Switch to second-line ART in HIV-infected children:

a Collaborative Initiative for Paediatric HIV Education & Research (CIPHER) Global Cohort Collaboration analysis

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for the CIPHER Duration of First-Line Project Team

Background

- WHO guidelines (2015) recommend universal ART in all children and adolescents (<19 years), irrespective of clinical stage or CD4
- Estimates of need for second-line ART in perinatally infected children/adolescents is critical to informing clinical care and programme planning
- Clinical trials report proportion of switch at 5 years of ART ranging from: 2% in CHER[1], 6% in ARROW[2] to 21% in PENPACT-1[3].

CIPHER network

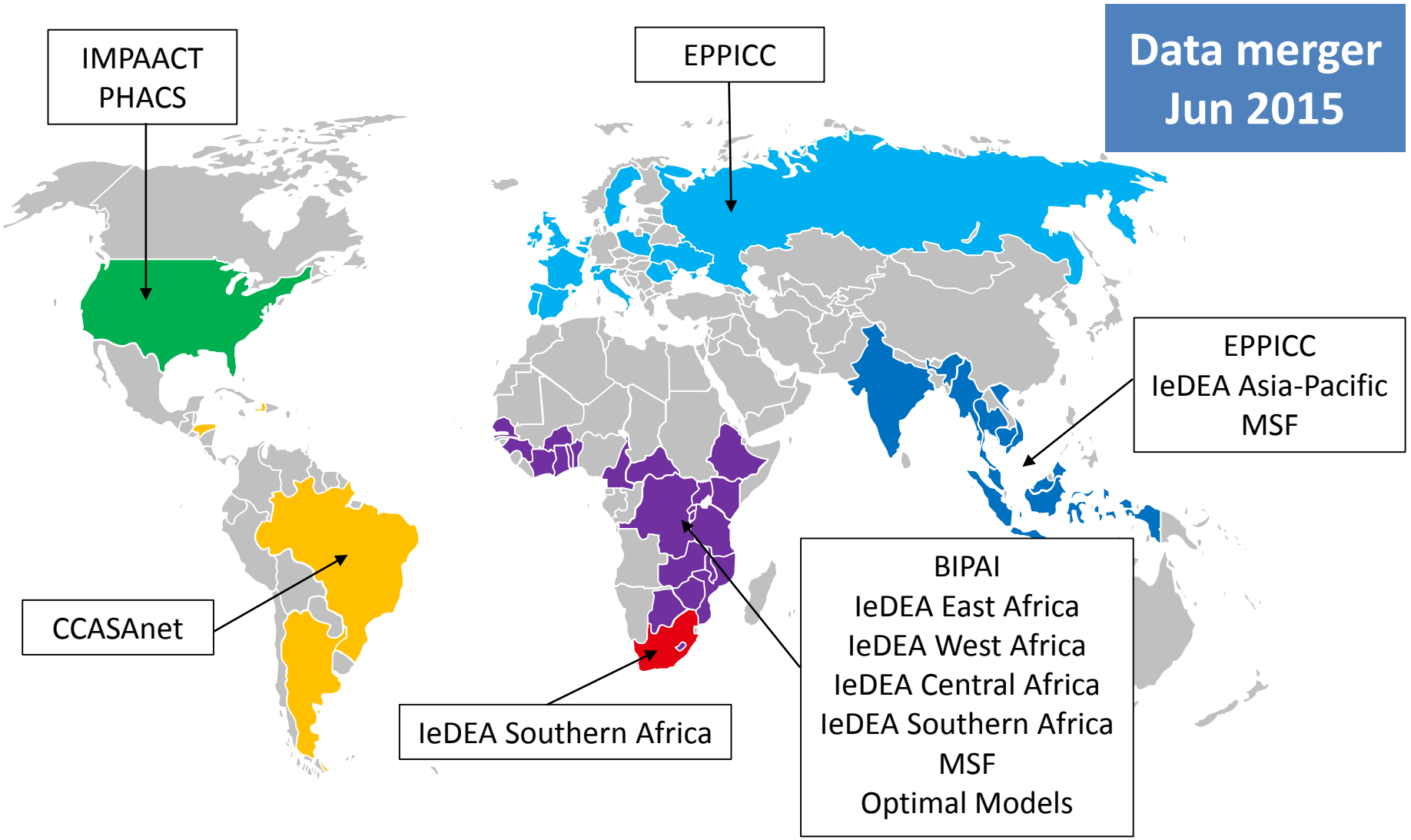
- Individual-level data pooled from 12 paediatric HIV cohort networks

Participating Cohort Networks

- **BIPAI**: Baylor International Pediatric AIDS Initiative
- **EPPICC**: European Pregnancy and Paediatric HIV Cohort Collaboration
- **IeDEA**: International Epidemiologic Databases to Evaluate AIDS (Asia-Pacific, CCASAnet, Central, East, West & Southern Africa)
- **IMPAACT P1074**: International Maternal Pediatric Adolescent AIDS Clinical Trials
- **MSF**: Médecins Sans Frontières
- **Optimal Models**: ICAP at Columbia University
- **PHACS**: Pediatric HIV/AIDS Cohort Study

Regions of CIPHER

CIPHER
Paediatric HIV Matters



Leading data centres: UCT (IeDEA Southern Africa), UCL (EPPICC), Harvard (PHACS)

Methods (1)

Inclusion criteria:

- <10 years at enrollment into cohort
- <18 years at ART initiation
- Initiated ART with ≥3 drugs (boosted PI or NNRTI-based)

Exclusion criteria:

- No follow-up after ART start
- Enrolled in trial of treatment monitoring, switch or interruption strategies

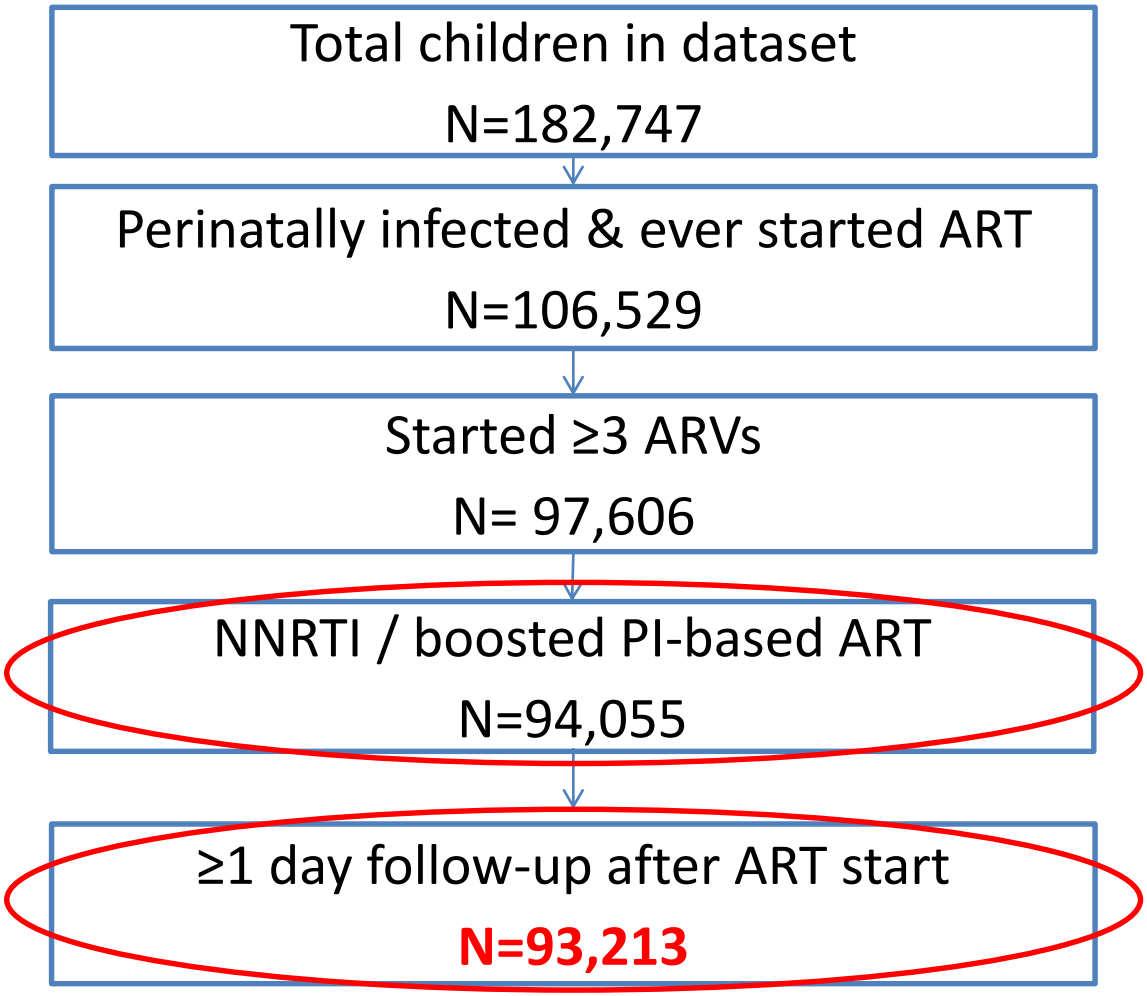
Methods (2)

Switch to second-line was defined as:

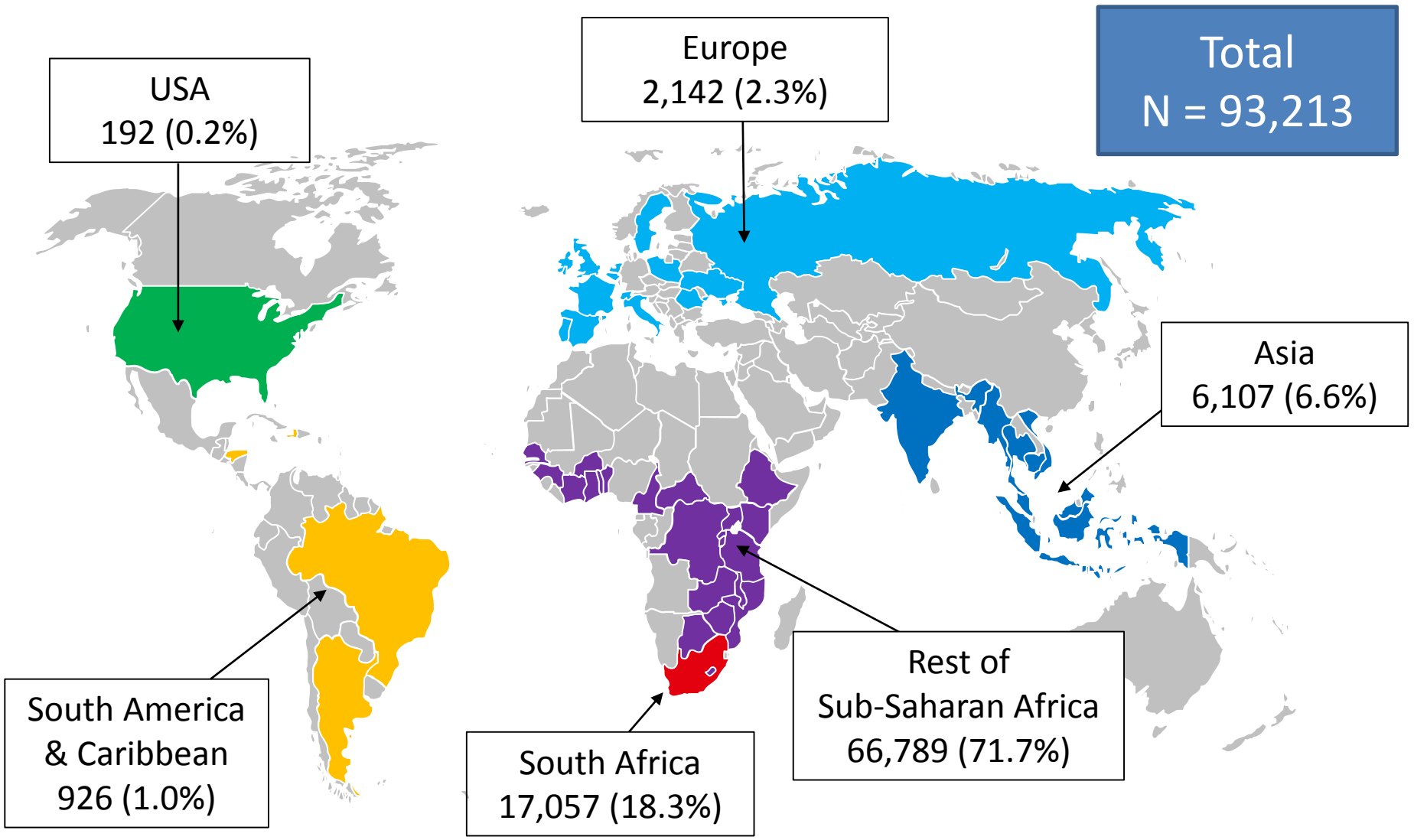
- A change in drug class and a change in ≥1 NRTI; or
- A change within PI drug class (ie. LPV/r to DRV) and a change in ≥1 NRTI; or
- Change from single PI to dual PI (ignoring ritonavir boosting); or
- Addition of new drug class

Time to switch: cumulative incidence accounting for the competing risks of death or loss to follow-up (LTFU)

Results


Total children in dataset
N=182,747
Perinatally infected & ever started ART
N=106,529
Started ≥3 ARVs
N= 97,606
NNRTI / boosted PI-based ART
N=94,055
≥1 day follow-up after ART start
N=93,213

Regions


USA
192 (0.2%)
Europe
2,142 (2.3%)
Total
N = 93,213
Asia
6,107 (6.6%)
South America
& Caribbean
926 (1.0%)
South Africa
17,057 (18.3%)
Rest of
Sub-Saharan Africa
66,789 (71.7%)

Demographics (1)

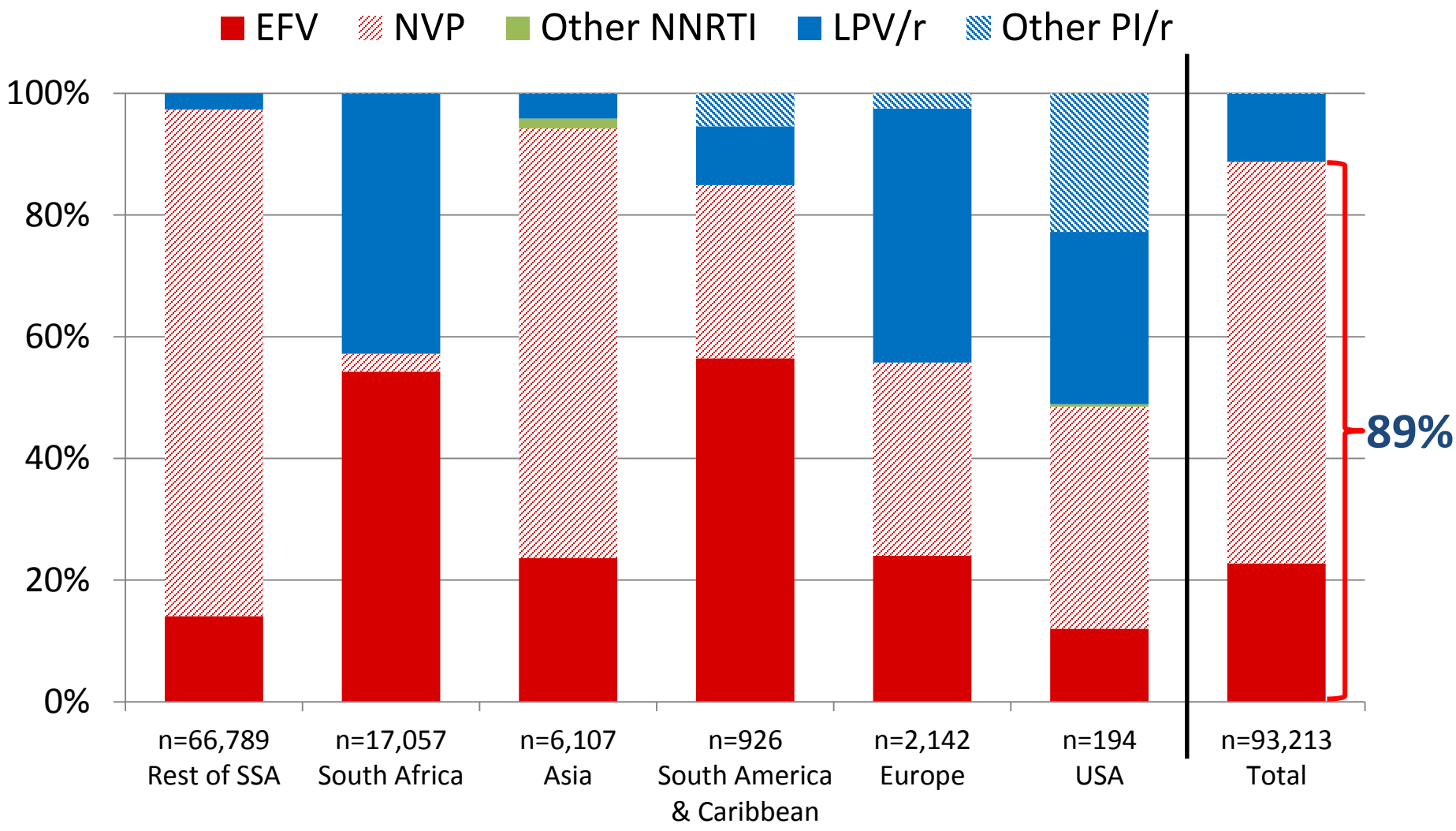
Characteristics at start of ART	Total (n=93,213)
Male sex	46,983 (50%)
Age group (years)	
<3	39,357 (42%)
3-5	23,749 (26%)
6-9	26,550 (28%)
≥10	3,557 (4%)
CD4 (n=50,011); Median (IQR)	
CD4 Percentage (<5 yrs)	16 (11-23)
CD4 cell count/mm^3 (≥5 yrs)	296 (148-506)
Reported AIDS event	40,217 (43%)
Weight-for-age z-score (n=88,130)	
<-2	30,340 (34%)
-2 to 0	27,756 (32%)
>0	30,034 (34%)

Demographics (2)

Characteristics	Total (n=93,213)
Calendar year at start of ART	
≤2004	4,694 (5%)
2005-2007	23,186 (25%)
2008-2010	36,573 (39%)
≥2011	28,760 (31%)
Cohort monitoring strategy*	
Routine viral load & CD4	25,984 (28%)
Targeted viral load, routine CD4	16,585 (18%)
No viral load, routine CD4	36,515 (39%)
Clinical monitoring only	14,129 (15%)
World Bank Income Group	
Low	40,234 (43%)
Low middle	30,290 (33%)
Upper middle	20,773 (22%)
High	1916 (2%)

*Monitoring strategy based on proportion with CD4/ VL measurements and frequency of measurements, within cohort.

Initial regimen by region

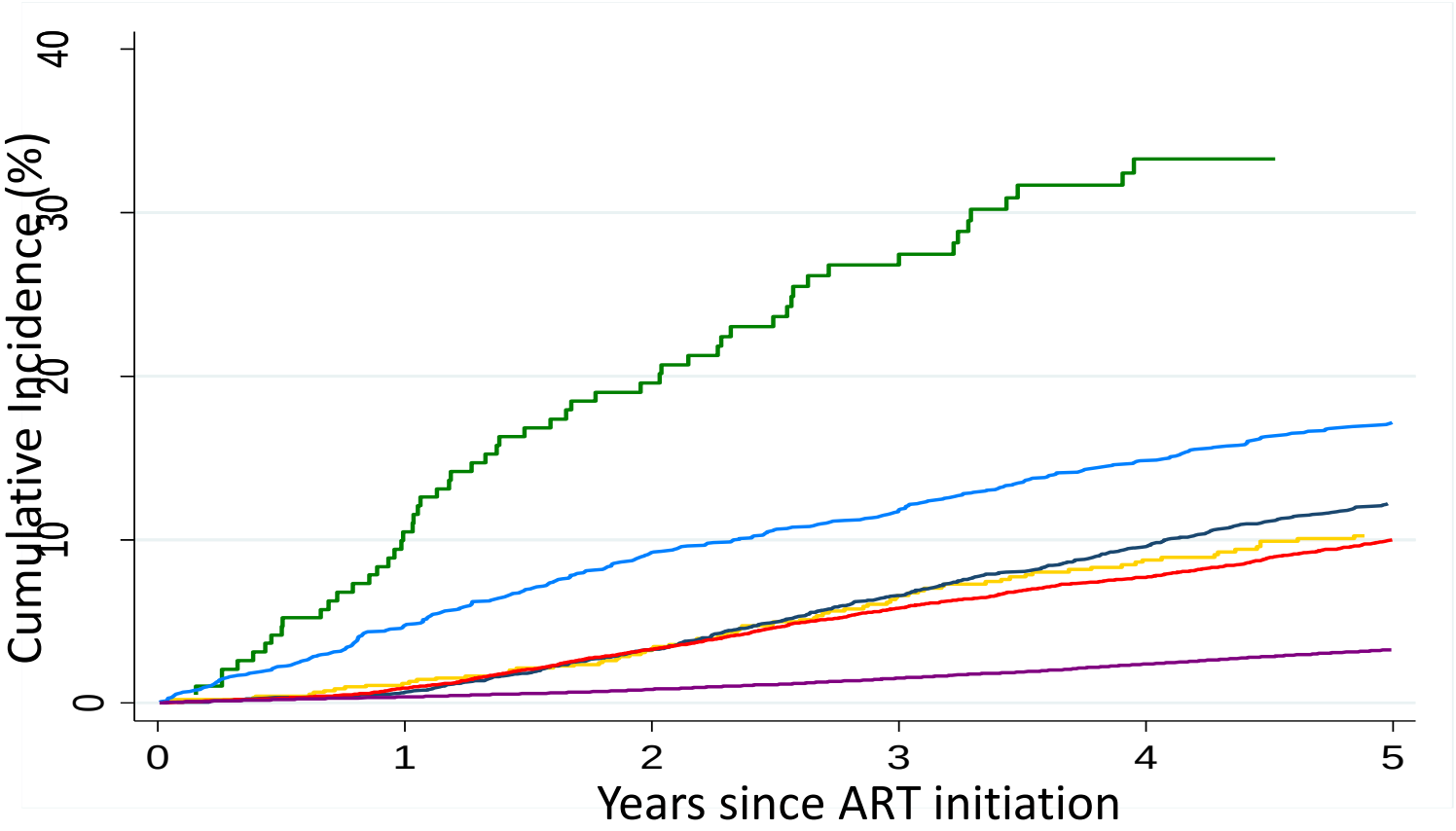


Follow-up

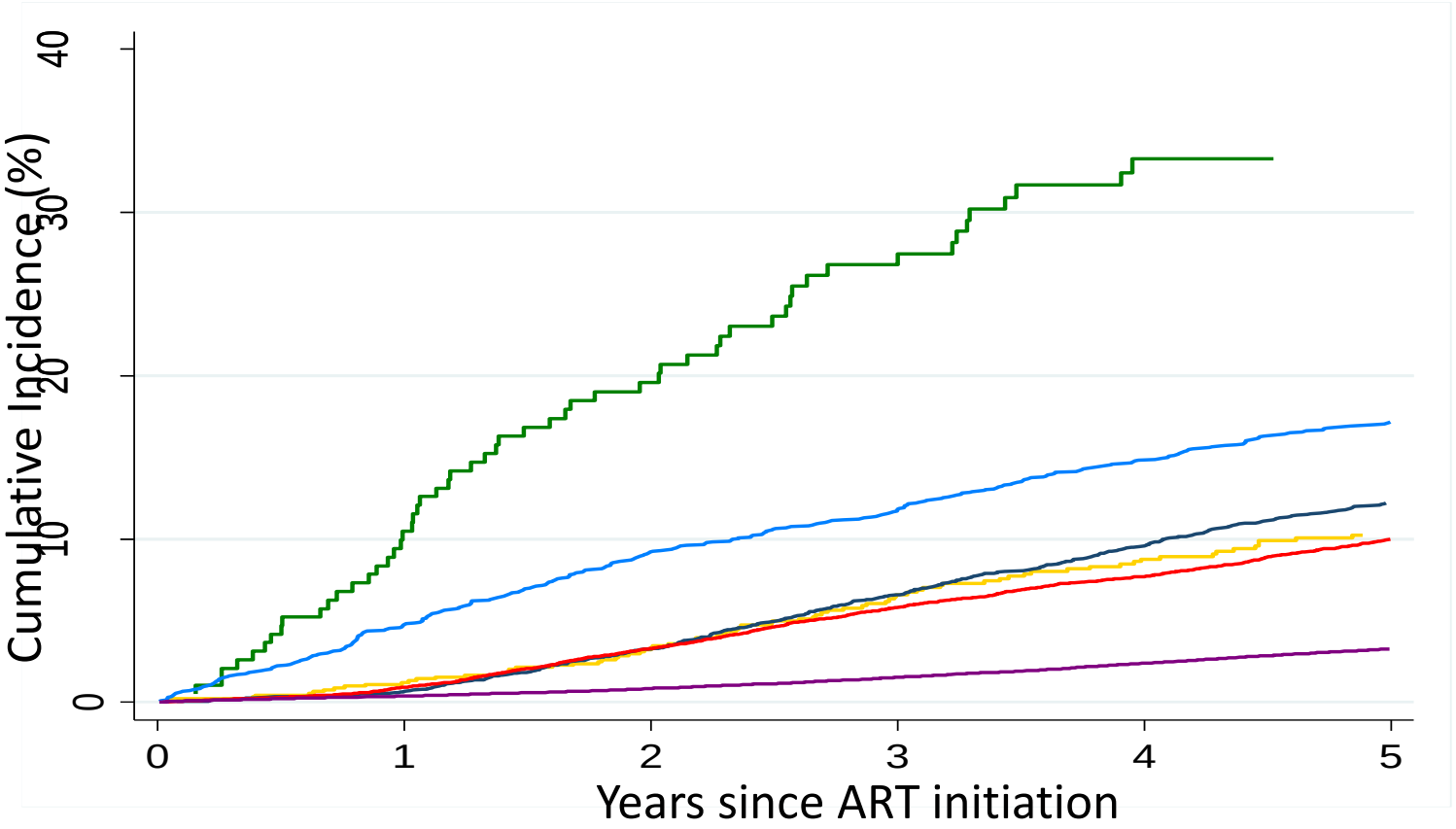
- Median follow-up from ART start: 27 mo (IQR 9, 54)
- 1% death, 25% LTFU, 20% transfer out
- LTFU range: 10% in USA to 27% in SSA

- 3,979 switches in 265,190 person-years
- Crude rate: 15.0 per 1,000 person-years
  - Median time to switch: 35 mo (IQR 19, 57)
  - 86% of switches were NNRTI → PI

Cumulative incidence of switch by region

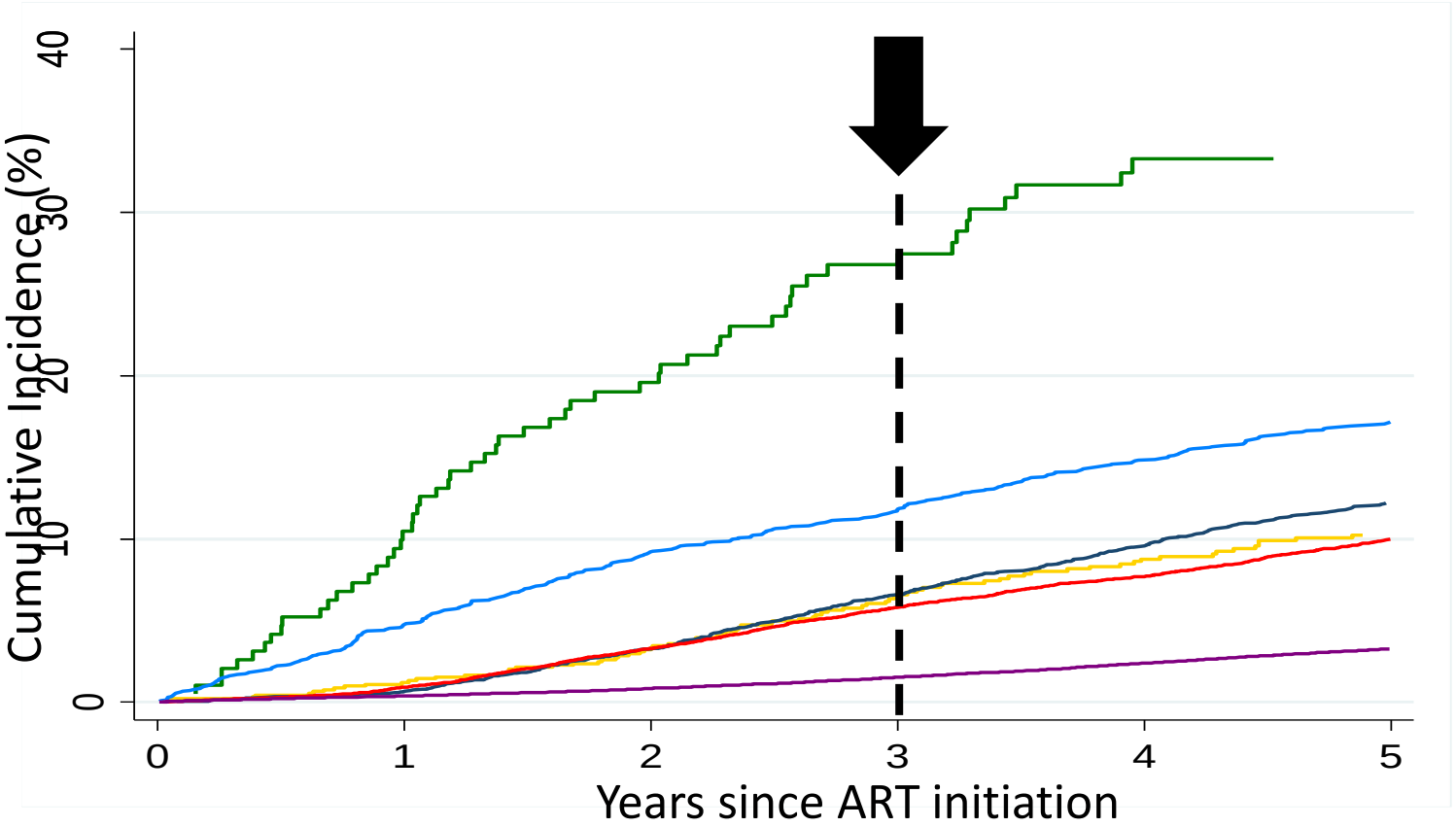


Cumulative incidence of switch by region



- Overall cumulative incidence of switch at 3 years after ART initiation: 3.1% (95% CI 3.0% to 3.2%).
- Range from 1.5% (1.4-1.6) in Rest of SSA to 26.1% (20.0-32.7) in USA

Cumulative incidence of switch by region



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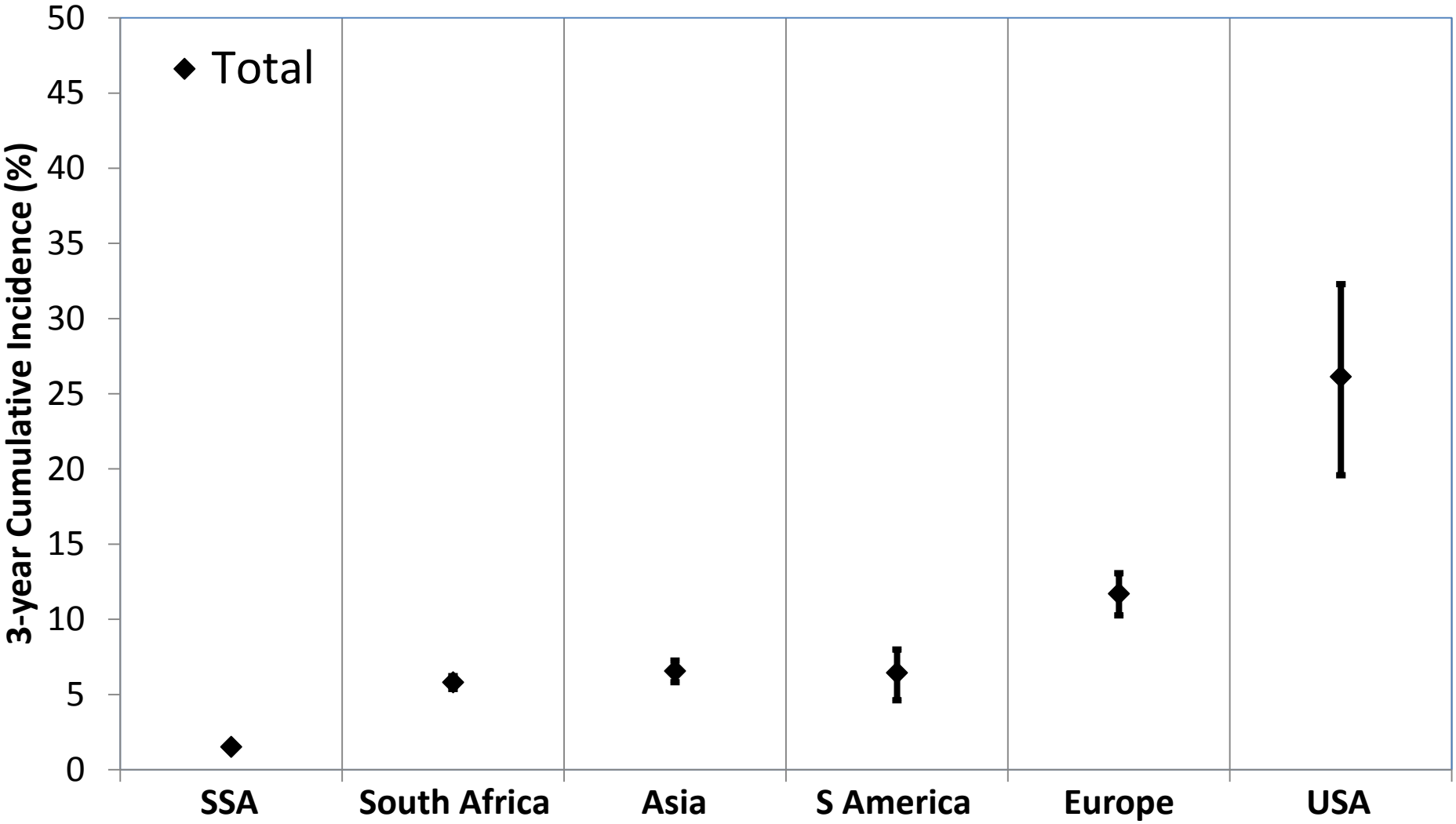
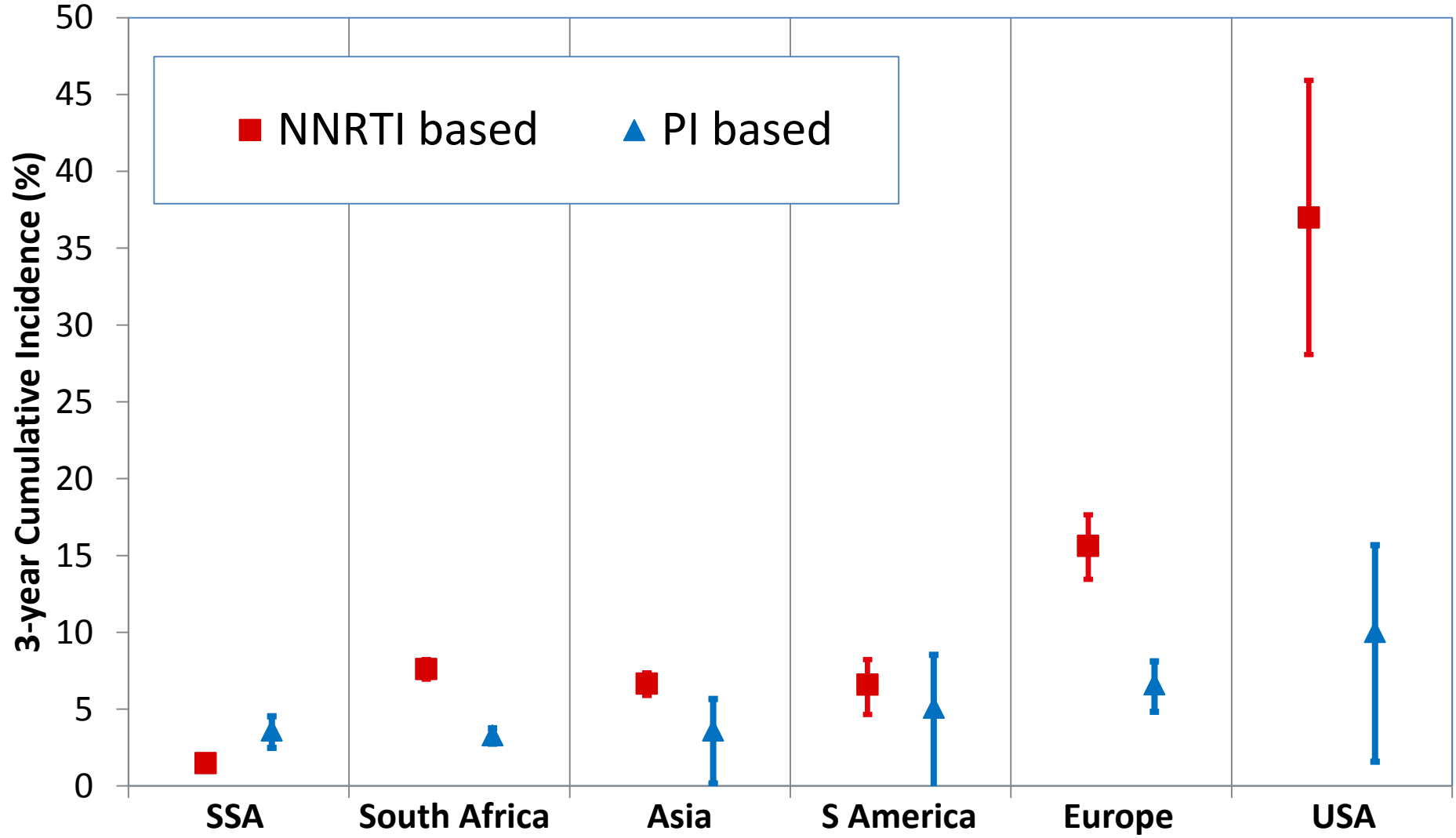
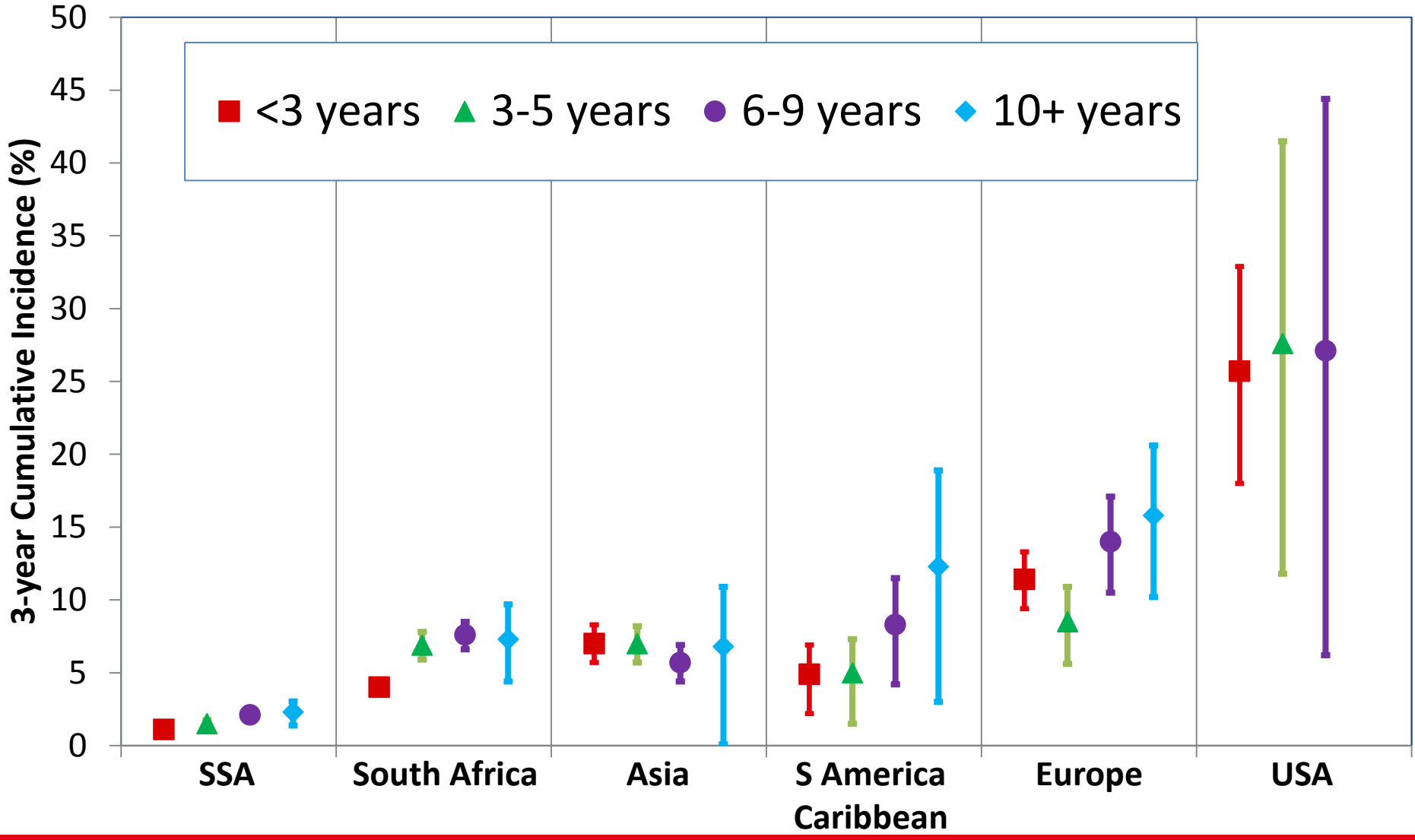
Cumulative incidence of switch at 3 years, by region



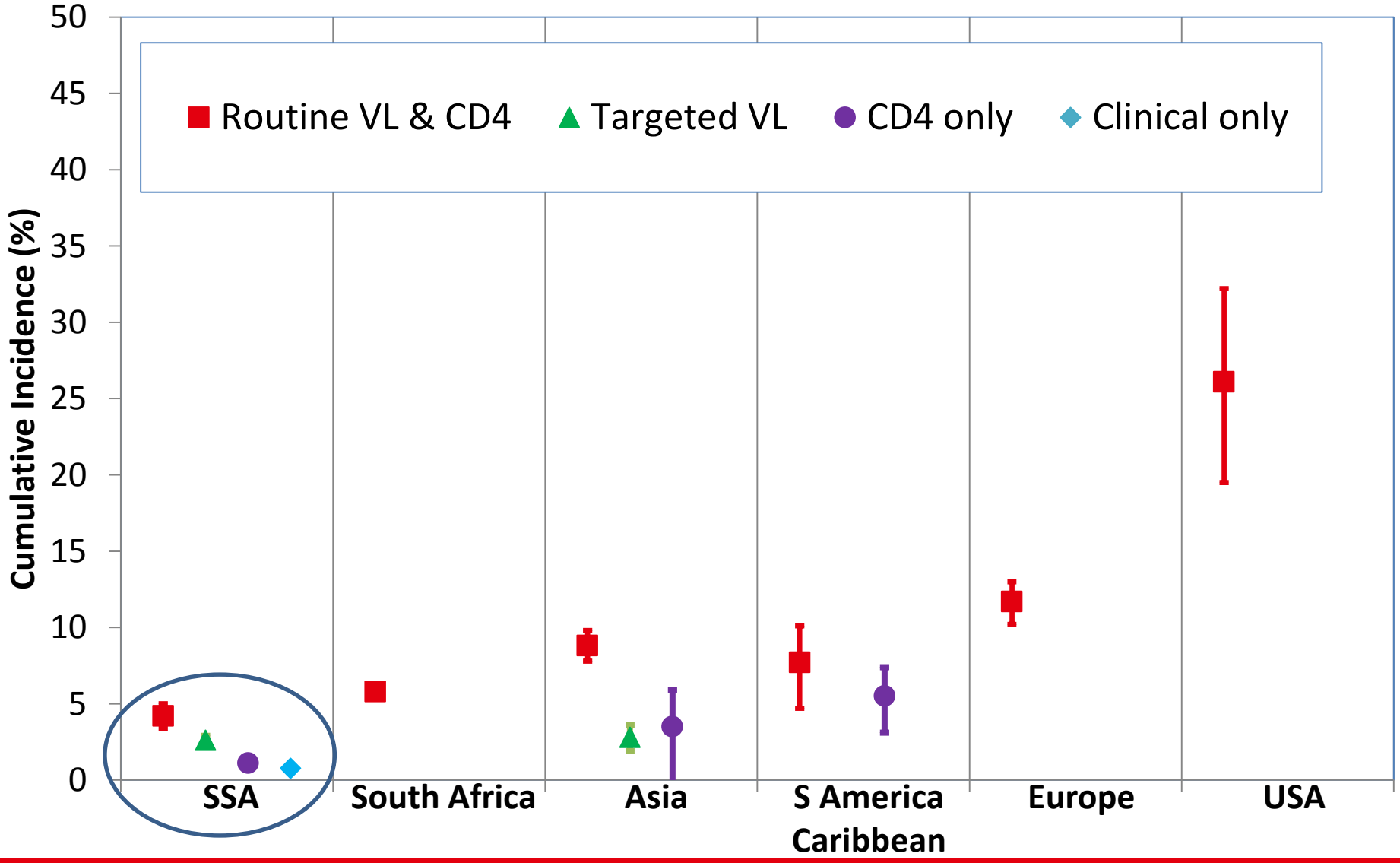
Cumulative incidence of switch at 3 years, by initial regimen



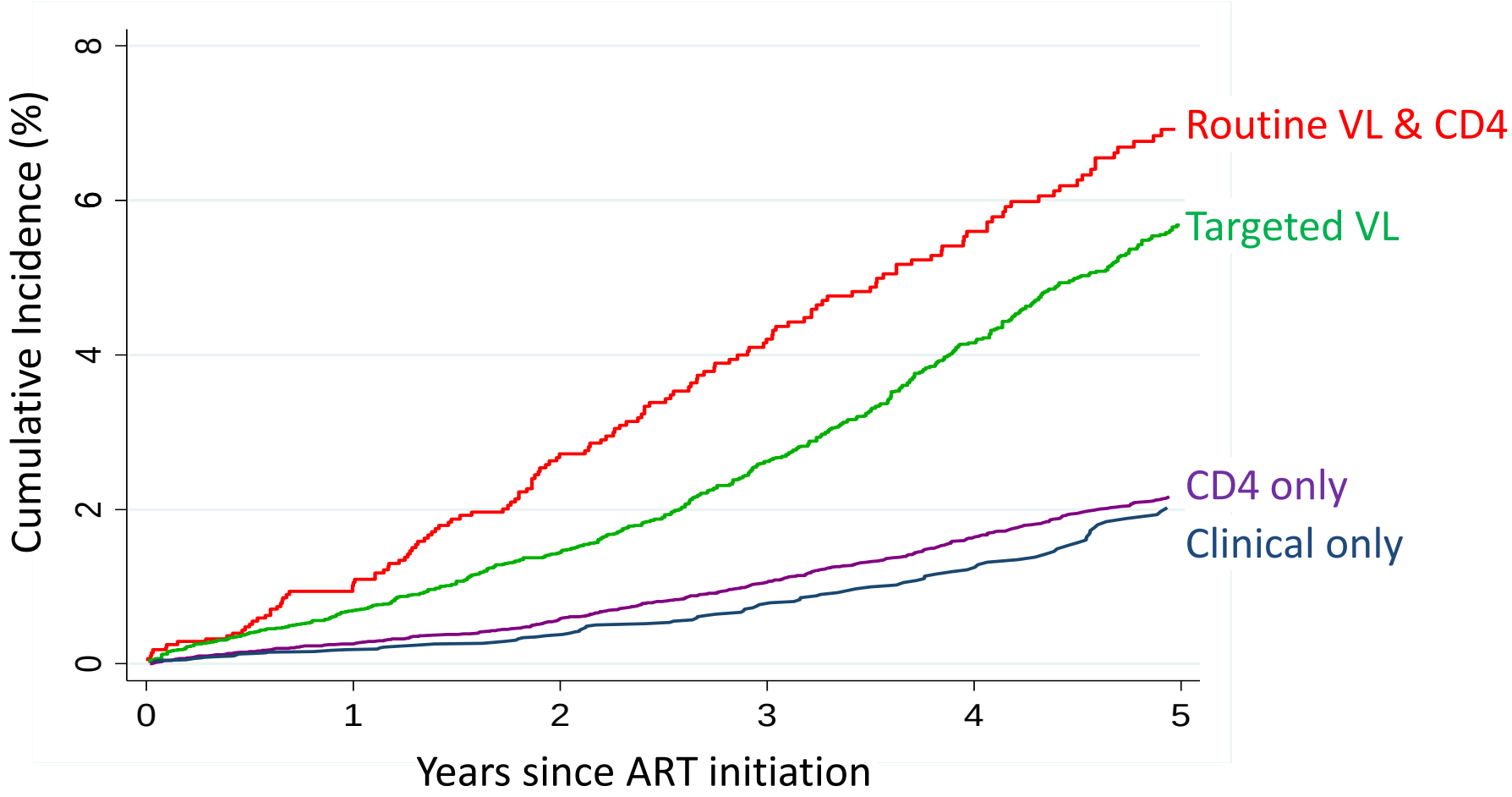
Cumulative incidence of switch at 3 years, by age at ART start



Cumulative incidence of switch at 3 years, by monitoring strategy



Cumulative incidence of switch by monitoring strategy in SSA



Discussion

- Overall, switch rates were low but with substantial regional variations
- Higher incidence of switch among children:
  - initiating NNRTI-based regimens except in SSA
  - older age at ART start
  - routine viral load and CD4 monitoring
- Limitations: lower bound of true need for switch
  - varying availability of second-line ART
  - high rates of LTFU and transferred out
- Further work includes multivariable modelling to adjust for confounding and outcomes on second-line

Acknowledgements

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