Has HIV Treatment Guideline Expansion Improved the Timely Uptake of ART?

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Disclosures and conflicts of interest

• I have no financial disclosures or conflicts of interest
### Background

- **WHO recommendations for major eligibility expansions** were issued in 2009 (CD4<200 → CD4≤350) and 2013 (CD4<350 → CD4≤500) and in 2015 (treat all).

- With highly suboptimal outcomes prior to ART eligibility and initiation, guideline expansion has the potential to improve HIV care continuum outcomes, especially for newly eligible persons.

- There is also a risk that expansion could negatively influence outcomes among persons with more advanced HIV disease.

<table>
<thead>
<tr>
<th>Year</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>2006</td>
<td>Treat CD4&lt;200</td>
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<td>2009</td>
<td>Treat CD4&lt;350</td>
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<tr>
<td>2013</td>
<td>Treat CD4&lt;500</td>
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<tr>
<td>2015</td>
<td>Treat all</td>
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Has HIV Treatment Guideline Expansion Improved the Timely Uptake of ART?

- Effective implementation of guideline expansion at the site level should result in an increase in timely ART uptake among all persons enrolling in HIV, especially those that are newly eligible under the new guidelines.
- Implementation of expanded guidelines should not crowd out the sickest patients (i.e., those eligible prior to guideline expansion).

Measurement:
- Exposure (guideline expansion)
- Outcome (timely ART initiation)
International Epidemiology Databases to Evaluate AIDS (IeDEA) Consortium

IeDEA is an international research consortium established in 2005 by the National Institute of Allergy and Infectious Diseases (NIAID) to provide a rich resource for globally diverse HIV/AIDS data. IeDEA is a trans-NIH initiative that collaborates with the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), the National Institute of Mental Health (NIMH), and the National Institute on Drug Abuse (NIDA). Sites in various regions throughout the world collaborate to collect and define key variables, and implement methodology to effectively analyze data as a cost-effective means of generating large data sets to address the high priority HIV/AIDS research questions that are unanswerable by a single cohort. For more information, please contact info@iedea.org.

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HIV treatment eligibility expansion and timely antiretroviral treatment initiation following enrollment in HIV care: A metaregression analysis of programmatic data from 22 countries

Olga Tymejczyk, Ellen Brazier, Constantin Yiannoutsos, Kara Wools-Kaloustian, Keri Althoff, Brenda Crabtree-Ramirez, Kinh Van Nguyen, Elizabeth Zaniewski, Francois Dabis, Jean d'Amour Sinayoby, Nanina Anderegg, Nathan Ford, Radhika Wikramanayake and Denis Nash

for the IeDEA Collaboration
Methods: Statistical Analysis (expansion to CD4<350 and CD4<500 cells/µL)

- Estimated the absolute change cumulative incidence of ART initiation (CI-ART) within 6 months of enrolment at each site in countries where national ART eligibility criteria expanded between 2007 and 2014.
  - CI-ART estimated via competing risks regression, with death and pre-ART loss to clinic treated as competing events.
- Random effects meta-regression models used to estimate absolute changes in CI-ART before/after national guideline expansion at the site level.
- Estimates of absolute changes in CI-ART stratified by site and patient characteristics
  - Site characteristics: IeDEA region; % patient population female; baseline median enrolment CD4; baseline CI-ART
  - Patient characteristics: sex; age (≤ 25 years, >25 years); CD4 at enrolment

Tymejczyk et al. PLoS Med 2018
Methods: Study Sample

• Of 40+ countries represented in the latest IeDEA database, guideline expansions to $\leq 350$ or $\leq 500$ cells/uL were known to have occurred at least once in 22 countries during 2007-2014.

• 239,311 adult ART-naïve patients at 145 IeDEA sites in 22 countries where ART eligibility criteria expanded between 2007 and 2014.
  
  • **Expansion to CD4$<350$ cells/uL**: 167,537 patients at 136 sites in 20 countries included in analysis.
  
  • **Expansion to CD4$<500$ cells/uL**: 73,393 patients at 86 sites in 6 countries included in analysis.
  
  • Most patients and sites from Southern Africa (54% and 85% of sites in the two analyses of expansion to CD4$<350$ and CD4$<500$, respectively)

Tymejczyk et al. PLoS Med 2018
Results: Overall change in CI-ART (prior to meta analysis)

- Overall change in 6-month CI-ART after guideline expansions:
  - 4.3 percentage points (95% CI: 3.8-4.8; expansion to CD4≤350)
  - 16.6 percentage points (95% CI: 16.0-17.3; expansion to CD4≤500)

Tymejczyk et al. PLoS Med 2018
Methods: Outcome Definition

Absolute percentage point change in the cumulative incidence of ART initiation at the original site within 6 months of enrolment at the site level (CI-ART6m) after vs. before the national guideline change (i.e., changes in timely ART initiation following enrolment in care)

\[ \text{Outcome}_{\text{Site A}} = \text{CI-ART6m}_{\text{post}} - \text{CI-ART6m}_{\text{pre}} \]

Tymejczyk et al. PLoS Med 2018
Absolute percentage point change in the cumulative incidence of ART initiation at the original site within 6 months of enrolment at the site level (CI-ART6m) after vs. before the national guideline change (i.e., changes in timely ART initiation following enrolment in care)

Methods: Outcome Definition

Outcome Site A = CI-ART6m_{post} - CI-ART6m_{pre}

Example: +6% = 61% - 55%

Tymejczyk et al. PLoS Med 2018
Results: Change in CI-ART6m following national guideline expansion to CD4≤350 cells/μL

- Pooled effect: +3.8 (95% CI: +2.0 to +5.6)
- Ranging from +1.4 (-0.8 to +3.7) in Southern Africa to +12.1 (-2.1 to +26.3) in Asia-Pacific
- Large effect among newly eligible patients (CD4 between 201-350): +18.7 (+15.8 to +21.6)
- No change among previously eligible
- No appreciable difference by sex or age

Overall effect=+3.8% (95% CI: 2.0%-5.6%)

- 167,537 patients
- 136 sites
- 20 countries
Results: Change in CI-ART6m following national guideline expansion to CD4≤500

- Pooled effect: +16.7 (95% CI: +14.3 to +19.0)

- Ranging from +6.5 (+0.3 to +12.8) in South and Central America to +18.0 (+15.4 to +20.5) in Southern Africa
  - NB: No sites from Asia-Pacific or East Africa in this analysis

- Larger effects among:
  - Newly eligible patients (CD4 between 351-500): +42.2 (+36.6 to +47.8)
  - Women: +19.3 (+16.7 to +21.3)
  - Patients ≤25 y.o.: +24.3 (+21.0 to +27.6)

- Small increase among previously eligible: +4.6% (2.5%-6.7%)

Overall effect = +16.7% (95% CI: 14.3%-19.0%)

- 73,393 patients
- 86 sites
- 6 countries
Results: Site-level effects by ART eligibility (secular trend)

![Box plot showing changes in 6-month CD4 count by ART eligibility status]

- Expansion to CD4 ≤350
- Expansion to CD4 ≤500

**ART eligibility status at enrollment in HIV care**

Previously eligible, Newly eligible, Previously eligible, Newly eligible
Results: Site-level effects by age

- **Expansion to CD4≤350:** No appreciable difference by age
- **Expansion to CD4≤500:** Greater effect among patients ≤25 y.o.
  - Age ≤25: +24.3 (+21.0 to +27.6) vs. age >25: +15.6 (+13.2 to +17.9)
Has 'Treat All' improved timely uptake of ART?

An 11-country analysis of timeliness of ART initiation following the national adoption of universal test and treat policies.

Olga Tymejczyk, Ellen Brazier, Constantin Yiannoutsos, Peter Rebeiro, Kara Wools-Kaloustantian, Keri Althoff, Mary-Ann Davies, Brenda Crabtree-Ramirez, Elizabeth Zaniewski, Mark Urassa, Jean d’Amour Sinayobye, Nanina Anderegg, Nathan Ford, and Denis Nash

for the IeDEA Collaboration
2015: WHO recommends immediate initiation of ART, regardless of clinical or immunological status

Will there be continued improvements in timely ART initiation, similar to observed under prior guideline expansions?
Methods: Study Sample

• Analysis includes 846,712 adult (≥16 years) patients newly enrolled in HIV care between 2004 and 2017, from 11 countries with:
  • Current national UTT policies,
  • Known dates of at least one prior major HIV eligibility expansion,
  • Pre-ART data available.

• Included in the analysis: Brazil, Burundi, Canada, Kenya, Malawi, Mexico, Rwanda, Uganda, USA, Zambia, Zimbabwe.
  • Canada and Mexico did not contribute data to the expansion to CD4<500 guideline period.
Results: Overview

Proportion of patients initiating ART at the original site within 3 months of enrollment by guideline period

Tymejczyk et al. In process
Results: Overview

- Increases in CI-ART3m under successive guideline expansions, including UTT, observed in all strata, especially in low-income countries.
- Greatest increases under CD4≤500 and UTT among young women.
• ART guideline expansion, including UTT, appears to have substantially improved timely ART initiation at the original site of enrolment among persons aged 16+ in a global sample of HIV clinics, including among young persons.
  • Largest improvements across all guideline periods were in low income countries, among patients aged 16-24 years and women.
  • Expansion to UTT may help close age and sex gaps.

• Improvements in timely ART initiation among newly eligible patients not offset by decreases among previously eligible patients.
  • That many clinics can absorb initiation of ART among new patients with less advanced disease may reflect a transition away from the emergency treatment era in some locations.

• Suboptimal CD4 counts at enrollment in care underscore the need to address delays in diagnosis and/or linkage, which limit the potential of UTT to reduce morbidity, mortality, and onward HIV transmission.

• Examination of outcomes post-ART initiation under UTT is critical.
There are two gifts we should give our children: one is roots, and the other is wings.

Sudanese proverb
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Extra slides
Strengths and Limitations

**Strengths:**

- Data from large number of patients and from sites with varying patient mix, across several regions
- The heterogeneous sample of real-world service delivery settings may be generalizable to contexts where treatment guidance lags behind WHO recommendations
- The within site pre-post design with 12-month buffer period helps to control for differences in patient mix and seasonal patterns of ART initiation

**Limitations:**

- Missing information on exact timing of guideline changes at country level
  - Mid-year dates assumed for some countries, and may obscure true associations
- Lack of information on timing of implementation of guidelines changes at site-level may also obscure effects
- No direct comparability of 350 and 500 analyses
  - Different site and country mix for each guideline change
- Inability to fully control for secular trends in ART initiation and lack of counterfactual within countries may inflate estimates of guideline change effects
  - Change in CI-ART for those previously eligible may be a good proxy for secular trend
Until 2015, decisions on when to start ART were based on clinical staging and CD4 cell count. The recommended CD4 cell count threshold for starting ART has gradually increased in national and international guidelines, in line with data from randomised trials and observational cohorts. WHO recommends starting ART in all individuals with HIV, irrespective of CD4 cell count, to reduce mortality, morbidity, and viral transmission, and most countries have adopted or are in the process of adopting this recommendation (figure 2).

Although WHO still recommends CD4 cell count at baseline to support clinical risk assessments, the fact that CD4 cell count is no longer required for ART initiation greatly simplifies clinical decision making, to the point that it is possible to consider starting ART on the same day that HIV is diagnosed.

**Figure 1:** Map of uptake of WHO first-line antiretroviral therapies as of July, 2017

Distribution of the preferred first-line antiretroviral combination among adults and adolescents, and initial shifts towards dolutegravir in low-income and middle-income countries (situation as of July, 2017). The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city, or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. Data source: WHO. Map production: Information Evidence and Research.

**Source:** N Ford et al. Lancet Infectious Diseases, 2017
Results: Change in CI-ART3m after Successive Guideline Expansions, by Country Income Level

- Largest increases in low-income countries: CI-ART3m increased from 36% before expansion to CD4≤350 to 86% under UTT.
CD4 Count at Enrollment in Care

• In 2014, median CD4 count at enrollment ranged from 213 in Asia-Pacific to 422 in North America, and was substantially higher among women than men (320 vs 252).

• Availability of CD4 counts at enrollment has declined in recent years in East and Southern Africa.
Results: Change in Cl-ART3m after Successive Guideline Expansions, by Sex and Age

- Age gaps narrowed with substantial increases in Cl-ART3m among those aged 16-24 years:
  - Among men and women alike, gap between those aged 16-24 and 25+ years old shrank by 8.3pp and 7.8pp, respectively.
- In both age groups, Cl-ART3m was lower among women than men before expansion to CD4≤500, but was higher among women under CD4≤500 and UTT.
ART Initiation by 3 Months after Enrollment, Across ART Eligibility Periods and Enrollment CD4 Counts

- At all CD4 levels, CI-ART 3m increased with each eligibility expansion (yellow dots representing higher CI-ART initiation levels under UTT than pink, green, or blue dots representing previous guidelines).

- After each expansion, gaps in CI-ART 3m between patients enrolling right below and right above the eligibility threshold narrowed:
  - After expansion to CD4≤350, the gap in CI-ART 3m between those enrolling with CD4 151-200 and 201-250 narrowed from 20.4 to 3.3pp.
  - After expansion to CD4≤500, the gap in CI-ART 3m between those enrolling with CD4 301-350 and 351-400 narrowed from 32.9 to 6.1pp.
  - After expansion to UTT, the gap in CI-ART 3m between those enrolling with CD4 451-500 and 501-550 narrowed from 22.6 to 6.3pp.
Results: Median CD4 Counts at Enrollment under UTT

- Under UTT, median CD4 counts at enrollment in HIV care ranged from 284 to 413 cells/μL across country income groups, and from 283 to 408 cells/μL across age groups.
Methods: Setting, Study Sample, and Design

  - 63% of included patients from Southern Africa, 27% from East Africa. No data included from West Africa.
  - 63% female, median age at enrollment 33.
  - At enrollment, 68% had a CD4 count, 25% - clinical stage.

- Competing risks analyses (with death and pre-ART loss to care treated as competing events) used to estimate cumulative incidence of ART initiation (CI-ART).

- For 22 countries with data on previous ART eligibility expansions to CD4≤350 and/or CD4≤500, site-level comparison of CI-ART by 6 months after enrollment (CI-ART6m) in periods before and after guideline expansion (284,740 patients at 171 sites).

- For 11 countries with current Universal Test and Treat (UTT) policies, comparison of cumulative proportion of ART initiation by 3 months after enrollment (CI-ART 3m) under successive national ART eligibility criteria (846,712 patients).
Implementation of ‘Treat-All’ at sites participating in the Global IeDEA Collaboration:

Results from the 2017 survey of HIV treatment sites in 44 countries

Ellen Brazier, Fernanda Maruri, Stephany Duda, Olga Tymejczyk, C. William Wester, Geoffrey Somi, Jeremy Ross, Aimee Freeman, Mary-Ann Davies, Armel Poda, April Kimmel, Marcel Yotebieng, and Denis Nash for the IeDEA Collaboration
In 2015, the World Health Organization recommended universal testing and treatment (UTT) for all persons living with HIV — also known as ‘Treat All’.

The adoption of WHO treatment guidelines often lags at national levels, contributing to suboptimal rates of ART initiation.

Little is known about the timing and nature of site-level implementation of UTT vis-à-vis national-level adoption, across world regions and countries.

IeDEA (International epidemiology Databases to Evaluate AIDS), an international research consortium established in 2005, provides a rich resource for monitoring trends in HIV care and outcomes across countries in six world regions.
• **Survey objectives:**
  • To describe site-level capacity and practice related to HIV care, including the current status of UTT implementation and the timing of site-level UTT implementation relative to national guideline adoption.

• **Study Design:** Cross-sectional survey administered to 255 IeDEA sites in 44 countries (July-December 2017).
  • Complete responses were received from 234 sites (92%).

• **Eligibility criteria:**
  • IeDEA sites that are active (contributing data to IeDEA cohort in 2017).
  • IeDEA sites which are not nested within a larger cohort or program (i.e., report data for own patients).
214/234 (91%) sites reported implementation of UTT (i.e., initiating all patients on ART regardless of CD4 count or clinical criteria).

Site-level implementation of UTT nearly universal across sites in most IeDEA regions, but lower among the Asia-Pacific and West Africa IeDEA sites.

- 25/214 UTT-implementing sites (12%) located in countries that have not yet adopted UTT guidelines nationally.
- In countries with national UTT adoption, 8/197 (4%) of sites not implementing UTT.
• 204/214 IeDEA sites (95%) reported year of UTT implementation at their site.
• Median year of site-level UTT implementation ranged from 2013 to 2017.
  – Median year of UTT implementation later among East, Central, and Southern Africa sites (2016) and in West Africa (2017).
Results: Time from national UTT adoption to site implementation

- 36% of sites reported implementing UTT prior to national adoption of UTT guidelines.
- Among sites in countries where UTT has been adopted nationally (N=181), median time from national guideline change to site implementation was +2 months (IQR: 0 to +7 months).
  - Time to site implementation was longest at sites in the Americas regions and in countries with earlier national adoption of UTT.
  - In the Asia-Pacific and West Africa regions, the majority of IeDEA sites began UTT implementation before national UTT adoption.
Results: Time from national UTT adoption to site implementation (2)

- Median times between national adoption and site-level implementation greatest among:
  - Rural sites (+2 months; IQR: +2 to +7 months), vs urban (0 months; IQR: 2 to +12 months)
  - Public hospitals/clinics (+2 months; IQR: 0 to +7 months) vs private (0 months; IQR: -20 to +4 months)

Time from national UTT adoption to site implementation, by facility characteristic
• Among sites implementing UTT, 37% reported that, on average, patients initiate ART on the same day that the HIV diagnosis is confirmed.
  – An additional 42% reported that patients generally initiate ART within two weeks of confirming HIV status.

• Among sites that are not implementing UTT (N=20), 15% reported that patients generally initiate ART on the day of confirming ART eligibility.
  – An additional 33% reported that patients generally initiate ART within two weeks of confirming ART eligibility.

• The mean number of ART readiness counseling sessions conducted prior to initiating patients on ART:
  – 1.6 sessions at UTT-implementing sites vs. 2.1 sessions at non-UTT sites (p=0.057)
Conclusions

• By mid- to late 2017, the vast majority of IeDEA sites had adopted WHO recommendations regarding universal testing and treatment (UTT), with a sizable proportion implementing UTT prior to changes in national treatment guidelines, particularly in the Asia-Pacific and West Africa regions.

• Site-level implementation of national UTT guidelines occurred earlier at urban sites and private hospitals/clinics than rural and public-sector sites.

• UTT-implementing sites more likely to initiate patients on ART soon after confirming HIV infection/eligibility and to conduct fewer ART readiness counseling sessions prior to ART initiation.

• Research to inform UTT implementation and assess the impact of UTT implementation on patient outcomes, including retention, and viral suppression, is needed.