IeDEA Global Cohort Consortium

2020 Research Highlights

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2020 IeDEA Asia-Pacific Research Highlights
Association of body mass index with immune recovery, virological failure and cardiovascular disease risk among PLHIV

• Longitudinal cohort: evaluate associations between pre-ART BMI with CD4 recovery, viral failure, CVD markers
• 4,993 PLHIV age ≥18 between 2003-2015, with pre-ART weight & height available included
  ➢ 66% male; median age at ART 34 years
  ➢ Pre-ART CD4 125 cells/μL; follow-up time 8.8 years
• Pre-ART BMI: 26% underweight (<18.5 kg/m²), 62% normal (18.5–25 kg/m²); 10% overweight (25–30 kg/m²); 2% obese (>30 kg/m²)

Pre-ART BMI associated with immune recovery & development of CVD risk factors

- Overweight, obese baseline BMI associated with larger CD4 increases: 15.6, 28.8 cells/μL
- Overweight, obese BMI: 1.27 times, 1.61 times more likely to develop CVD risk factors
- No relationship between pre-ART BMI and viral failure observed

Incidence, clearance, persistence and factors related with high-risk anal HPV persistence in South-East Asian MSM and TGW

• Prospective cohort: assess incidence, clearance and persistence of anal high risk (HR)-HPV in MSM & TGW

• 325 MSM & TGW age ≥18 from Indonesia, Malaysia & Thailand enrolled between 2011-2015

• Baseline: 72% HIV-positive; 88% MSM; mean age 34.3 years; 60% prevalent anal HR-HPV

• Anal HR-HPV incidence higher in HIV-positive than HIV-negative MSM (28.4/1000 vs. 13.9/1000 person-months)

• Clearance rate in HIV-positive lower than HIV-negative participants (OR 0.3; 95% CI 0.1–0.7).

HIV-positive MSM and TGW had higher risk of persistent anal HR-HPV infection

- Persistence of anal HR-HPV: 40% in HIV-positive, 23% in HIV-negative participants
  - HPV-16 most common
- Associated with anal HR-HPV persistence:
  - HIV infection (aOR 2.87; 95% CI 1.47–5.61)
  - Living in Kuala Lumpur (aOR 4.99; 95% CI 2.22–11.19)
  - Being employed/freelance (aOR 3.99; 95% CI 1.48–10.77)
  - Not being circumcised (aOR 2.29; 95% CI 1.07–4.88)
- Highlights need to establish accessible prevention programs for HPV & associated diseases for MSM & TGW in Southeast Asia

The perfect ice storm: the mix of meth and HIV spreads hepatitis C in Thai MSM

- Longitudinal amphetamine-type stimulant (ATS) use study among MSM & TGW presenting for HIV testing in Bangkok
- 470 MSM (93.6%) and 32 TGW (6.4%) enrolled
  - 161 (32%) HIV-positive
  - Consistent condom use 38% for receptive anal sex
  - STI common: syphilis (16%), chlamydia (16%), gonorrhea (8%)
- ATS use reported by 131: meth (n=122), ecstasy (n=43), oral amphetamines (n=18)
- Over one-third (n=45) of meth users reported IV injection in previous 6 months

HCV infection spreading rapidly among MSM with HIV in Bangkok & closely associated with meth use

Anti-HCV prevalence by ATS use and HIV status

- Overall HCV prevalence 3.6%
- Associated with HCV:
  - HIV infection (OR 16.15; 95% CI 3.3-78.99)
  - Ever using meth (OR 9.13, 3.3-78.99)
  - Ever using oral amphetamine (OR 9.48, 1.63-55.03)
  - Being anal sex receptive partner (OR 4.3, 1.1-16.71)
  - History of STI in previous 6 months (OR 5.98, 1.54-23.2)

Determining Standardized Causes of Death of Infants, Children, and Adolescents Living With HIV in Asia

- Implement standardized cause of death reporting & review process to disaggregate causes of HIV-related deaths in Asian children/adolescent cohort
- Cause of death reported using standardized CoDe forms developed for D:A:D study
- 5523 children ever on cART & in routine HIV care between 2008-2017: 52% male; 312 (5.6%) deaths
  - Median age at death 7 (2.9–13) years; median CD4 73 (16–325) cells/μl

Continued importance of opportunistic and non-opportunistic infection causes of death

- Common causes of death: pneumonia (unspecified; 17%); TB (16%), sepsis (8%); AIDS (6.7%); unknown (12%)
- Higher CD4 count, better weight-for-age z-score protective against death

Impact of low-level viraemia (LLV) on virological failure among Asian children with perinatally acquired HIV on first-line combination ART

• Retrospective cohort study to determine impact of LLV on viral failure among Asian CLHIV on first-line cART

• CLHIV <18 years, on first-line cART for ≥12 months, & had viral suppression (2 consecutive VL<50 copies/mL)
  ➢ 508 CLHIV eligible between 2008–2016
  ➢ 55% female; baseline median age 9.6 years, cART duration 1.4 years, 97% on NNRTI, median CD4 25%
  ➢ 86 CLHIV (17%) experienced LLV over median follow-up 6 years from baseline

• Increased risk of LLV: Female; family member other than biological parent/grandparent as primary caregiver; baseline CD4 <25%

LLV increased risk of subsequent VF among Asian CLHIV previously suppressed on first-line cART

- 115 CLHIV (23%) developed viral failure: 4 per 100 PYFU (95%CI: 3.4-4.9)
- Ever experiencing LLV → increased risk of subsequent failure (aHR 3.01; 95%CI 1.97-4.60)
- Adherence interventions, additional targeted VL monitoring for children with LLV to facilitate earlier detection of failure

Kaplan–Meier estimates of cumulative probability for VF by LLV experienced

CCASAnet Publication Highlights: 2020
Dolutegravir (DTG) has been widely available in Brazil since 2017.

Objective: Following initial reports of its possible association of neural tube defects (NTDs) among infants, we launched a national retrospective cohort investigation of pregnancy outcomes of women on DTG at pregnancy conception.

Methods: Using data from the Brazilian computerized ART distribution program (SICLOM) and detailed medical chart validation and abstraction, we identified 382 women on DTG around conception (± 8 weeks) and 1045 women on EFV (controls). Women on RAL at time of conception were also included given unknown class-wide effects.

- **Primary outcomes:** NTDs, miscarriage, and stillbirths (composite outcome)
- **Statistical approach:** Matched propensity score weighted logistic regression given rare outcome
Results:

• Of the 1452 birth outcomes, there were no NTD events observed in women on DTG nor EFV in the analysis cohort (incidence among women on DTG: 0 [95% CI: 0-0.001]).
• Compared to women on EFV, a higher proportion of women on DTG experienced stillbirths or miscarriages (3 vs. 6%, \( p=0.004 \)).
• DTG exposure was associated with increased risk of composite outcome in regression models but results were no longer significant when prenatal covariates were added nor in sensitivity analyses (Figure 2).

Conclusion: DTG use was not associated with NTD risk among pregnant women with HIV in Brazil.

Impact:

• Following the initial reports from Botswana, this was the largest cohort of women with DTG exposure at pregnancy conception.
• These results informed 2019 updated WHO guidance on DTG use in women and adolescent girls.
Novel stepwise approach to assess representativeness of a large multicenter observational cohort of tuberculosis patients: The example of RePORT Brazil

Maria B. Arraga • Gustavo Amorim • Artur T.L. Queiroz • Moreno M.S. Rodrigues • Mariana Araújo-Pereira • Betania M.F. Nogueira • Alexandra Brito Souza • Michael S. Rocha • Aline Benjamin • Adriana S.R. Moreira • Jamie G. de Oliveira • Marina C. Figueiredo • Megan M. Turner • Kleydson Alves • Betina Durvoni • José R. Lapa-e-Silva • Afrânio L. Kritski • Solange Cavalcante • Valeria C. Rolla • Marcelo Cordeiro-Santos • Timothy R. Sterling 1 • Bruno B. Andrade 1 for the RePORT Brazil consortium • Show less

• Comparison of Regional Prospective Observational Research for Tuberculosis (RePORT)-Brazil with SINAN, the Brazilian national tuberculosis registry
• June 2015 – June 2019
• RePORT-Brazil: 1,060 culture-confirmed TB cases enrolled
  – Study sites in Manaus, Salvador, Rio de Janeiro
• SINAN: 455,873 TB cases reported

PMID: 33197582, PMCID: pending
Method: comparison of cohorts via second-generation p-value

Results:

• Cohorts were similar regarding age, sex, use of antiretroviral therapy, smear-positive TB.

• Diabetes, HIV infection, smoking were more frequently documented in RePORT-Brazil.

• Illicit drug use, diabetes, history of prior TB were associated with unfavorable TB outcomes.

Conclusion: There are key similarities in demographic characteristics and determinants of clinical outcomes between the two cohorts.
Background: KS remains the most frequent cancer diagnosed in PWH in Latin America but trends in KS incidence in settings of increased ART availability in the region are unknown.

Methods: Longitudinal analyses of PWH aged ≥16yo from cohorts from Honduras, Brazil, Peru, Mexico, Argentina, Chile from 2000-2017 to examine:

- KS incidence trends over time (and KS relative [before or after] to ART initiation)
- Patient factors associated with risk of KS
- Factors associated with mortality after KS (in particular, timing relative to ART)
Results

• Of 25,981 PWH included, 481 had incident KS (200 before ART, 281 after ART).
• Overall incidence decreased from 55.1 to 3.0 per 1000py from 2000 to 2017.
• After adjusting for CD4 cell count and other confounders, relative risk of KS decreased during the study period. Since 2010, relative risk of KS increased before ART and was stable within 90d of ART but decreased for those >90d since ART start (Figure 1).
• Low CD4 cell count and MSM HIV transmission risk factor were strongly associated with KS risk before or after ART.
• Timing of KS relative to ART initiation was not associated with risk of mortality (Figure 2).

Conclusions

• Relative risk for KS before or shortly after ART initiation has remained stable in Latin America after accounting for confounders.
• With overall mortality of 25% in 5 years, KS remains associated with high risk of death and timing of KS relative to ART initiation is not associated with mortality.
Estimated life expectancy gains among adults with HIV with antiretroviral therapy in Latin America and the Caribbean: a multisite retrospective cohort study

Casey L. Smiley, M.D., Peter F. Rebeiro, Ph.D., Carina Cesar, M.D., Pablo F. Belaunzaran-Zamudio, M.D., Brenda Crabtree Ramirez, M.D., Denis Padgett, M.D., Professor Eduardo Gotuzzo, M.D., Claudia P. Cortes, M.D., Professor Jean Pape, M.D., Professor Valdiléa G. Veloso, Ph.D., Catherine C. McGowan, M.D., Jessica L. Castilho, M.D. on behalf of the Caribbean, Central and South America network for HIV epidemiology (CCASAnet)

Objective: To estimate trends in life expectancy at age 20yo among PWH ever started on ART at CCASAnet sites (2003-2017)

Methods:

• Chiang method was used to create abridged life tables to estimate life expectancy at age 20yo across three calendar eras.

• Mortality rate estimates weighted for likelihood of loss to follow-up were used to account for informative censoring.

• Trends were examined according to key characteristics including sex, HIV transmission risk group, education, and TB at ART start.

• All analyses were stratified by Haiti and all other sites to account for differences in ART roll out.

Overall life expectancy improved over time, approaching general populations

PMID/PMCID: pending

Accepted Dec 17, 2020

in press
More Results: Disparities in life expectancies persisted among sex and HIV transmission risk groups (above) as well as CD4 at ART start (A), history of TB (B), and education (C).

Conclusions:

• Life expectancy among PWH on ART has significantly improved in Latin America.
• Persistent disparities in life expectancy by demographic and clinical factors at ART initiation highlight vulnerable populations in the region.

PMID/PMCID: pending
Background:

- There are concerns about data quality with the use of routinely collected observational data such as that used in IeDEA studies.
- Data quality can be assessed via chart reviews/data audits of subsamples of the data.
- Data audit information can be used in analyses to improve estimation.
This paper describes an efficient and robust approach to combine original and audit data in linear regression models with error-prone, continuous exposure and outcome variables.

The new method (SMLE) outperforms analyses that only use the original error-prone data (naïve), analyses that only use the audited data (LSE), and a previously proposed method (MBE).

The method was illustrated using CCASAnet data estimating the association between CD4 count at ART initiation and calendar year (Table 5 below; the estimates correspond to expected change in square-root transformed CD4).

This is one example in a line of research we have been involved in to improve estimation and study designs in the presence of error-prone data.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>LSE</th>
<th>Naive</th>
<th>MBE</th>
<th>SMLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART initiation date (per year)</td>
<td>$-0.248$ ( $-0.688$, $0.191$)</td>
<td>$0.117$ ( $-0.009$, $0.243$)</td>
<td>$0.187$ ( $0.006$, $0.368$)</td>
<td>$0.174$ ( $0.042$, $0.305$)</td>
</tr>
<tr>
<td>Male</td>
<td>$0.177$ ( $-1.513$, $1.867$)</td>
<td>$-0.736$ ( $-1.182$, $-0.290$)</td>
<td>$-0.740$ ( $-1.192$, $-0.288$)</td>
<td>$-0.725$ ( $-1.17$, $-0.280$)</td>
</tr>
</tbody>
</table>
Central Africa – IeDEA

Research Highlights 2020
Gone but not lost: implications for estimating HIV care outcomes when loss to clinic is not loss to care


**AIMS:** To account for ambiguity between censoring and competing events when estimating the time to key milestones along the HIV care continuum.

**METHODS:**

- When estimating milestones along the HIV care continuum, loss to follow-up is sometimes treated as a censoring event and sometimes as a competing event. However, the choice of how to handle loss to follow-up impacts estimated time to milestones along the care continuum.

- We illustrate an approach to address this ambiguity when estimating the 2-year risk of antiretroviral treatment initiation among 19,506 people living with HIV who enrolled in the Central Africa IeDEA cohort between 2006 and 2017, along with published estimates from tracing studies in Africa.

- We also assessed the finite sample properties of the proposed approach using simulation experiments.
Gone but not lost: implications for estimating HIV care outcomes when loss to clinic is not loss to care


**RESULTS:**

The proposed approach relaxes the assumptions inherent in treating loss to follow-up as a censoring or competing event in clinical HIV cohort studies.

- The estimated 2-year risk of ART initiation was 69% if patients were censored at loss to follow-up or 59% if losses to follow-up were treated as competing events. Using the proposed approach, we estimated that the 2-year risk of ART initiation was 61.6% (95% confidence interval: 61.0, 62.3).

- The proposed approach had little bias and appropriate confidence interval coverage under scenarios examined in the simulation experiments.

![Risk of ART initiation over 2 years since entry into care](Image)
AIMS: To assess the availability and changes in availability of substance use-related education, screening, and referral to treatment at HIV treatment centers participating in the IeDEA consortium from 2014 to 2017.

METHODS:

• We assessed substance use-related education, screening, and referral practices from two surveys of HIV care and treatment sites participating in the IeDEA consortium and compared changes over time for 147 sites that participated in both surveys.

• 286 sites in 45 countries participated in the 2014-2015 site survey; 237 sites in 44 countries participated in the 2017 site survey.
Substance use service availability in HIV treatment programs: Data from the global IeDEA consortium, 2014-2015 and 2017


RESULTS:

• In 2014–2015, on-site substance use-related education, screening, and referral for treatment were reported by 75%, 52%, and 51% of sites, respectively.

• In 2017, the proportion of sites providing on-site substance use-related education, screening, or referrals increased by 9%, 16%, and 8%, respectively.

• In 2017, on-site screening and referral were most commonly reported at sites serving only adults compared to sites serving only children or children and adults and at sites in high-income countries compared to sites in middle or low-income countries.

Changes in availability of on-site substance use-related education, screening, and referral at HIV treatment programs participating in the 2014-2015 and 2017 IeDEA site surveys (n=147)
High levels of viral load monitoring and viral suppression under Treat All in Rwanda – a cross-sectional study


AIMS: To describe the prevalence and predictors of viral load testing and viral suppression after implementation of Treat All in Rwanda.

METHODS: Cross-sectional study of PLWH ≥15 years of age established in care at 10 IeDEA-affiliated health centers in Rwanda.

• Calculated proportions of patients on ART, retained on ART (among those on ART), who had available viral load test results (among those retained on ART), and who were virally suppressed (among those with available viral load results).

• Examined factors associated with viral suppression (<200 copies/mL), using modified Poisson regression models with robust variances to calculate crude and adjusted prevalence ratios (aPRs), with generalized estimating equations to account for clustering within health centers.
RESULTS:
Among 12,238 patients, 97% were on ART, 91% were retained on ART, 83% had a viral load test available, and 76% were virally suppressed.

- Viral suppression less likely among younger PLWH (age 15-24) and baseline CD4 count <500 cells/mm³.
- Findings suggest that medication adherence may be a driver of lower viral suppression among younger PLWH, as minimal differences were observed in receipt of ART or retention on ART when examined by age.

![Graph showing predictors of suppression](image.png)

<table>
<thead>
<tr>
<th>Predictors of suppression</th>
<th>RR (95% CI)</th>
<th>aRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female vs Male</td>
<td>1.01 (1.00-1.03)</td>
<td>1.01 (0.99-1.02)</td>
</tr>
<tr>
<td>25-49 vs &gt;49 years</td>
<td>0.96 (0.94-0.98)</td>
<td>0.96 (0.95-0.98)</td>
</tr>
<tr>
<td>15-24 vs &gt;49 years</td>
<td>0.84 (0.79-0.89)</td>
<td>0.83 (0.76-0.90)</td>
</tr>
<tr>
<td>WHO Stage III/IV vs I/II</td>
<td>0.98 (0.97-1.00)</td>
<td>0.99 (0.97-1.00)</td>
</tr>
<tr>
<td>CD4 350-500 vs &gt;500</td>
<td>0.98 (0.96-0.99)</td>
<td>0.97 (0.95-0.99)</td>
</tr>
<tr>
<td>CD4 200-349 vs &gt;500</td>
<td>0.98 (0.97-0.99)</td>
<td>0.97 (0.96-0.98)</td>
</tr>
<tr>
<td>CD4 &lt;200 vs &gt;500</td>
<td>0.92 (0.91-0.93)</td>
<td>0.92 (0.90-0.93)</td>
</tr>
</tbody>
</table>

High levels of viral load monitoring and viral suppression under Treat All in Rwanda – a cross-sectional study

Demographic and clinical characteristics of adults entering care in Central Africa IeDEA 2004-2018


AIMS: To describe the demographic, clinical and immunological characteristics, and antiretroviral therapy (ART) use among adult patients aged >15 years at enrollment in HIV care at clinics that participate in CA-IeDEA.

METHODS:

• Information on socio-demographic characteristics, height, weight, body mass index (BMI), CD4 cell count, WHO staging and ART status at entry into care were extracted from clinic records for adult patients, aged >15 years, who enrolled in HIV care at CA-IeDEA sites in Burundi, Cameroon, DRC, ROC and Rwanda between 2004 and 2018.

• We assessed trends in patient characteristics at enrollment in HIV care including ART initiation within 30 days after enrollment in care and calculated proportions, means and medians (interquartile ranges) for the main variables of interest.
Demographic and clinical characteristics of adults entering care in Central Africa IeDEA 2004-2018


RESULTS:

• 69,176 adult patients enrolled in HIV care at CA-IeDEA sites between 2004 and 2018. Patients from Rwanda comprise 39% of the cohort, followed by ROC (24%), Cameroon (18%), Burundi (14%) and DRC (5%).

• The majority of patients (66%) enrolling in care and initiating ART were women. Women were younger than men at enrollment (33 vs. 38 years).

• Trends over time show increases in median CD4 cell count at enrollment from 190 cells/µL in 2004 to 334 cells/µl in 2018 at enrollment. Among those with complete data on CD4 counts (60%), women had higher median CD4 cell count at care entry than men (299 vs. 249 cells/µl).

• The proportion of patients using ART within 30 days of enrollment increased from 16% in 2004 to 75% in 2018.

• While increased weight and BMI at enrollment indicate improving immunological status over time, many patients lack CD4 and WHO staging data, and missingness varies across CA-IeDEA countries.
Determinants of Retention in HIV Antiretroviral Treatment Programs under Treat All in Cameroon


AIMS: To identify determinants of ART retention at 24 months at HIV clinics in Cameroon.

METHODS:

• A medical chart review was done at 24 months after ART initiation for 423 patients who initiated ART between July and September 2016 at Limbe, Bamenda and Jamot Hospitals in Cameroon.

• Sociodemographic, clinical characteristics and ART retention data were abstracted using structured paper forms.

• Chi square tests were used to assess bivariate associations, and logistic regression was used to estimate care retention, controlling for potential confounders.
RESULTS:

• The mean age of patients was 39 years (+/-11 years), and 65.1% were females.

• ART retention at 24 months was 78.8%, with 7.1% of patients being documented transfers to another site of care, 2.6% deceased, and 17.3% lost to follow-up. Retention at 24 months ranged from 74.0% to 89.9%.

• Advanced HIV disease (CD4 cell count <200 cells/µL), self-reported substance use (e.g., alcohol use or smoking) were not significantly associated with ART retention.

• Being a widow(er) was associated with being retained in ART (AOR 5.98, 95% CI: 1.25 - 28.54).

• Disclosure of HIV status (AOR 0.18 95% CI: 0.06 - 0.53) and unemployment (AOR 0.48, 95% CI: 0.14 - 0.17) were associated with lower ART retention.
A Qualitative Examination of Perceived Stigma and Its Impact on Health Status and Care Preferences Among Kenyan Adolescents Living with HIV (ALHIV)

Background

• Perceived stigma = fear of stigmatization and discrimination

• Sources and impact of perceived stigma in ALWH are not well-defined

• Goal: identify sources of perceived stigma and its impact on health status and individual care preferences

Methods

• Semi-structured interviews were conducted with 46 ALWH, ages 14-21

• Interviews were transcribed, translated, coded based on common themes

• Thematic analysis was performed by GC and FS using Dedoose® software

Callen G et al, International Workshop on HIV 2020
A Qualitative Examination of Perceived Stigma

Sources of Perceived Stigma
- Primary source: stories of stigmatization & directly observed discrimination
- Perpetrators: Friends & schoolmates
- Specific fears: social isolation, subject of gossip & vengeful disclosure

Impact on Mental Health and Medication Adherence
- Feelings of isolation, depression, and suicidality
- Most participants had been non-adherent to prevent disclosure

Impact on Care Preferences
- Prioritize secrecy in choosing their providers and clinic settings
- Decreased clinic attendance
- Barrier to participation in peer support groups
A comparison of the outcomes of women retained versus lost during the prevention of mother to child HIV transmission (PMTCT) cascade: the IeDEA-Kenya PMTCT cohort

**Setting:** 5 AMPATH PMTCT clinics

**Eligibility criteria:**

- **Retained women:**
  - Age $\geq 18$ years, PLHIV
  - Pregnant in 3rd trimester, Enrolled in ANC
  - Visits $\leq 90$ days apart
  - No documented death or transfer

- **LTFU women** - as about except:
  - $> 90$ days since last attended visit
  - Pregnant or $\leq 6$ months postpartum

**Analysis:**

- **Primary endpoints:**
  - Viral suppression $< 1000$ c/mL
  - Mother to Child Transmission = positive HIV DNA PCR

- Descriptive analyses were used to compare groups

Humphrey J et al, International Workshop on HIV 2020
A comparison of the outcomes of women retained versus lost during the PMTCT cascade

Characteristics by retention status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Retained (n=239) n(%)</th>
<th>LTFU (n=99) n(%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moi Teaching &amp; Referral Hospital</td>
<td>76 (32)</td>
<td>27 (27)</td>
<td>0.49a</td>
</tr>
<tr>
<td>Kitale District Hospital</td>
<td>51 (21)</td>
<td>18 (18)</td>
<td></td>
</tr>
<tr>
<td>Busia District Hospital</td>
<td>46 (19)</td>
<td>18 (18)</td>
<td></td>
</tr>
<tr>
<td>Usain Gishu District Hospital</td>
<td>37 (15)</td>
<td>17 (17)</td>
<td></td>
</tr>
<tr>
<td>Huruma District Hospital</td>
<td>29 (12)</td>
<td>19 (19)</td>
<td></td>
</tr>
<tr>
<td>Age at enrollment in antenatal clinic, median years, (IQR)</td>
<td>32 (26 – 35)</td>
<td>26 (22 – 33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Has mobile phone</td>
<td>215 (90)</td>
<td>75 (76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Changed residence location within past 2 years</td>
<td>57 (24)</td>
<td>36 (36)</td>
<td>0.02</td>
</tr>
<tr>
<td>First pregnancy</td>
<td>34 (14)</td>
<td>26 (26)</td>
<td>0.01</td>
</tr>
<tr>
<td>Newly diagnosed with HIV</td>
<td>61 (26)</td>
<td>50 (51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disclosure to anyone</td>
<td>215 (90)</td>
<td>82 (83)</td>
<td>0.07</td>
</tr>
<tr>
<td>Disclosure to partner</td>
<td>184 (77)</td>
<td>64 (65)</td>
<td>0.02</td>
</tr>
<tr>
<td>Woman knows partners HIV status</td>
<td>168 (70)</td>
<td>41 (41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current pregnancy was planned</td>
<td>115 (48)</td>
<td>44 (44)</td>
<td>0.54</td>
</tr>
<tr>
<td>Plan to deliver at facility</td>
<td>237 (99)</td>
<td>91 (92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHO stage 1 or 2 at enrollment in care</td>
<td>214 (93)</td>
<td>80 (90)</td>
<td>0.35</td>
</tr>
<tr>
<td>Time on ART, median yrs (IQR)</td>
<td>2.1 (0.4 – 5.9)</td>
<td>0.5 (0.2 – 2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NNRTI-based ART at study enrollment</td>
<td>219 (92)</td>
<td>91 (92)</td>
<td>0.93</td>
</tr>
<tr>
<td>VS &lt;1000 copies/mL at study enrollment</td>
<td>220 (92)</td>
<td>54 (55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delivered at a facility</td>
<td>218 (93)</td>
<td>76 (82)</td>
<td>0.002</td>
</tr>
<tr>
<td>Stillbirth or miscarriage</td>
<td>3 (1)</td>
<td>10 (10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Characteristics of infant by retention status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Retained infants (n=228) n(%)</th>
<th>LTFU infants (n=85) n(%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>133 (58)</td>
<td>43 (51)</td>
<td>0.22</td>
</tr>
<tr>
<td>Birth weight, median kg (IQR)</td>
<td>3.2 (2.8 – 3.6)</td>
<td>3.2 (2.7 – 3.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Exclusive breastfeeding at first HIV DNA PCR</td>
<td>222 (98)</td>
<td>70 (92)</td>
<td>0.02</td>
</tr>
<tr>
<td>Positive infant HIV DNA PCR</td>
<td>2 (1)</td>
<td>4 (6)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Reasons for Disengagement
Lower rates of ART initiation and decreased retention among ART-naïve patients who consume alcohol enrolling in HIV care and treatment programs in Kenya and Uganda

**Setting:** 5 clinics (4 Kenya, 1 Uganda)

**Recruitment:** 1/25/13 to 6/25/14

**Population:**
- ≥18 years of age
- newly enrolling in HIV-care
- ART-naïve

**Data:**
- Alcohol Use Disorder Identification Test (AUDIT)
- Routine care data (e.g. age, gender, CD4 count and WHO stage)

**Follow-up:**
- Missed visit > 60 days = tracing

**Outcomes:** ART initiation, Mortality, & Retention

**Alcohol Use**
- Non-alcohol (AUDIT = 0)
- Hazardous (AUDIT ≥ 8)
- High (AUDIT ≥16)

**Analysis:** Mann-Whitney test, The Pearson chi-square test, survival analysis (Fine and Gray)

Patsis I et al, PlosOne 2020
Lower rates of ART initiation and decreased retention

**Results:** Fine & Gray competing events survival models, adjusting for age, gender, CD4 count and WHO stage at enrollment, disclosure of HIV status, marital status and site of enrollment; aSHR: adjusted sub-distribution hazard

<table>
<thead>
<tr>
<th>Main event</th>
<th>Competing risk</th>
<th>Any alcohol use</th>
<th>Hazardous alcohol consumption</th>
<th>Harmful alcohol consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-retention</td>
<td>Death</td>
<td>aSHR [95% CI]</td>
<td>(p-value)</td>
<td>aSHR [95% CI]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.766 [1.083, 2.879]</td>
<td>0.023</td>
<td>1.380 [0.737, 2.389]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.480 [0.817, 2.681]</td>
</tr>
<tr>
<td>Death</td>
<td>Non-retention</td>
<td>aSHR [95% CI]</td>
<td>(p-value)</td>
<td>aSHR [95% CI]</td>
</tr>
<tr>
<td>ART initiation</td>
<td>Non-retention Death</td>
<td>0.770 [0.636, 0.933]</td>
<td>0.008</td>
<td>0.841 [0.680, 1.040]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.814 [0.623, 1.064]</td>
</tr>
</tbody>
</table>

https://doi.org/10.1371/journal.pone.0240654.t003

- After adjustment, consumption of alcohol versus non-consumption = 77% higher hazard of being non-retained
- After adjustment, consumption of alcohol versus non-consumption = approximately 25% lower likelihood of ART initiation
- Other alcohol exposure classifications (hazardous versus non-hazardous & harmful versus non-harmful) were not associated with retention or ART initiation
A method for estimating death under-reporting probabilities in settings with patient outreach*

- The analysis of disengagement from care and death is complicated in EA-IeDEA due to the significant death under-reporting.

- Unreported deaths are automatically (and incorrectly) classified as disengagements from HIV care and this leads to misclassification bias.

- This issue can be addressed in settings where a subset of lost patients is actively outreached in the community using appropriate methods for missing outcome data (Bakoyannis et al., Statistica Sinica, 2019; Bakoyannis et al., Lifetime Data Analysis, 2020).

- For settings without active patient outreach one needs to utilize estimates of the probabilities of death under-reporting from external settings with active patient outreach, and then use these probabilities to adjust the estimates of disengagement from care and death for death under-reporting.

- We have developed appropriate methodology for estimating death under-reporting probabilities given a set of patient and clinic characteristics using incomplete outreach data from AMPATH (Mpofu et al., Biometrical Journal, 2020*).

- These estimates can then be used in appropriate estimators (Edwards et al., Statistics in Medicine, 2019) to adjust for death under-reporting.
Adjusting for death under-reporting in FACES using misclassification probabilities estimated in AMPATH

- We applied the methodology in the incomplete outreach data from AMPATH to estimate the probabilities of death under-reporting.
- We estimated the cumulative mortality in FACES using i) the unadjusted estimator approach and ii) the adjusted estimator that uses our estimated death under-reporting probabilities from AMPATH.
- The analysis showed that ignoring for death under-reporting leads to seriously under-estimated mortality.
PS-SiZer map to investigate features of body-weight profile changes in HIV infected patients*

• We extend the Significant Zero Crossings of Derivatives (SiZer) to address within-subject correlations of repeatedly collected longitudinal biomarker data.

• The issue (see figure) is to determine which features are most significant to identify.

• We apply this to determine durability of weight gain after ART initiation.

Harezlak J et al., PLoS ONE, 2020 https://doi.org/10.1371/journal.pone.0220165
PS-SiZer map for features of longitudinal trajectories

• We compared durability of weight gain in patients receiving D4T vs. non-D4T-based ART regimens

• SiZer maps (bottom row) show when weight gain stops (change of color) in all smoothing levels

• Splines of weight gain (top left) and derivative (top right) from the optimum level, show that weight stops increasing (derivative = 0) more quickly in d4T vs. non-d4T-based regimens

• SiZer is a useful global data visualization method to address many complex biomarker evolution problems.

Fig. 3: Southern Africa: Plot of weight change and its first derivative (top row) and PS-SiZer Maps (bottom row), for d4T-containing and non-d4T-containing ART regimens (left and right columns respectively).

https://dx.doi.org/10.1371/journal.pone.0250461.g006
IeDEA Southern Africa
Risk factors for COVID-19 death in a population cohort study from the Western Cape Province, South Africa

**Background:**
- Risk factors for COVID-19 death in sub-Saharan Africa and the effects of HIV and tuberculosis on COVID-19 outcomes are unknown.

**Results:**
- Among 3,460,932 patients (16% HIV positive), 22,308 were diagnosed with COVID-19, of whom 625 died.
- As in other settings, COVID-19 death was associated with:
  - Male sex
  - Increasing age
  - Diabetes
  - Hypertension
  - Chronic kidney disease

**Associations between different characteristics and COVID-19 death in public sector patients ≥20 years with a public sector health visit in the previous 3 years (n=3,460,932)**

Risk factors for COVID-19 death in a population cohort study from the Western Cape Province, South Africa

Results:
• HIV was associated with COVID-19 mortality (aHR 2.14; 95%CI 1.70-2.70), with similar risks across strata of viral load and immunosuppression.
• Current and previous tuberculosis were associated with COVID-19 death (aHR 2.70; [95%CI:1.81-4.04] and 1.51 [1.18-1.93] respectively).
• The standardized mortality rate for COVID-19 death associated with HIV was 2.39 (95%CI 1.96-2.86); population attributable fraction 8.5% (95%CI 6.1-11.1).

Conclusion:
• While our findings may over-estimate HIV- and tuberculosis-associated COVID-19 mortality risks due to residual confounding, both HIV and current tuberculosis were independently associated with increased COVID-19 mortality.
• The associations between age, sex and other comorbidities and COVID-19 mortality were similar to other settings.
Excess mortality associated with mental illness in people living with HIV in Cape Town

• Objectives:
  ▪ To quantify excess mortality associated with mental illness in people living with HIV
  ▪ To examine associations between mental illness and HIV treatment outcomes

• Inclusion criteria: HIV-positive adults receiving ART at three public sector HIV treatment programs in Cape Town

• Data: The Western Cape Provincial Health Data Centre linked ART program data with mental health treatment records and death certificates from the national vital registration system

• Exposure: Patients were considered as having a history of mental illness if they had ever received psychiatric medication or been hospitalized for a mental disorder

• Outcomes: Mortality from all causes, natural causes, and unnatural causes, loss to follow-up (>180 days late for a clinic visit), viral rebound (viral load ≥1000 copies/mL after viral load suppression)

Mental illness is associated with substantial excess mortality and adverse HIV treatment outcomes

- 58,664 patients were followed up for a median of 4.3 years, 2,927 (5.0%) of whom had a history of mental illness
- History of mental illness was associated with increased risk of mortality from
  - all causes: adjusted hazard ratio (aHR) 2.98, 95% CI 2.69–3.30
  - natural causes: aHR 3.00, 95% CI 2.69–3.36
  - unnatural causes: aHR 2.10, 95% CI 1.27–3.49
- History of mental illness was associated with increased risk of HIV viral rebound (aHR 1.50, 95% CI 1.32–1.69) and loss to follow-up (aHR 1.19, 95% CI 1.06–1.34)

Trends in CD4 and viral load testing 2005 to 2018: multi-cohort study of people living with HIV in Southern Africa

Background:
- Guidelines recommend CD4 testing prior to antiretroviral therapy (ART) start to detect advanced HIV disease and routine viral load (VL) testing following ART start to detect treatment failure.
- Donor support for CD4 testing has decreased to prioritize VL testing.
- This study examined trends in CD4 and VL testing among adults (≥15 years of age) on ART in six countries of IeDEA Southern Africa.

What we found:
- In earlier years, frequency of CD4 testing increased alongside an increasing number of adults on ART and in care.
- Frequency of CD4 testing plateaued or declined in many countries after 2010, despite increasing numbers of adults in care.

Figure 1. Frequency of CD4 cell count testing per day and cumulative number of adult patients in care by country. The vertical lines indicate the change in WHO guidelines. Scale of y-axis differs across countries.


SA173
What we found:

- The percentage with CD4 testing at ART initiation decreased from a high of 78.1% in 2008 to a low of 38.0% in 2017.
- Although the percentage with advanced HIV disease declined over time, nearly a quarter (23.5%) of adults still started ART with advanced HIV disease in 2018.
- VL testing coverage was low in most countries; overall, it fluctuated between 10% and 23% between 2005 and 2016.
- There was no evidence of a decrease in unsuppressed VL over time (OR 1.00; 95% CI 0.99 to 1.01).

Conclusion:

- Without expanded CD4 and VL testing, many patients with advanced HIV disease and treatment failure may go undetected.

Figure 2. Trends of CD4 cell count testing at antiretroviral therapy (ART) start and viral load (VL) testing after ART start among adult patients by year of ART start. The vertical lines indicate the change in WHO guidelines.

Temporal trends of reduced paediatric mortality on antiretroviral therapy in the multiregional IeDEA Collaboration
Implications for UNAIDS models

**Background.** The UNAIDS mathematical model Spectrum is used to produce global HIV statistics. As an input, IeDEA provides estimates of mortality among children younger than 15 years on ART.

**Objectives.** Update estimates of mortality and investigate its temporal trends, while adjusting for the possible underreporting of deaths by treatment programmes.

**Data sources.** (1) Participating treatment programmes, globally. (2) A tracing study in Southern Africa (2017-2019), providing outcomes in a sample of children considered lost-to-follow-up (LTFU).

**Mortality analysis model.** Multivariable Poisson regression – controlling for sex, current age, current time since ART start, CD4 at ART start, region (as per Spectrum requirements); and calendar time (in the form of linear splines); with random effects for inter-programme heterogeneity.
Two distinct analyses. (1) **Unadjusted** analysis: uses routine programme data as is (>40 000 children on ART during 2004-2017). (2) **Adjusted** analysis: Programme data that is modified by simulating the mortality outcomes in children considered LTFU for 6 months after LTFU, based on a simulation model trained on the tracing study data (Gompertz frailty model).

### Results highlight 1.

**Clear temporal declines in mortality over time** (after accounting for lower mortality at larger ART durations, older ages, and higher CD4 values) – these have been **incorporated into Spectrum**, for more accurate HIV modelling.

### Results highlight 2.

The adjusted mortality rate is, on average†, 54% higher than the unadjusted, more so in recent years and at higher CD4 values.

† Averaging across all combinations of covariate patterns and calendar years

**I.e. accounting for worse outcomes among those (mis)classified as LTFU increased mortality**, suggesting caution in interpreting analyses based only on programme data.
High Rates of HBV Functional Cure Among HIV-HBV Coinfected Patients on Antiretroviral Therapy in Zambia

• 284 HIV/HBV-coinfected on tenofovir-containing ART in Zambia (median age 34 years, 38% women, median CD4 202 cells/µL)

• Within 2 years of ART, 29 (10.2%) experienced HBsAg loss

• HBsAg loss was more likely if baseline CD4 <350 cells/µL (aOR 4.94, 95% CI 1.02–23.80)
Liver Fibrosis Changes Over 3 Years of Tenofovir-Based ART in HIV-HBV Coinfection

- 234 HIV/HBV-coinfected on tenofovir-containing ART in Zambia (median age 34 years, 39% women, 44% HBeAg+)

- Of 17% with significant liver fibrosis at ART start, the majority had a reduction of fibrosis during ART

- On ART, 90% had a suppressed HBV viral load but 20% had elevated transaminases
Age-specific mortality rate ratios in adolescents and youth aged 10-24 years living with perinatally versus nonperinatally acquired HIV (MR136)


- **Objective:** to provide mortality differentials for adolescents and youth with perinatally (YPHIV) vs non perinatally acquired HIV (YNPHIV), by region and sex during the periods of 10-14, 15-19 and 20-24 years. Use these data to contribute to Spectrum model mortality estimates in adults > 15 years.

- **Methods**
  - Study population: 104,846 participants who initiated ART in an IeDEA program between 2004-2016
  - Proxy for perinatal infection: enrolled < 10 years
  - Post-ART mortality rates per 100 person-years of follow-up
  - Negative binominal regression model
    - Mortality rate ratios YNPHIV vs YPHIV stratified by age, region and sex
    - Adjusted for time-varying age, sex, CD4 count at ART initiation (<350 cells/µL, ≥350 cells/µL, unknown) and time on ART (<12 months, ≥12 months).
• Results

- Significantly higher mortality rates in YNPHIV vs YPHIV in 10-14 years and 15-19 years
- Higher RR in males compared to females
- Mortality rates were comparable in YNPHIV and YPHIV at the ages 20-24 years.
Ten-year attrition and antiretroviral therapy response among HIV-positive adults: a sex-based cohort analysis from eight West African countries


• Background
  Sex differences have already been reported in sub-Saharan Africa for attrition and immunological response after antiretroviral therapy (ART) initiation, but follow up was usually limited to the first 2-3 years after ART initiation.

• Objective
  We evaluated sex differences attrition (no-follow-up, death or lost to follow-up) and immunological response (CD4 gain) in the ten years following ART initiation in West African adults.

• Methods
  We used cohort data of patients included in the IeDEA West Africa collaboration, who initiated ART between 2002 and 2014. We modelled no-follow-up and 10-year attrition risks (The overall follow-up time was divided into three periods [Year 1 (M0-M12), Years 2-4 (M13-M24) & Years 5-10 (M25-M120) following ART initiation]), and immunological response by sex using logistic regression analysis, survival analysis (Cause-specific hazard models) with random effect and linear mixed models, respectively.
Results

• A total of 71,283 patients (65.8% women) contributed to 227,311 person-years of follow-up in 16 clinics in eight West African countries.

• The cumulative attrition incidence at 10-year after ART initiation reached 75% and 68% for men and women, respectively.

• Overall, patients lost to follow-up accounted for 85% of patients not retained in care.

• Being male was associated with
  ➢ Increased risk of no follow-up after starting ART (5.1% vs. 4.0%, adjusted Odds Ratio: 1.25 [95% CI: 1.15-1.35])
  ➢ Increased risk of 10-year attrition throughout the 10-year period following ART initiation: adjusted Hazard Ratios were 1.22 [95% CI: 1.17-1.27], 1.08 [95% CI: 1.04-1.12] and 1.04 [95% CI: 1.01-1.08] during year 1, years 2-4 and 5-10, respectively.

• Better immunological response (CD4 gain) was achieved by women than men: monthly CD4 gain was 30.2 and 28.3 cells/ml in the first four months and 2.6 and 1.9 cells/μl thereafter.

Conclusion:

In West Africa, attrition is unacceptably high in both sex. Men are more vulnerable than women on both attrition and immunological response to ART in the 10 years following ART initiation. Better Innovative tracing strategies that are sex-adapted are needed for patients in care to better monitor attrition, detect early high-risk groups so that they can stay in care with a durably controlled infection.
Validation of the D:A:D chronic kidney disease risk score in people living with HIV: the IeDEA West Africa Cohort Collaboration


**Background / Objective**

A risk score for long-term prediction of chronic kidney disease (CKD) in PLHIV has been developed using data from the D:A:D cohort. We assessed the performance of the D:A:D risk score in a cohort of PLHIV in West Africa.

**Methods**

- Four IeDEA WA cohorts (Côte d’Ivoire, Burkina, Togo), PLHIV with baseline (ART initiation and ≥2 follow-up creatinine measures)
- CKD was defined as two consecutive estimated glomerular filtration rates (eGFRs) of ≤ 60 mL/min/1.73 m2
- The D:A:D score (short version) was calculated using age, gender, nadir CD4 and baseline eGFR and was categorized into: *low, medium, and high-risk groups*
Results

• 14,930 participants followed for a median duration of 5.7 years
• 660 (4.4%) progressed to CKD: incidence 7.8 (CI 7.2–8.4) per 10^4 PY
• 79.4% of people who progressed to CKD were classified in the medium- to high-risk group at baseline (sensitivity)
• 66.5% of people classified in the low risk group at baseline did not progress to CKD (specificity)

Conclusion

• Confirm the validity of the D:A:D score in identifying individuals at risk of developing CKD who could benefit from enhanced kidney monitoring in West African HIV clinics
Objective: To evaluate the prevalence and the factors associated with severe depressive symptoms in older PLHIV living in this region of the world

Methods
- Cross-sectional survey
- Inclusion Sites: 1 in Dakar, Senegal; 2 in Abidjan, Cote d'Ivoire
- PLHIV aged ≥50 and on ART ≥6 months
- Severity depressive symptoms: Center for Epidemiological Studies Depression scale (CES-D) Scores ≥17 for men and ≥23 for women

Characteristics of the sample
- N=334
- Median age: 56.7 (53.5–61.1)
- Female: 57.8%
- Undetectable viral load: 87.1%
- CDC stage C: 14.4%
- Tobacco use: 17.1%
- Alcohol or drug consumption <8%
Results

✓ Prevalence of severe depressive symptoms = 17.9% [IC 95% : 13.8 – 22.0]
✓ Associated factors (multivariate logistic regression analysis):

- **Unemployment**
  - aOR=2.8
  - IC 95% [1.4-5.7]
  - p=0.003

- **Tobacco use**
  - aOR=2.6
  - IC 95% [1.3-5.4]
  - p=0.01

- **Overweight/Obesity**
  - aOR=0.4
  - IC 95% [0.2 – 0.8]
  - p=0.01

**Conclusion:**
- High prevalence of severe depressive symptoms among older PLHIV living in West Africa
- Unemployed PLHIV and tobacco smokers should be vulnerable and in need of additional support

To guarantee the achievement of the 3×90 objectives, and encourage successful aging further studies are needed to describe in more details the reality of the aging experience of PLHIV in SSA

The integration of screening / management of depression in the standard of care of PLHIV is crucial
Changes in HIV-related Cervical Cancer over a Decade in Côte d’Ivoire

Antoine Jaquet, Simon Boni, Boris Tchounga, KouassiComoe, Aristophane Tanon, Apollinaire Horo, Isidore Diomandé, Judith Didi-Kouko-Coulibaly, Didier K. Ekouevi, Innocent Adoubi. JCO Global Oncology (2021) [Accepted].

Objectives

• to compare HIV-related Invasive Cervical Cancer (ICC) over a decade and document factors associate with HIV infection in women with ICC in Côte d’Ivoire

Methods

• Repeated cross-sectional study conducted in referral hospitals of the urban area of Abidjan trough the 2009-2011 and 2018-2020 periods
• Women diagnosed with ICC were systematically tested for HIV
• Demographics, ICC risk factors, cancer stage (FIGO) and HIV characteristics collected through questionnaires
• Characteristics of HIV-related ICC compared between the time periods
• Factors associated with HIV in women diagnosed with ICC in 2018-2020 documented through a multivariable logistic model
During the 2009-2011 and 2018-2020 periods, 147 and 297 women with ICC were included with estimated HIV prevalence of 24.5% and 21.9% (p=0.53).

In HIV-infected women, access to ART increased from 2.8% to 73.8% (p<10^{-4}) median CD4 cell count from 285 [IQR 250 – 441] to 492 [IQR 377 – 833] (p=0.03).

During the 2018-2020 period, HIV infection was associated with:

- Less advanced clinical stage (FIGO I/II stage): aOR=2.2 (CI 1.1-4.4)
- Cancer diagnosed through a systematic screening: aOR=10.5 (CI 2.5-45.5)

Conclusion

- Persistently high proportion of HIV-related ICC over time in Côte d’Ivoire
- HIV was associated with less advanced clinical stage at ICC diagnosis in recent years
- Recent improvements in ICC screening services across HIV clinics might explain this association and support their implementation across non-HIV health facilities
NA-ACCORD
Risk of Incident Diabetes Mellitus, Weight Gain, and Their Relationships With Integrase Inhibitor–Based Initial Antiretroviral Therapy Among Persons With Human Immunodeficiency Virus in the US and Canada

• **Background.** Integrase strand transfer inhibitor (INSTI)–based combination antiretroviral therapy (cART) is associated with greater weight gain among persons with human immunodeficiency virus (HIV), though metabolic consequences, such as diabetes mellitus (DM), are unclear. We examined the impact of initial cART regimen and weight on incident DM in a large North American HIV cohort (NA-ACCORD).

• **Methods.** cART-naive adults (≥18 years) initiating INSTI-, protease inhibitor (PI)–, or nonnucleoside reverse transcriptase inhibitor (NNRTI)–based regimens from January 2007 through December 2017 who had weight measured 12 (—6) months after treatment initiation contributed time until clinical DM, virologic failure, cART regimen switch, administrative close, death, or loss to follow-up. Multivariable Cox regression yielded adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for incident DM by cART class. Mediation analyses, with 12-month weight as mediator, similarly adjusted for all covariates.
**Results.** Among 22,884 eligible individuals, 47% started NNRTI-, 30% PI-, and 23% INSTI-based cART with median follow-up of 3.0, 2.3, and 1.6 years, respectively. Overall, 722 (3%) developed DM. Persons starting INSTIs vs NNRTIs had incident DM risk (HR, 1.17 [95% CI, .92–1.48]), similar to PI vs NNRTI initiators (HR, 1.27 [95% CI, 1.07–1.51]). This effect was most pronounced for raltegravir (HR, 1.42 [95% CI, 1.06–1.91]) vs NNRTI initiators. The INSTI–DM association was attenuated (HR, 1.03 [95% CI, .71–1.49] vs NNRTIs) when accounting for 12-month weight.

**Conclusions.** Initiating first cART regimens with INSTIs or PIs vs NNRTIs may confer greater risk of DM, likely mediated through weight gain.

Figure: Adjusted hazard ratios (with 95% CIs) for incident diabetes mellitus by initial combination antiretroviral therapy regimen classes and core agents, among those in participating NA-ACCORD cohorts initiating cART of ≥45 days’ duration between 2007 and 2016. Abbreviations: aHR, adjusted hazard ratio; DM, diabetes mellitus; DTG, dolutegravir; EVG, elvitegravir; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAL, raltegravir.
Timing of Antiretroviral Therapy Initiation and Risk of Cancer Among Persons Living With Human Immunodeficiency Virus

• **Background.** Persons living with human immunodeficiency virus (HIV; PLWH) experience a high burden of cancer. It remains unknown which cancer types are reduced in PLWH with earlier initiation of antiretroviral therapy (ART).

• **Methods.** We evaluated AIDS-free, ART-naive PLWH during 1996–2014 from 22 cohorts participating in the North American AIDS Cohort Collaboration on Research and Design. PLWH were followed from first observed CD4 of 350–500 cells/μL (baseline) until incident cancer, death, lost-to-follow-up, or December 2014. Outcomes included 6 cancer groups and 5 individual cancers that were confirmed by chart review or cancer registry linkage. We evaluated the effect of earlier (in the first 6 months after baseline) versus deferred ART initiation on cancer risk. Marginal structural models were used with inverse probability weighting to account for time-dependent confounding and informative right-censoring, with weights informed by subject’s age, sex, cohort, baseline year, race/ethnicity, HIV transmission risk, smoking, viral hepatitis, CD4, and AIDS diagnoses.
• **Results.** Protective results for earlier ART were found for any cancer (adjusted hazard ratio [HR] 0.57; 95% confidence interval [CI], .37–.86), AIDS-defining cancers (HR 0.23; 95% CI, .11–.49), any virus-related cancer (HR 0.30; 95% CI, .16–.54), Kaposi sarcoma (HR 0.25; 95% CI, .10–.61), and non-Hodgkin lymphoma (HR 0.22; 95% CI, .06–.73). By 15 years, there was also an observed reduced risk with earlier ART for virus-related NADCs (0.6% vs 2.3%; adjusted risk difference −1.6; 95% CI, −2.8, −.5).

• **Conclusions.** Earlier ART initiation has potential to reduce the burden of virus-related cancers in PLWH but not non-AIDS defining cancers (NADCs) without known or suspected viral etiology.

**Figure 2.** Adjusted hazard ratios for intention-to-treat analysis of earlier versus deferred ART initiation and risk of cancer among the primary study population (baseline CD4 350–500 cells/μL). HR and 95% CI for earlier versus deferred (reference) ART and risk for cancer are shown. Results from intention-to-treat marginal structural working models, with weights for ART initiation, and right-censoring due to death and loss to follow-up. With deferred ART as reference and as indicated on the figure, an HR < 1 indicates earlier ART is protective and an HR > 1 indicates deferred ART is protective. E-values presented in italics below HR estimates and CIs and interpreted as the minimum strength of an unmeasured confounder with both the exposure and outcome (on a risk ratio scale) that would account for the observed HR or CI above and beyond what is already accounted for in the models.

Abbreviations: ADC, AIDS-defining cancer; CI, confidence interval; HL, Hodgkin lymphoma; HR, hazard ratio; KS, Kaposi sarcoma; NADC, non-AIDS-defining cancer; NHL, non-Hodgkin lymphoma.

• **Background.** To assess the possible impact of antiretroviral therapy improvements, aging, and comorbidities, we examined trends in all-cause and cause-specific hospitalization rates among persons with HIV (PWH) from 2005 to 2015.

• **Methods.** In 6 clinical cohorts, we followed PWH in care (≥1 outpatient CD4 count or HIV load [VL] every 12 months) and categorized ICD codes of primary discharge diagnoses using modified Clinical Classifications Software. Poisson regression estimated hospitalization rate ratios for calendar time trends, adjusted for demographics, HIV risk factor, and annually updated age, CD4, and VL.

• **Results.** Among 28,057 patients (125,724 person-years), from 2005 to 2015, the median CD4 increased from 389 to 580 cells/μL and virologic suppression from 55% to 85% of patients. Unadjusted all-cause hospitalization rates decreased from 22.3 per 100 person-years in 2005 (95% confidence interval [CI], 20.6–24.1) to 13.0 in 2015 (95% CI, 12.2–14.0). Unadjusted rates decreased for almost all diagnostic categories. Adjusted rates decreased for all-cause, cardiovascular, and AIDS-defining conditions, increased for non-AIDS–defining infection, and were stable for most other categories.
Conclusions. Among PWH with increasing CD4 counts and viral suppression, unadjusted hospitalization rates decreased for all-cause and most cause-specific hospitalizations, despite the potential effects of aging, comorbidities, and cumulative exposure to HIV and antiretrovirals.
• **Background.** Integrase strand transfer inhibitor (InSTI)–based regimens are now recommended as first-line antiretroviral therapy (ART) for adults with human immunodeficiency virus, but evidence on long-term clinical effectiveness of InSTI-based regimens remains limited. We examined whether InSTI-based regimens improved longer-term clinical outcomes.

• **Methods.** We included participants from clinical cohorts in the North American AIDS Cohort Collaboration on Research and Design who initiated their first ART regimen, containing either InSTI (ie, raltegravir, dolutegravir, and elvitegravir-cobicistat) or efavirenz (EFV) as an active comparator, between 2009 and 2016. We estimated observational analogs of 6-year intention-to-treat and per-protocol risks, risk differences (RDs), and hazard ratios (HRs) for the composite outcome of AIDS, acute myocardial infarction, stroke, end-stage renal disease, end-stage liver disease, or death.
**Results.** Of 15,993 participants, 5,824 (36%) initiated an InSTI-based and 10,169 (64%) initiated an EFV-based regimen. During the 6-year follow-up, 440 in the InSTI group and 1,097 in the EFV group incurred the composite outcome. The estimated 6-year intention-to-treat risks were 14.6% and 14.3% for the InSTI and EFV groups, respectively, corresponding to a RD of 0.3% (95% confidence interval, −2.7% to 3.3%) and a HR of 1.08 (.97–1.19); the estimated 6-year per-protocol risks were 12.2% for the InSTI group and 11.9% for the EFV group, corresponding to a RD of 0.3% (−3.0% to 3.7%) and a HR of 1.09 (.96–1.25).

**Conclusions.** InSTI- and EFV-based initial ART regimens had similar 6-year composite clinical outcomes. The risk of adverse clinical outcomes remains substantial even when initiating modern ART.

![Figure 1. Risk of the composite outcome (AIDS-defining illnesses, acute myocardial infarction or stroke, end-stage renal disease, end-stage liver disease, or death) among 15,993 HIV-infected adults initiating an integrase strand transfer inhibitor (InSTI)—based or an efavirenz (EFV)—based regimen between July 2009 and December 2016 in the NA-ACCORD. Left, Intention-to-treat analyses that accounted for baseline confounding and differential loss-to-follow-up. Right, Per-protocol analyses that accounted for baseline confounding, differential loss to follow-up, and treatment changes.](image)
CD4 count at entry into HIV care and at Antiretroviral therapy prescription in the US, 2005–2018

**Background:** Effective antiretroviral therapy (ART) has considerably reduced morbidity and mortality in people with HIV (PWH). Within the context of evolving ART guidelines, we expected to observe reduced time from entry into care to prescription of ART, and subsequent increases in CD4 counts at ART prescription.

**Methods:** The study population comprised 32,013 PWH who entered care with a CD4 count measurement; this sample was used to calculate median CD4 at entry into care. Of the total sample, 26,555 (83%) were prescribed ART during the study period with a CD4 measurement at ART prescription; this subsample was used to calculate median CD4 at ART prescription and time from entry into care to ART prescription.

**Results:** From 2005 to 2018, among 32,013 adults entering HIV care, median time to ART prescription declined from 69 to 6 days, median CD4 at entry into care increased from 300 to 362 cells/μL, and median CD4 at ART prescription increased from 160 to 364 cells/μL (see Figure).

**Conclusion:** These findings indicate progress towards prompt diagnosis, referral to care, and ART prescription in PWH between 2005 and 2018. Further increases in median CD4 count at both entry into care and at ART prescription may be possible with expanded implementation of effective test-and-treat strategies, particularly those focused on reaching women, racial and ethnic minorities, and other marginalized populations.

**Figure.** Median CD4 count at entry into care (black circles) and at ART prescription (red triangles) overlaying median days from entry into care to ART prescription (blue bars), by calendar year.