 >500 vs. <500, HIV VL <4 vs. ≥5 log, exposure group, MSM vs. other men vs. women, first-line non-PI ART vs. boosted PI, first-line non-PI ART vs. nonboosted PI , year enrolled | Yes (see web appendix 4) | Within 30 days |

aIRR=adjusted incidence rate ratio. ART=combination antiretroviral therapy. ARV=antiretroviral drug. BMI=body mass index. dx=diagnoses. CASCADE=Concerted Action on Seroconversion to AIDS and Death in Europe. FHDH-ANRS=French Hospital Database on HIV-Agence Nationale, de Recherches sur le SIDA. IRIS=immune reconstitution inflammatory syndrome. KS=Kaposi sarcoma. KS⁺=PLWH who developed incident KS. MSM=men who have sex with men. NR=not reported. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=nucleoside reverse transcriptase inhibitor. PI=protease inhibitor. PLWH=people living with HIV. VL=viral load.

Bold indicates significantly lower KS incidence at p<0.05. *Interaction. †Excluded KS diagnoses within the specified time following ART initiation (IRIS or prevalent KS).

‡Significance and category definitions NR. §aIRR is significantly lower if ART duration > 6 months, compared to < 6 months, but not stratified by ART class.

Web Appendix 3: KS incidence in patients taking boosted and nonboosted PIs, according to ART duration

| | | Adjusted hazard ratio (95% confidence interval)* | | | | | |
|--|---------------------------------------|--|------------------|------------------|------------------|------------------|------------------|
| | | 30-90 d of therapy | 91-180 d | 6-12 mo | 1-2 y | 2-5 y | 5-8 y |
| COHERE29, COHERE (2016) | Boosted PI (Referent group) | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| | NNRTI | 0.58 (0.42-0.81) | 1.10 (0.72-1.69) | 1.05 (0.66-1.65) | 0.84 (0.50-1.41) | 0.90 (0.60-1.36) | 0.61 (0.32-1.14) |
| | Nonboosted PI | 0.53 (0.32-0.90) | 0.82 (0.46-1.46) | 1.65 (0.96-3.41) | 3.08 (1.56-6.09) | 5.34 (3.20-8.92) | 9.72 (5.34-17.7) |

ART=combination antiretroviral therapy. d=days. KS=Kaposi sarcoma. mo=months. NNRTI=non-nucleoside reverse transcriptase inhibitor. PI=protease inhibitor. y=years.

*First-line regimen only. P value for change over time from test of interaction=0.12 (boosted PI vs. NNRTI or boosted vs. nonboosted PI).