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AND PREVENTION  
ADHERENCE



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# Changing Trends in ART Prescription, Durability, and Modification

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# Background

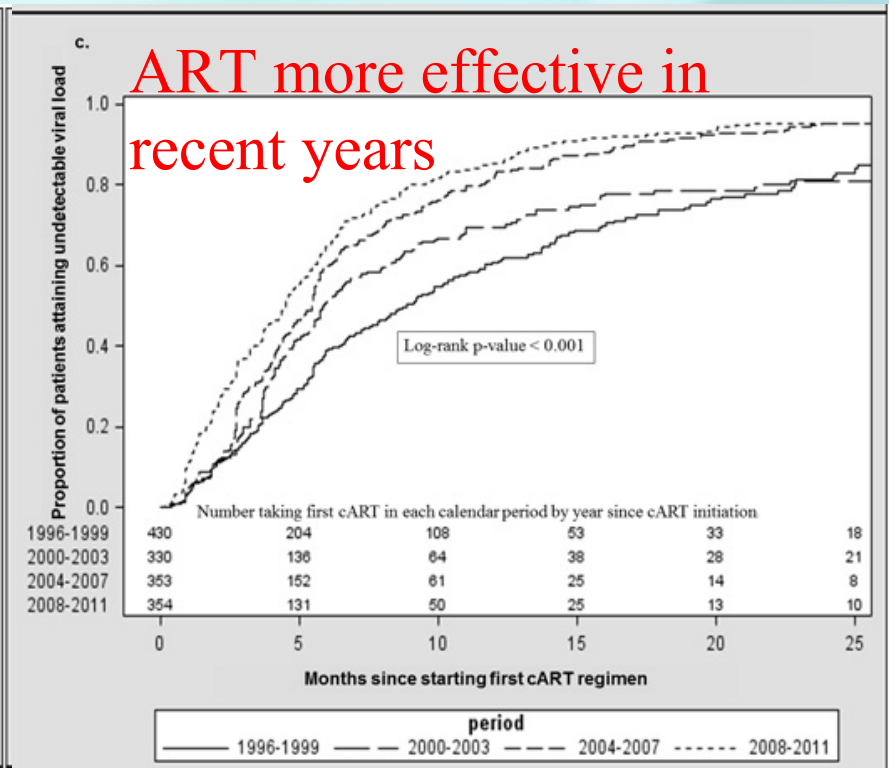
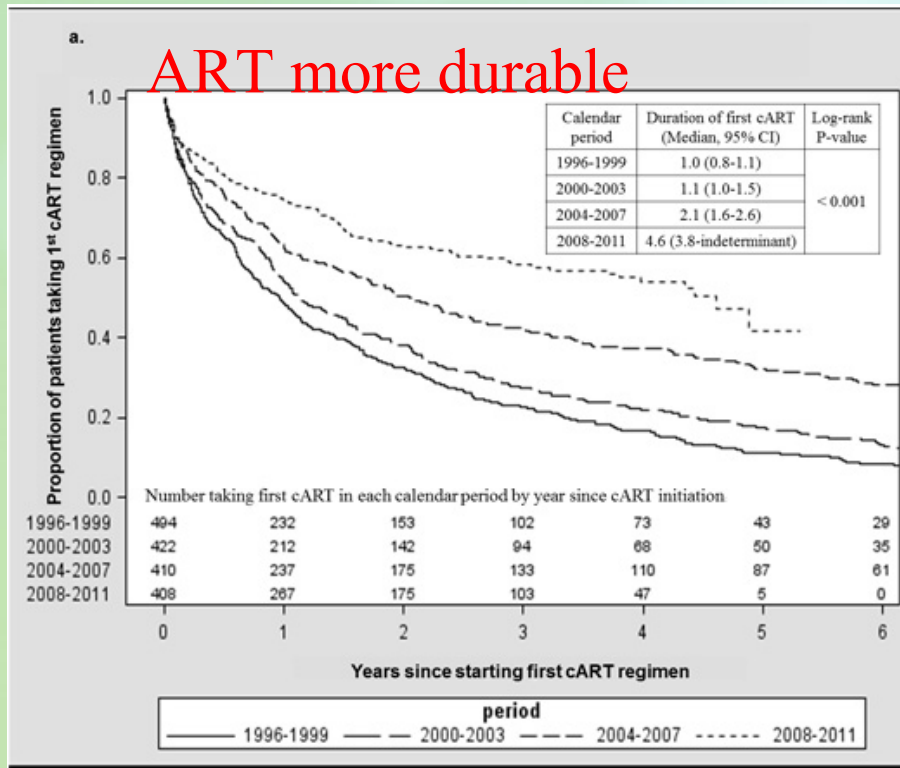
- New antiretroviral therapy (ART) agents and combinations require iterative evaluation of clinical outcomes, including durability, in real world cohorts
- Durability, defined as time from ART start to discontinuation, is positively associated with HIV viral suppression, reduced drug resistance, and lower morbidity and mortality





# Background

- Sheth evaluated durability in the HOPS cohort
- 1,734 treatment naïve HIV positive persons

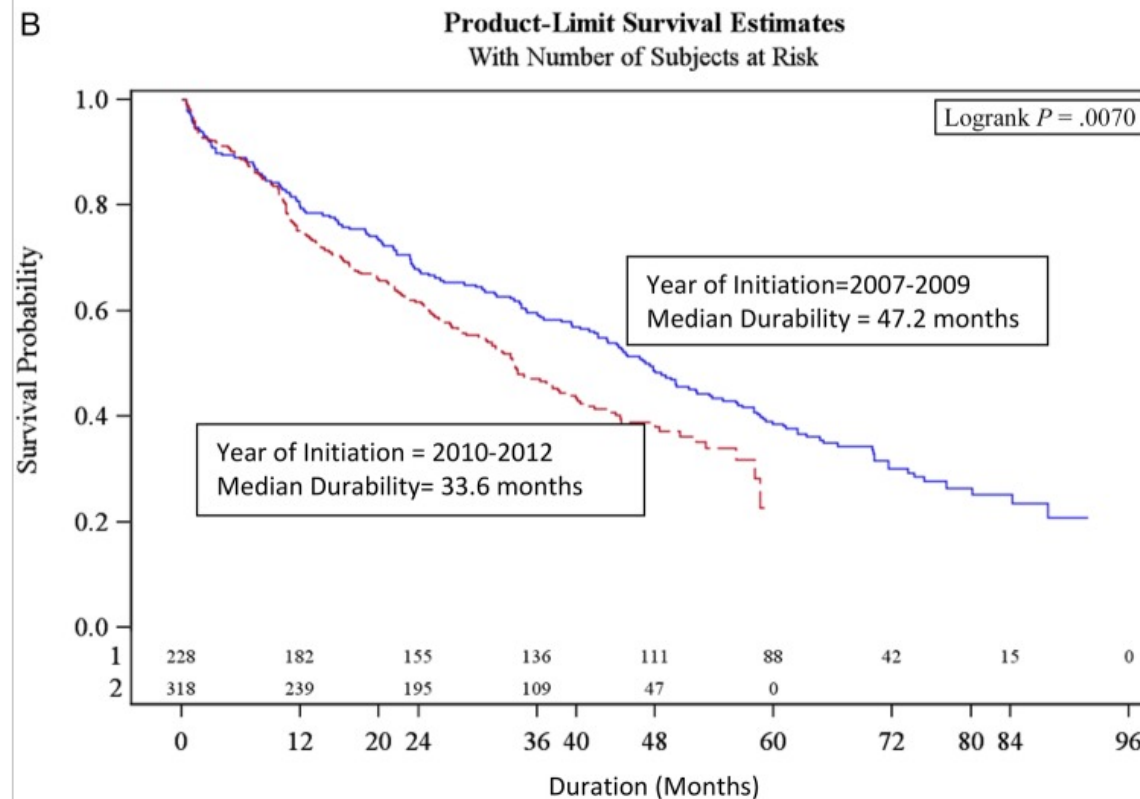




# UAB 1917 Clinic Experience:

ART less durable, more effective

67% had a VL<200 copies/mL at discontinuation

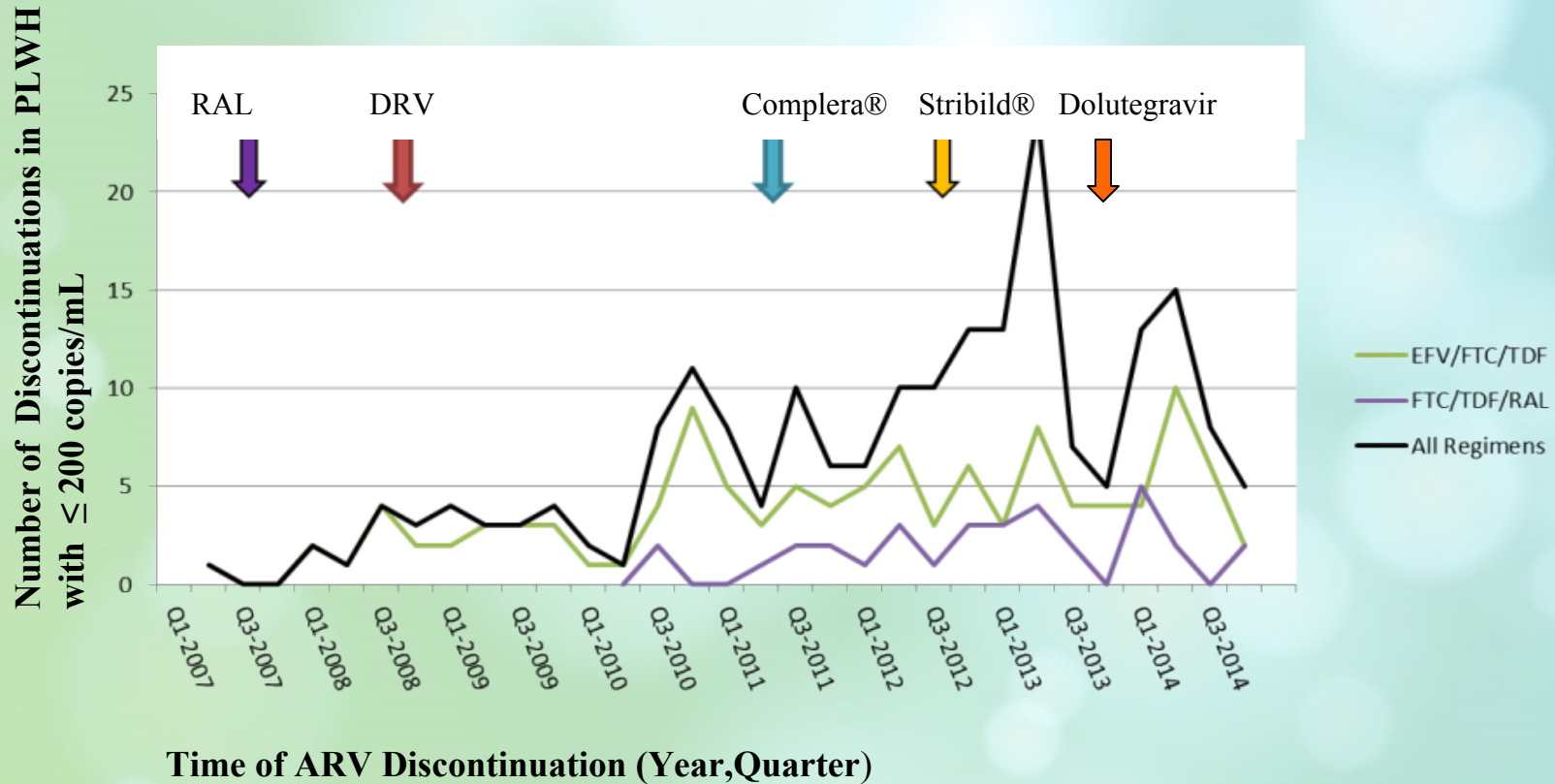


(A) Duration of initial antiretroviral (ARV) regimen with and without fixed-dose combination (FDC) pill in treatment-naïve HIV-in Alabama at Birmingham (UAB) HIV clinic. (B) Duration of initial ARV regimen by year of initiation at the UAB HIV clinic bet



## UAB 1917 Clinic Experience:

Older ART also discontinued even in the setting of HIV viral suppression (VL<200 copies/mL)





# Objective

- Analyze contemporary ART durability in a real world, multisite cohort of persons living with HIV (PLWH)





# Hypothesis

- ART durability is declining in the current ART treatment landscape in a multisite cohort
- ART effectiveness is increasing



# Methods

- Retrospective study of the CNICS (CFAR Network of Integrated Clinical Systems) cohort including 8 Center for AIDS Research (CFARs) sites:
  - University of Alabama at Birmingham; University of Washington; University of California, San Francisco; University of California, San Diego; Case Western Reserve University; University of North Carolina, Chapel Hill; Johns Hopkins University; and Fenway Health/Harvard University
- Treatment-naïve PLWH ( $\geq 18$  years of age) initiating ART ( $\geq 3$  drugs) for at least 14 days between January 1, 2007 and December 31, 2014 in the CNICS Cohort



# Methods

- Durability = time from the initiation to discontinuation/modification or death, whichever came first
- “Discontinue/Modify” included changes in any of the  $\geq$  3ART components for any reason
  - multitablet  $\rightarrow$  fixed dose combination not considered modification
- Cox Proportional Hazards measured associations with various socio-demographic and clinical characteristics
  - age, race, sex, transmission risk factor (MSM, IVDU, heterosexuality), CD4 count, VL, initiation era, and class of ART regimen



# Results

- 5,373 participants met study inclusion
- Median durability of all ART regimens = 49 months (95% CI: 45, 51)





# Treatment naïve PLWH initiating care in the CNICS Cohort, 2007 - 2015

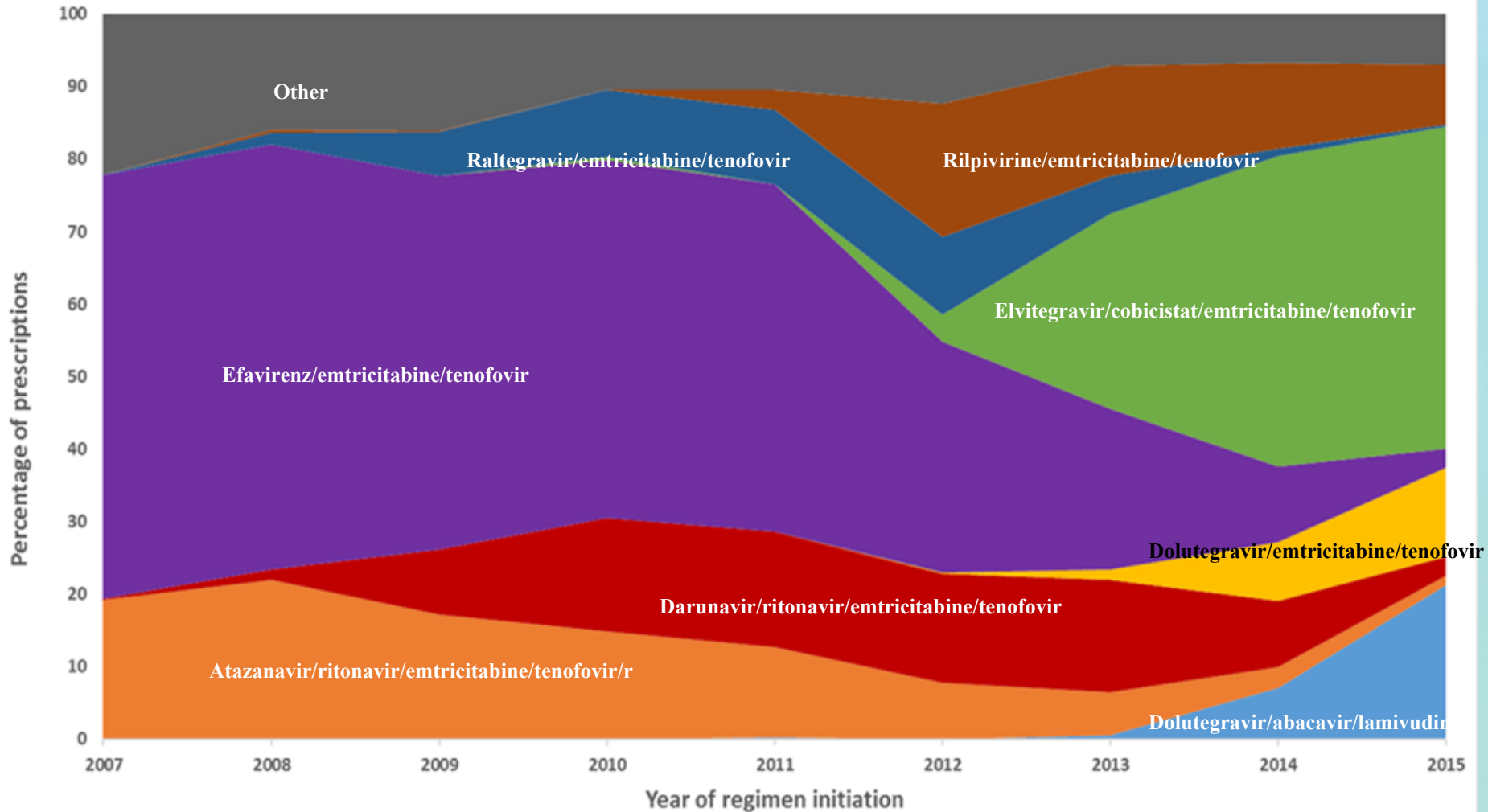
| Characteristic                                    | Total=5373 | Modified=2285 | Continued=3088 |
|---------------------------------------------------|------------|---------------|----------------|
|                                                   | N (%)      | N (%)         | N (%)          |
| <b>Age (years)</b>                                |            |               |                |
| <30                                               | 1468 (27)  | 596 (26)      | 872 (28)       |
| 30-45                                             | 2511 (47)  | 1049 (46)     | 1462 (47)      |
| <b>Race</b>                                       |            |               |                |
| White                                             | 2638 (49)  | 1098 (48)     | 1540 (50)      |
| Black                                             | 2015 (38)  | 911 (40)      | 1104 (36)      |
| <b>Sex</b>                                        |            |               |                |
| Male                                              | 4546 (85)  | 1841 (81)     | 2705 (88)      |
| <b>Insurance</b>                                  |            |               |                |
| Private                                           | 663 (12)   | 248 (11)      | 415 (13)       |
| Public                                            | 997 (19)   | 451 (20)      | 546 (18)       |
| Uninsured                                         | 1336 (25)  | 495 (21)      | 841 (27)       |
| <b>Transmission Mode</b>                          |            |               |                |
| MSM/Homosexual                                    | 3463 (64)  | 1380 (60)     | 2083 (67)      |
| Heterosexual                                      | 1160 (22)  | 540 (24)      | 620 (20)       |
| <b>CD4 cell count* (mm<sup>3</sup>), baseline</b> |            |               |                |
| ≥200                                              | 3804 (71)  | 1507 (66)     | 2297 (75)      |
| <b>Initiation Era (Year)</b>                      |            |               |                |
| 2007-2009                                         | 1882 (35)  | 1003 (44)     | 879 (28)       |
| 2010-2012                                         | 2135 (40)  | 938 (41)      | 1197 (39)      |
| 2013-2015                                         | 1356 (25)  | 344 (15)      | 1012 (33)      |
| <b>Drug class</b>                                 |            |               |                |
| InSTI                                             | 1110 (21)  | 279 (12)      | 831 (27)       |
| NNRTI                                             | 2637 (49)  | 1079 (47)     | 1558 (50)      |
| PI                                                | 1547 (29)  | 875 (39)      | 672 (22)       |

Patients in whom initial regimen was discontinued/modified or those who died while on the initial regimen were grouped as “Modified” while patients who remained on the initial regimen during the study period were grouped as “Continued.”

\*Missing data: Modified=6, Continued=12.



## Prescribing patterns for treatment naïve PLWH in the CNICS cohort initiating ART 2007-2015





## Summary of median durability of ART regimen by regimen class, composition, and year of initiation

| Class of ART backbone                           | Treatment share<br>N (%) | Median durability,<br>months (95% CI) |
|-------------------------------------------------|--------------------------|---------------------------------------|
| Integrase Inhibitor                             | 1110 (21)                | 44 (40, 57)                           |
| Integrase Inhibitor/Protease Inhibitor          | 76 (1)                   | 18 (10, 24)                           |
| Non-nucleoside reverse transcriptase inhibitor  | 2637 (49)                | 61 (56, 65)                           |
| Protease Inhibitor                              | 1547 (29)                | 32 (29, 35)                           |
| ART regimen composition                         | Treatment share<br>N (%) | Median durability,<br>months (95% CI) |
| Dolutegravir/abacavir/lamivudine                | 106 (2)                  | 9 <sup>‡</sup> , *                    |
| Atazanavir/ritonavir/emtricitabine/tenofovir/r  | 665 (12)                 | 36 (31,42)                            |
| Darunavir/ritonavir/emtricitabine/tenofovir     | 546(10)                  | 41 (36, 47)                           |
| Dolutegravir/emtricitabine/tenofovir            | 89 (2)                   | 8 <sup>‡</sup> ,                      |
| Efavirenz/emtricitabine/tenofovir               | 2173 (40)                | 62 (56,65)                            |
| Elvitegravir/cobicistat/emtricitabine/tenofovir | 571 (11)                 | 33 <sup>‡</sup> , *                   |
| Raltegravir/emtricitabine/tenofovir             | 286 (5)                  | 43 (36,57)                            |
| Rilpivirine/emtricitabine/tenofovir             | 336 (6)                  | 70 (47, *)                            |
| Other                                           | 601 (11)                 | 18 (15,22)                            |
| Year of ART regimen initiation                  | Treatment Share<br>N (%) | Median durability,<br>months (95% CI) |
| 2007-2009                                       | 1882 (35)                | 56 (51,61)                            |
| 2010-2012                                       | 2135 (40)                | 44 (42,47)                            |
| 2013-2015                                       | 1356 (25 )               | 12 <sup>‡</sup> ,                     |

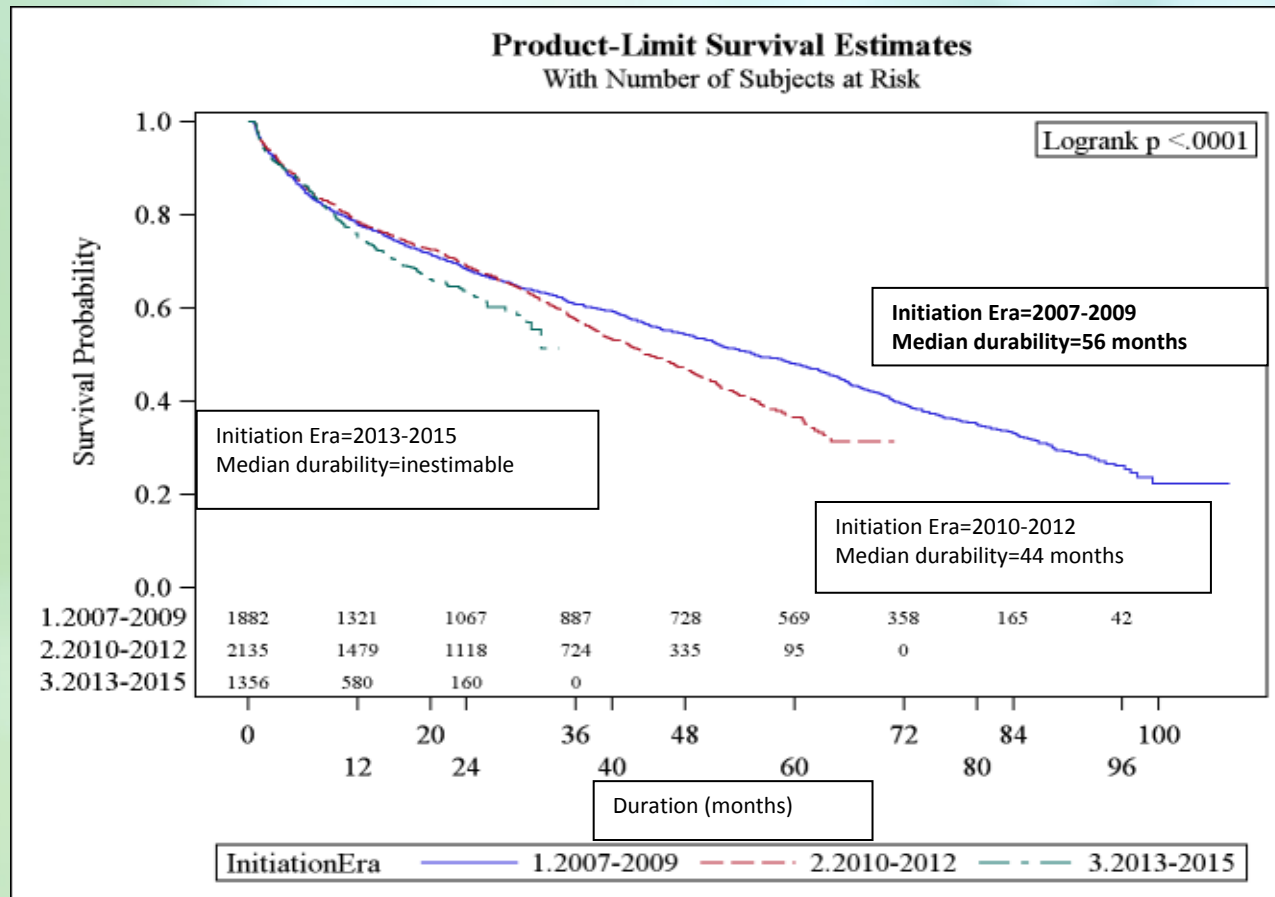
Median durability calculated using Kaplan-Meier survival curves

<sup>‡</sup> Point estimate not estimable thus 25<sup>th</sup> and 75<sup>th</sup> percentile is shown

\* Not estimable

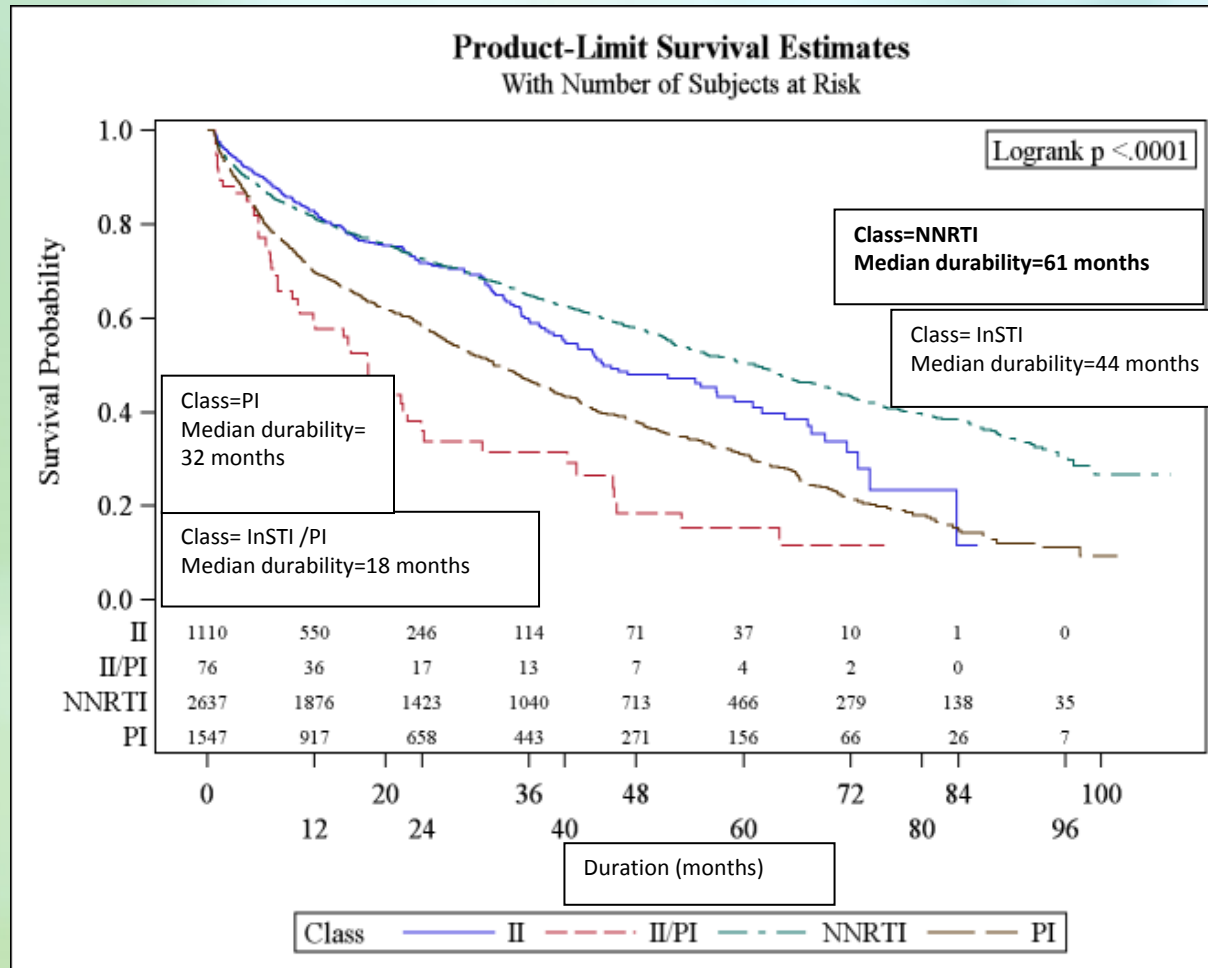


- Significantly greater ART durability for men, whites, ages 30-45, those **initiating in an earlier era**, and those initiating an NNRTI-based regimen





- Significantly greater ART durability for men, whites, ages 30-45, those initiating in an earlier era, and those **initiating an NNRTI-based regimen**







| Unadjusted and adjusted hazard ratios for initial regimen modification for treatment naïve PLWH |                                  |                  |                                |                  |                                |                  |
|-------------------------------------------------------------------------------------------------|----------------------------------|------------------|--------------------------------|------------------|--------------------------------|------------------|
| Characteristic                                                                                  | Univariate analysis              |                  | Multivariate analysis          |                  | Multivariate analysis          |                  |
|                                                                                                 |                                  |                  | Model 1                        |                  | Model 2                        |                  |
|                                                                                                 | Unadjusted Hazard Ratio (95% CI) | P-value          | Adjusted Hazard Ratio (95% CI) | P-value          | Adjusted Hazard Ratio (95% CI) | P-value          |
| <b>Age (yrs)</b>                                                                                |                                  |                  |                                |                  |                                |                  |
| <30*                                                                                            | 1.0                              |                  | 1.0                            |                  | 1.0                            |                  |
| 30-45                                                                                           | 0.9 (0.8, 1.0)                   | 0.01             | <b>0.8 (0.7, 0.9)</b>          | <b>&lt;0.001</b> | <b>0.8 (0.7, 0.9)</b>          | <b>&lt;0.001</b> |
| >45                                                                                             | 1.0 (0.9, 1.2)                   | 0.52             | 0.9 (0.8, 1.0)                 | 0.12             | 0.9 (0.8, 1.0)                 | 0.01             |
| <b>Race</b>                                                                                     |                                  |                  |                                |                  |                                |                  |
| White*                                                                                          | 1.0                              |                  | 1.0                            |                  | 1.0                            |                  |
| Black                                                                                           | <b>1.2 (1.1, 1.3)</b>            | <b>&lt;0.001</b> | <b>1.1 (1.0, 1.2)</b>          | <b>0.05</b>      | 1.0 (0.9, 1.1)                 | 0.53             |
| Other                                                                                           | 0.9 (0.8, 1.0)                   | 0.19             | 0.9 (0.8, 1.0)                 | 0.19             | 0.9 (0.8, 1.0)                 | 0.09             |
| <b>Sex</b>                                                                                      |                                  |                  |                                |                  |                                |                  |
| Male*                                                                                           | 1.0                              |                  | 1.0                            |                  | 1.0                            |                  |
| Female                                                                                          | <b>1.5 (1.3, 1.7)</b>            | <b>&lt;0.001</b> | <b>1.4 (1.2, 1.6)</b>          | <b>&lt;0.001</b> | <b>1.4 (1.2, 1.6)</b>          | <b>&lt;0.001</b> |
| <b>Insurance</b>                                                                                |                                  |                  |                                |                  |                                |                  |
| Uninsured                                                                                       | 1.0                              |                  | --                             | --               | --                             | --               |
| Private                                                                                         | 0.9 (0.8, 1.0)                   | 0.16             | --                             | --               | --                             | --               |
| Public                                                                                          | <b>1.2 (1.1, 1.4)</b>            | <b>0.004</b>     | --                             | --               | --                             | --               |
| Unknown                                                                                         | <b>1.2 (1.1, 1.3)</b>            | <b>0.002</b>     | --                             | --               | --                             | --               |
| <b>Transmission Mode</b>                                                                        |                                  |                  |                                |                  |                                |                  |
| Homosexual*                                                                                     | 1.0                              |                  | 1.0                            |                  | 1.0                            |                  |
| Heterosexual                                                                                    | <b>1.2 (1.1, 1.3)</b>            | <b>&lt;0.001</b> | 1.0 (0.8, 1.1)                 | 0.59             | 1.0 (0.9, 1.1)                 | 0.67             |
| IVDU                                                                                            | <b>1.9 (1.6, 2.2)</b>            | <b>&lt;0.001</b> | <b>1.6 (1.3, 1.9)</b>          | <b>&lt;0.001</b> | <b>1.5 (1.3, 1.8)</b>          | <b>&lt;0.001</b> |
| Other                                                                                           | <b>1.2 (1.1, 1.4)</b>            | <b>0.01</b>      | 1.1 (0.9, 1.3)                 | 0.32             | 1.1 (0.9, 1.3)                 | 0.21             |
| <b>CD4 cell count</b>                                                                           |                                  |                  |                                |                  |                                |                  |
| ≥ 200                                                                                           | 1.0                              |                  | 1.0                            |                  | 1.0                            |                  |
| <200                                                                                            | <b>1.3 (1.1, 1.3)</b>            | <b>&lt;0.001</b> | <b>1.2 (1.1, 1.3)</b>          | <b>&lt;0.001</b> | <b>1.2 (1.1, 1.3)</b>          | <b>&lt;0.01</b>  |
| Unknown                                                                                         | 0.8 (0.4, 1.8)                   | 0.64             | 0.8 (0.4, 1.9)                 | 0.65             | 0.9 (0.4, 1.9)                 | 0.70             |
| <b>Viral Load (copies/m<sup>3</sup>)</b>                                                        |                                  |                  |                                |                  |                                |                  |
| ≥10,000                                                                                         | 1.0                              |                  | 1.0                            |                  | 1.0                            |                  |
| <10,000                                                                                         | 1.0 (0.9, 1.1)                   | 0.84             | 1.0 (0.9, 1.1)                 | 0.68             | 1.0 (0.9, 1.1)                 | 0.47             |
| <b>Initiation Era</b>                                                                           |                                  |                  |                                |                  |                                |                  |
| 2007-2009*                                                                                      | 1.0                              |                  | 1.0                            |                  | 1.0                            |                  |
| 2010-2012                                                                                       | <b>1.2 (1.1, 1.3)</b>            | <b>&lt;0.001</b> | <b>1.2 (1.1, 1.3)</b>          | <b>&lt;0.001</b> | <b>1.3 (1.2, 1.6)</b>          | <b>&lt;0.001</b> |
| 2013-2015                                                                                       | <b>1.3 (1.1, 1.5)</b>            | <b>&lt;0.001</b> | <b>1.5 (1.3, 1.8)</b>          | <b>&lt;0.001</b> | <b>2.6 (2.0, 3.0)</b>          | <b>&lt;0.001</b> |
| <b>Class</b>                                                                                    |                                  |                  |                                |                  |                                |                  |
| InSTI *                                                                                         | 1.0                              |                  | 1.0                            |                  | --                             | --               |
| InSTI /PI                                                                                       | <b>2.5 (1.8, 3.4)</b>            | <b>&lt;0.001</b> | <b>2.7 (2.0, 3.7)</b>          | <b>&lt;0.001</b> | --                             | --               |
| NNRTI                                                                                           | 0.9 (0.8, 1.0)                   | 0.21             | 1.1 (1.0, 1.3)                 | 0.16             | --                             | --               |
| PI                                                                                              | <b>1.6 (1.4, 1.8)</b>            | <b>&lt;0.001</b> | <b>1.9 (1.6, 2.2)</b>          | <b>&lt;0.001</b> | --                             | --               |



- Relative to elvitegravir/cobicistat/emtricitabine/tenofovir, all regimens more likely to be discontinued

| Regimen                                         | Univariate Analysis              |                  | Multivariate Analysis Model 1  |         | Multivariate Analysis Model 2  |                  |
|-------------------------------------------------|----------------------------------|------------------|--------------------------------|---------|--------------------------------|------------------|
|                                                 | Unadjusted Hazard Ratio (95% CI) | P-value          | Adjusted Hazard Ratio (95% CI) | P-value | Adjusted Hazard Ratio (95% CI) | P-value          |
| Dolutegravir/abacavir/lamivudine                | 1.4 (0.8, 2.7)                   | 0.26             | --                             | --      | 1.5 (0.8, 2.8)                 | 0.24             |
| Atazanavir/ritonavir/emtricitabine/tenofovir    | <b>2.6 (2.0, 3.3)</b>            | <b>&lt;0.001</b> | --                             | --      | <b>5.1 (3.8, 6.7)</b>          | <b>&lt;0.001</b> |
| Darunavir/ritonavir/emtricitabine/tenofovir     | <b>2.4 (1.8, 3.1)</b>            | <b>&lt;0.001</b> | --                             | --      | <b>4.0 (3.0, 5.3)</b>          | <b>&lt;0.001</b> |
| Dolutegravir/emtricitabine/tenofovir            | <b>2.7 (1.6, 4.4)</b>            | <b>&lt;0.001</b> | --                             | --      | <b>2.6 (1.6, 4.3)</b>          | <b>&lt;0.001</b> |
| Efavirenz/emtricitabine/tenofovir               | <b>1.6 (1.3, 2.1)</b>            | <b>&lt;0.001</b> | --                             | --      | <b>3.3 (2.5, 4.4)</b>          | <b>&lt;0.001</b> |
| Elvitegravir/cobicistat/emtricitabine/tenofovir | <b>1.0</b>                       |                  | --                             | --      | <b>1.0</b>                     |                  |
| Raltegravir/emtricitabine/tenofovir             | <b>2.2 (1.6, 2.9)</b>            | <b>&lt;0.001</b> | --                             | --      | <b>3.9 (2.9, 5.4)</b>          | <b>&lt;0.001</b> |
| Rilpivirine/emtricitabine/tenofovir             | <b>1.2 (0.9, 1.7)</b>            | <b>0.22</b>      | --                             | --      | <b>1.7 (1.2, 2.3)</b>          | <b>&lt;0.01</b>  |
| Other                                           | <b>4.2 (3.3, 5.4)</b>            | <b>&lt;0.001</b> | --                             | --      | <b>8.0 (6.1, 10.7)</b>         | <b>&lt;0.001</b> |



# Effectiveness

- 49% of participants had VL collected at time of regimen discontinuation
- Of them, only 14% had VL $\geq$ 200 copies/mL (viral failure)

| Class                                                  | N (%)    |
|--------------------------------------------------------|----------|
| NNRTI                                                  | 60 (51)  |
| PI                                                     | 53 (35)  |
| InSTI                                                  | 35 (10)  |
| InSTI/PI                                               | 3 (3)    |
| <b>Regimens</b>                                        |          |
| Rilpivirine,Dolutegravir,<br>Raltegravir, Elvitegravir | (<10%)   |
| Atazanavir                                             | 21 (15)  |
| Efavirenz                                              | 46 (43)  |
| Other                                                  | 17 (21)  |
| <b>Initiation Era</b>                                  |          |
| 2007-2009                                              | 172 (44) |
| 2010-2012                                              | 252 (33) |
| 2013-2015                                              | 275 (18) |



# Limitations

- Lack of data on reasons for regimen modification
  - side effects, toxicity, and/or desire for more convenient dosing (ie. single tablet regimen)
  - Missing data on VL at time of discontinuation for many
- Small number and short follow up time for PLWH receiving most novel regimens (ie. dolutegravir/abacavir/lamivudine) make it difficult to interpret durability at the regimen level
- We did not analyze the ART regimen that participants were switched to which would allow understanding of switches for convenience, simplicity



# Conclusions

- New classes and ART agents are highly durable
- The adoption of these novel regimens has contributed to a reduction in durability and increase in regimen modifications over time
- There has been a dramatic temporal reduction in virologic failure
- The availability of simple, well tolerated ART has resulted in treatment changes for convenience and side effects, rather than virologic failure
  - paradoxically resulting in less durable regimens in more recent years
- Minorities, youth, women and IVDU have worse ART durability outcomes, which *may suggest* ongoing disparities in ART therapy and deserves further evaluation





# Acknowledgements

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  - Michael Mugavero, MD
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