AETC AIDS Education & Training Center Program Southeast

Immediate Antiretroviral Therapy Initiation

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OBJECTIVES

- **To Understand the reasoning to Implement Immediate ART Initiation for newly diagnosed HIV infected persons.**

- **Review data on the Implementation of Immediate ART Initiation.**

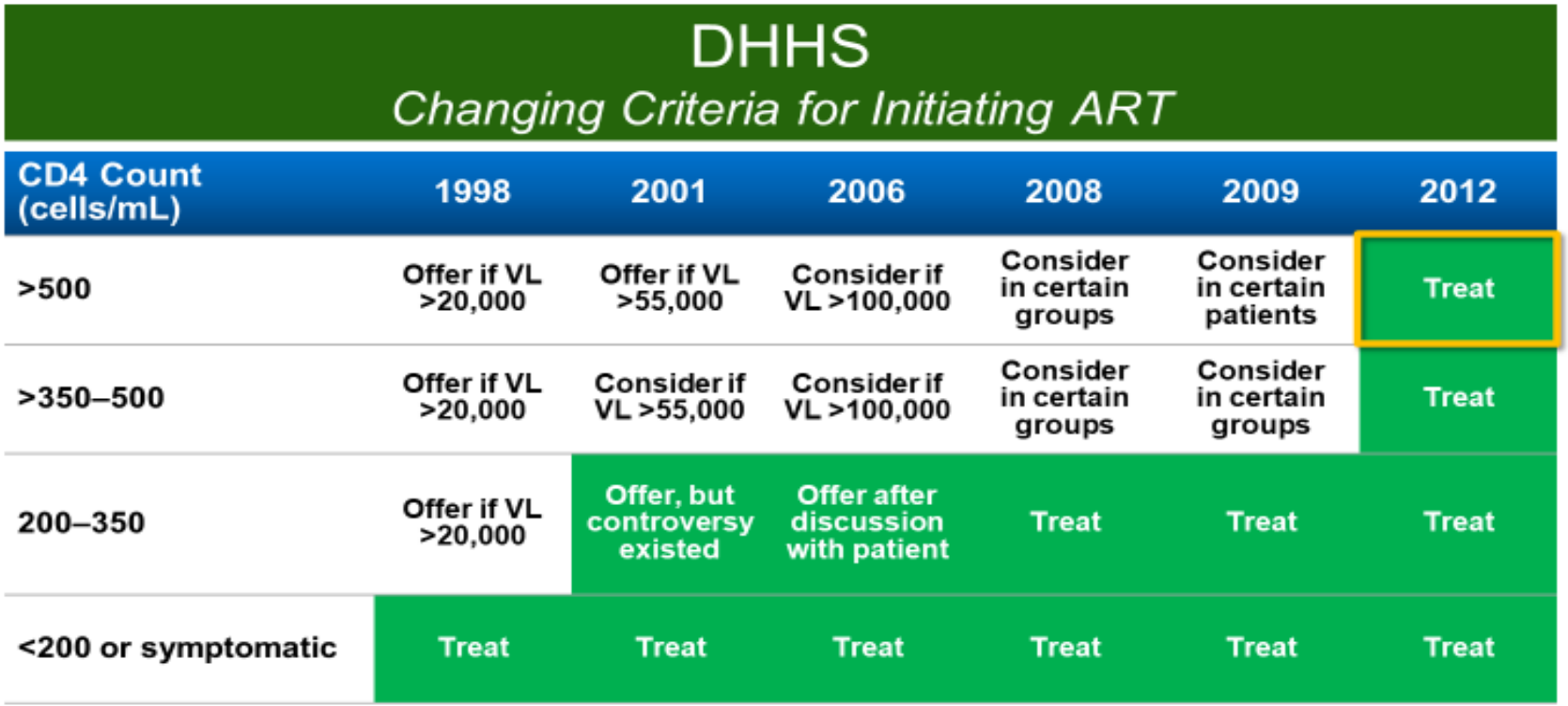
- **Review the Implementation of Immediate ART Initiation in Miami**

- **Discuss potential barriers to the implementation of Immediate ART Initiation**

Definition

- ART initiation at the time of diagnosis or as soon as possible
  - ART be prescribed on the same day of the confirmed diagnosis or at their initial clinic visit, even if all baseline laboratory test results haven't returned

DHHS
Changing Criteria for Initiating ART



DHHS
Changing Criteria for Initiating ART

CD4 Count (cells/mL)	1998	2001	2006	2008	2009	2012
>500	Offer if VL >20,000	Offer if VL >55,000	Consider if VL >100,000	Consider in certain groups	Consider in certain patients	Treat
>350–500	Offer if VL >20,000	Consider if VL >55,000	Consider if VL >100,000	Consider in certain groups	Consider in certain groups	Treat
200–350	Offer if VL >20,000	Offer, but controversy existed	Offer after discussion with patient	Treat	Treat	Treat
<200 or symptomatic	Treat	Treat	Treat	Treat	Treat	Treat

VL, viral load.
DHHS. Guidelines for Use of Antiretroviral Agents in HIV-1–Infected Adults and Adolescents. 2017. Last updated May 30, 2018. https://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed May 31, 2018.

When to Start ARV

When to Start Therapy

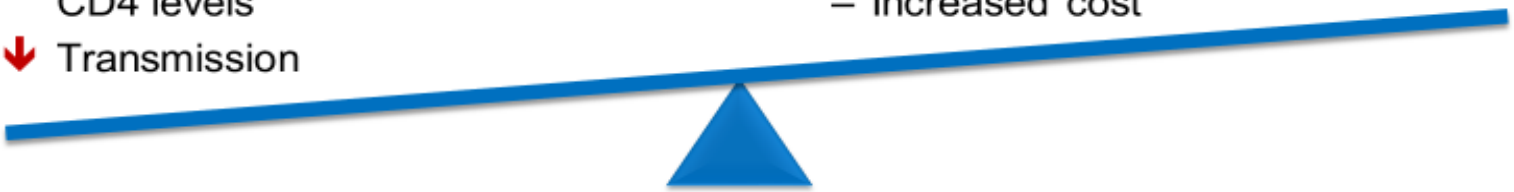
Balance Now Favors Earlier ART Initiation

EARLY ART

- ↑ Potency, durability, simplicity, and safety of current regimens
- ↓ Emergence of resistance
- ↓ Toxicity with earlier therapy
- ↑ Subsequent treatment options
- ↓ Risk of uncontrolled viremia at all CD4 levels
- ↓ Transmission

DELAYED ART

- – Drug toxicity
- – Preservation of limited Rx options
- – Risk of resistance
- – Risk of transmission of resistant virus
- – Increased cost



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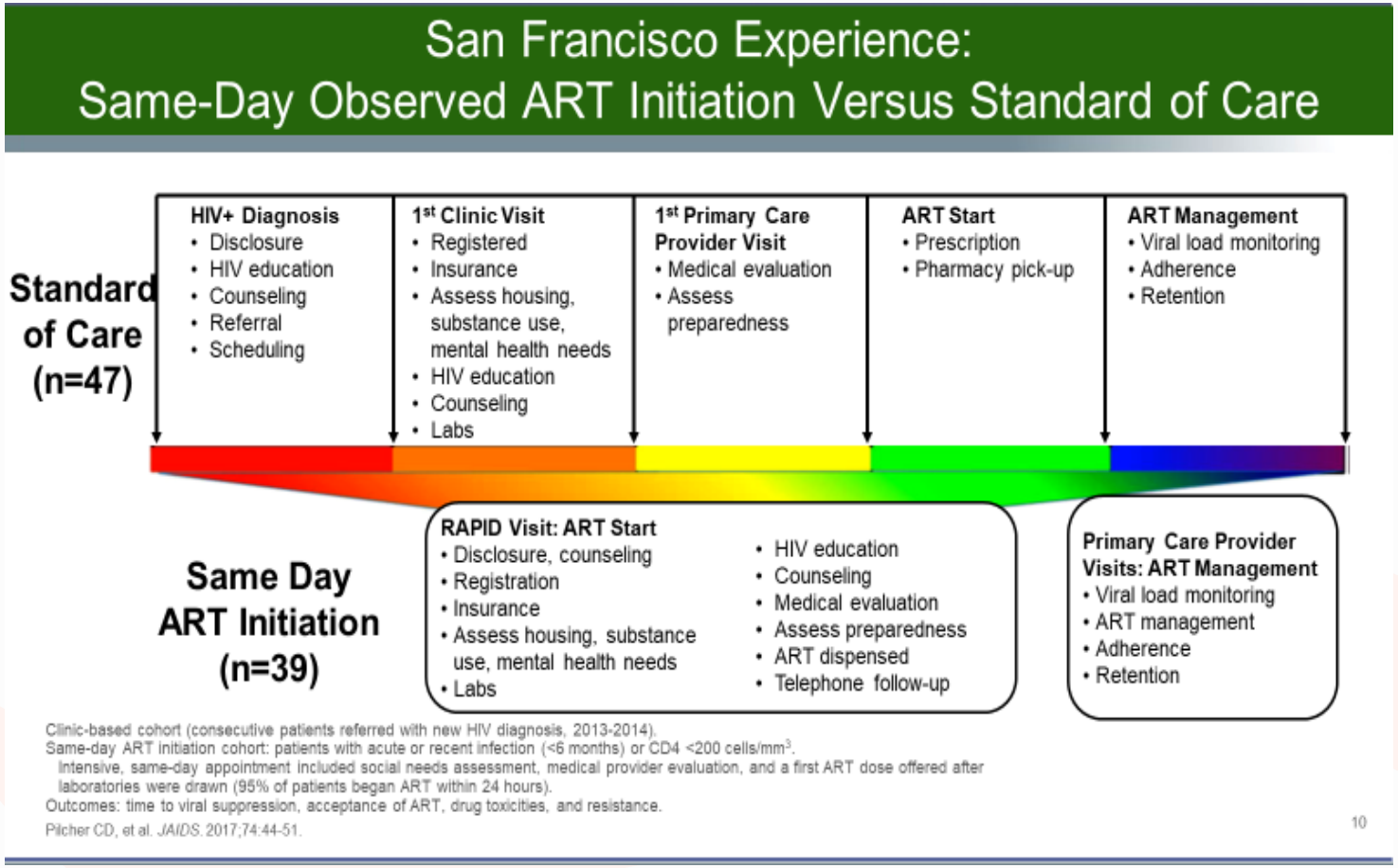
Reasons for Rapid ARV

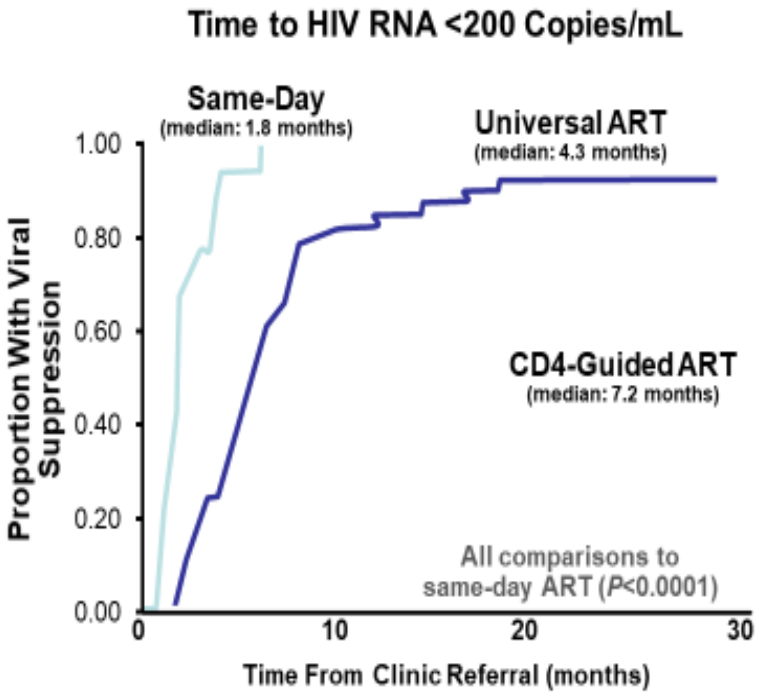
- Shifting guidelines (DHHS and WHO)
- High attrition rates between time of positive HIV test and ART initiation
- Delays in treatment are associated with
  - Increased mortality
  - Diminished CD4 recovery
  - Avoidable hospitalizations
  - Higher costs of treatment for opportunistic infections
  - HIV transmission
- Improved ART tolerability and durability
- Lower risk for viral resistance with current ART regimens

In 2013, the Ward 86 HIV Clinic at the University of California, San Francisco (UCSF) at San Francisco General Hospital (SFGH) became the first clinic in the United States to provide immediate antiretroviral therapy (ART) upon HIV diagnosis.



San Francisco Experience: Same-Day Observed ART Initiation Versus Standard of Care

- Significantly shorter time to viral suppression (P<0.0001)
  - Same-day ART versus universal ART (2010-2013) and CD4-guided ART (2006-2009)
- Similar rates of loss to follow-up
  - Same-day (10%) versus non-same-day ART (15%)
- Most same-day patients received INSTI-based regimens
  - Similar safety and tolerability with non-same day ART
  - No regimen modifications due to virologic failure
  - No cases of treatment-emergent resistance (35% had transmitted mutations, 24% with major NNRTI mutations)



Dolutegravir (69%), elvitegravir/cobicistat (18%), darunavir/r (10%), raltegravir (2%).
Pilcher CD, et al. *JAIDS*. 2017;74:44-51.

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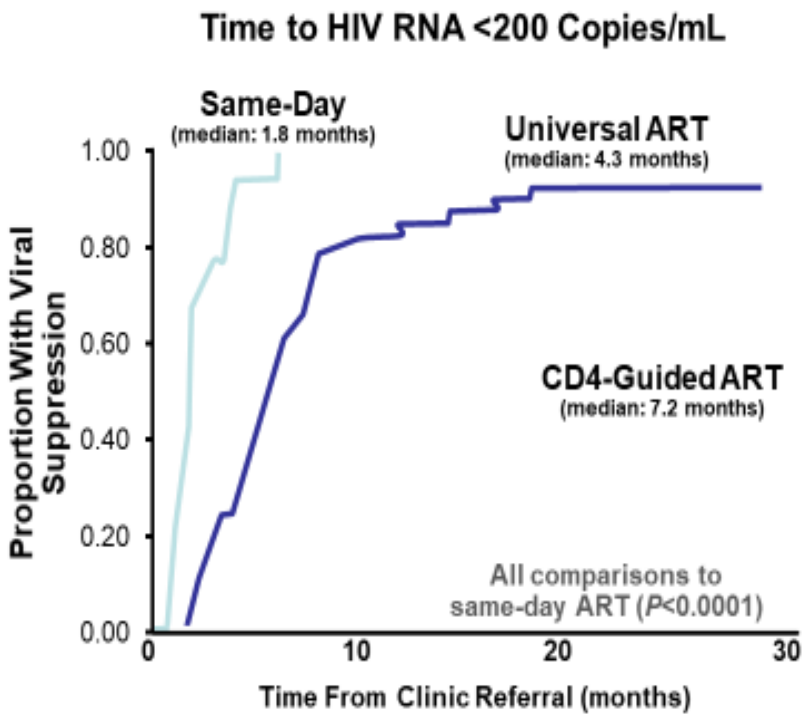

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RAPID Safety Data

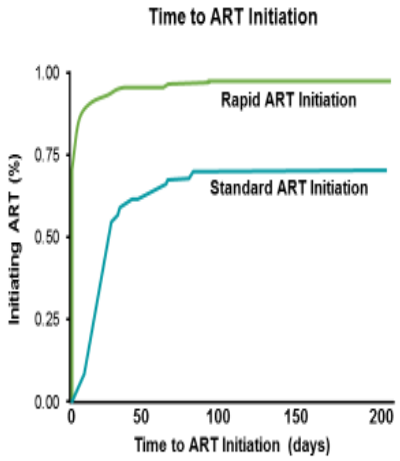
- INSTI-based regimen in 87% (NS difference between arms)
  - Most common initial regimen in RAPID: DTG + TDF/FTC (67%)
- ART modifications more frequent among RAPID arm
  - 2 ART changes due to rash
  - 10 ART changes for simplification
  - **No changes for VF**
  - **No changes based on genotype results**
- Transmitted drug resistance (n=75 with genotype results)
  - 82% in RAPID vs 92% in non-RAPID obtained genotype results (NS)
    - Of those with a mutation, 35% with any major resistance mutation
    - Of those with a mutation, 24% with NNRTI resistance mutation

3TC, lamivudine; ABC, abacavir; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor (integrase inhibitor); NNRTI, nonnucleoside/tide reverse transcriptase inhibitor; NS, nonsignificant; VF, virologic failure.
Pilcher CD, et al. *J Acquir Immune Defic Syndr*. 2017;74(1):44-51.

Rapid ART Randomized Trials

RapIT Trial: Initiating ART at First Clinic Visit (2013-2014)

- Randomized, controlled trial in South Africa clinics (n=377)
  - Primary care and hospital-based clinics
  - Rapid initiation: single-visit ART initiation (n=187)
  - Standard initiation: 3 to 5 clinic visits over 2 to 4 weeks before ART initiation (n=190)
  - Primary outcome: HIV RNA <400 copies/mL within 10 months
- Rapid versus standard ART initiation
  - Primary outcome (HIV RNA <400 copies/mL ≤10 months)
    - 64% versus 51% (RR 1.26 [95% CI: 1.05, 1.50])
  - Secondary outcome (ART initiation ≤90 days)
    - 97% versus 72% (RR 1.36 [95% CI: 1.24, 1.49])



ART eligible: CD4 ≤350 cells/mm³.

Rosen S, et al. *PLoS Med*. 2016;13(5):e1002015.

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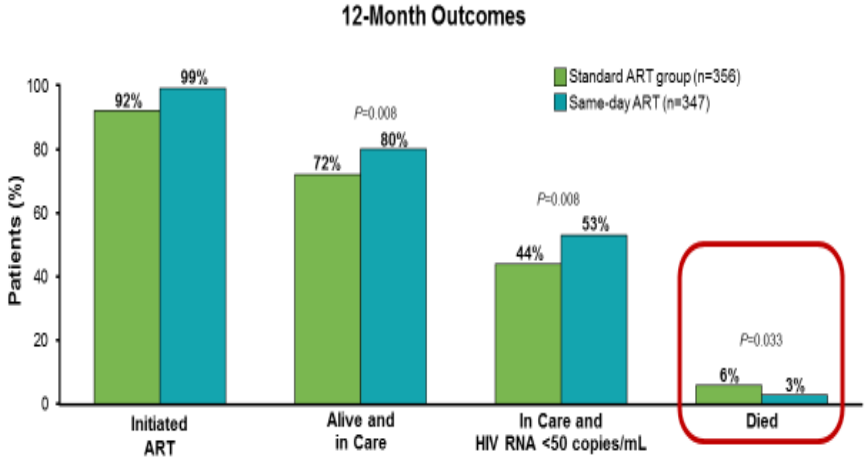
GHESKIO Centers (Haiti): Same-Day HIV Testing and ART Initiation



Baseline characteristics: female (49%), mean age (37 years), CD4 count (247-249 cells/mm³), WHO stage 1 (31%) or 2 (69%).
Lost to follow-up: standard ART group (n=80), same-day ART group (n=60).

Koenig S, et al. *PLoS Med*. 2017;14(7):e1002357.

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The study was stopped early by DSMB due to better outcomes in the same-day ART group

REACH: Atlanta Georgia

Rapid Entry and ART in Clinic for HIV

Goals

1. Facilitate provider appointment and ART access within 72 hours of patients' first presenting to clinic for enrollment[a]
2. Decrease time to viral suppression

Health System Changes to Facilitate Program Implementation

ACTION	LEVEL
Remove eligibility restrictions for clinic enrollment	**EMA Ryan White office**
Loosen administrative requirements for clinic enrollment	EMA Ryan White office; **hospital system**
Remove TB skin test as requirement for clinic enrollment	**Clinic administration**
Enhance access to *New Patient* provider visits	Hospital system; clinic administration
Enhance provider education on *Rapid Starts*	**Clinician**
Enhance support for accessing ART, regardless of payer	**Pharmacy administration**
Continue access to ongoing ART-adherence education	**Nursing**

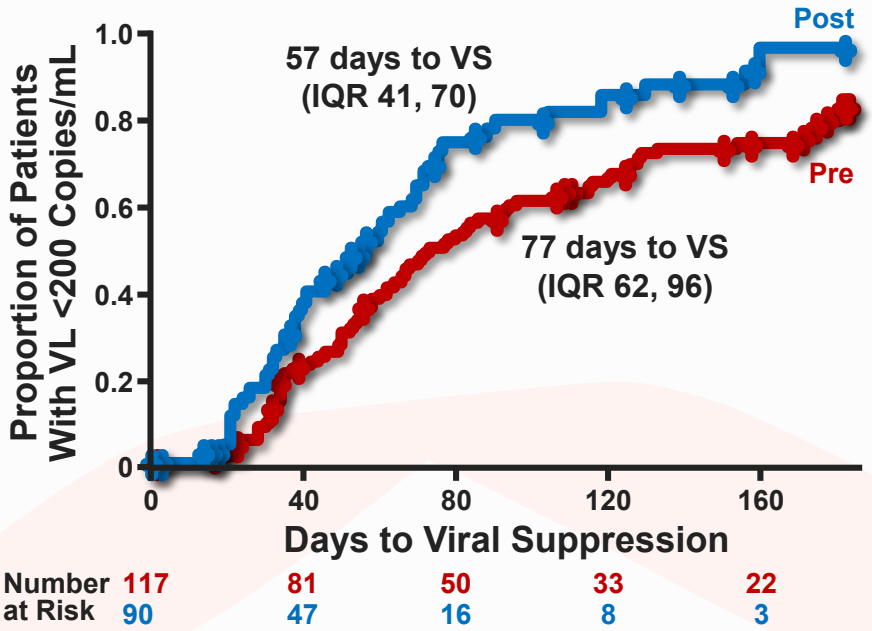
REACH: Results

Days to Clinical Events

Days to Clinical Events

	Pre-REACH N=117	Post-REACH N=90	
Event	**Mean (95% CI) *or* n(%)**	**Mean (95% CI)**	***P* value**
Days to 1st scheduled provider visit	14.0 (11.9, 16.2)	3.7 (1.1, 6.2)	<0.0001
Days to 1st attended provider visit	12.1 (6.4, 22.8)	2.1 (0.9, 4.4)	<0.0001
Days to ART start	22.0 (12.7, 38.1)	4.4 (2.3, 8.4)	<0.0001
Attended 1st scheduled visit	85 (73)	73 (81)	NS
Viral suppression	87 (74)	61 (68)	NS

Days to Viral Suppression



Evidence for Rapid ARV

- Demonstration projects from clinics in New Orleans, Los Angeles, and Atlanta have found that implementation of immediate ART programs led to earlier linkage to care and shorter time to virologic suppression than seen in historical controls

- Current guidelines from the U.S. Department of Health and Human Services and the International Antiviral Society--USA endorse ART initiation at the time of diagnosis or as soon as possible afterwards.

Rapid ARV literature: Better outcomes, such as improved ART uptake, sustained ART adherence, and decreased time to virologic suppression

Scheer S, Hsu L, Schwarcz S, Pipkin S, Havlir D, Buchbinder S, et al. Trends in the **San Francisco** Human Immunodeficiency Virus Epidemic in the "Getting to Zero" Era. Clin Infect Dis. 2018 Mar 19;66(7):1027–34.

Pilcher CD, Ospina-Norvell C, Dasgupta A, Jones D, Hartogensis W, Torres S, et al. The Effect of Same-Day Observed Initiation of Antiretroviral Therapy on HIV Viral Load and Treatment Outcomes in a US Public Health Setting. J Acquir Immune Defic Syndr. 2017 Jan 1;74(1):44–51. (**San Francisco**)

CUNY Institute for Implementation Science in Population Health. Ending the AIDS Epidemic Dashboard: New Diagnoses and Linkage [Internet]. Ending the Epidemic. 2016 [cited 2019 Mar 20]. Available from: http://etedashboardny.org/data/new-diagnoses-and-linkage/

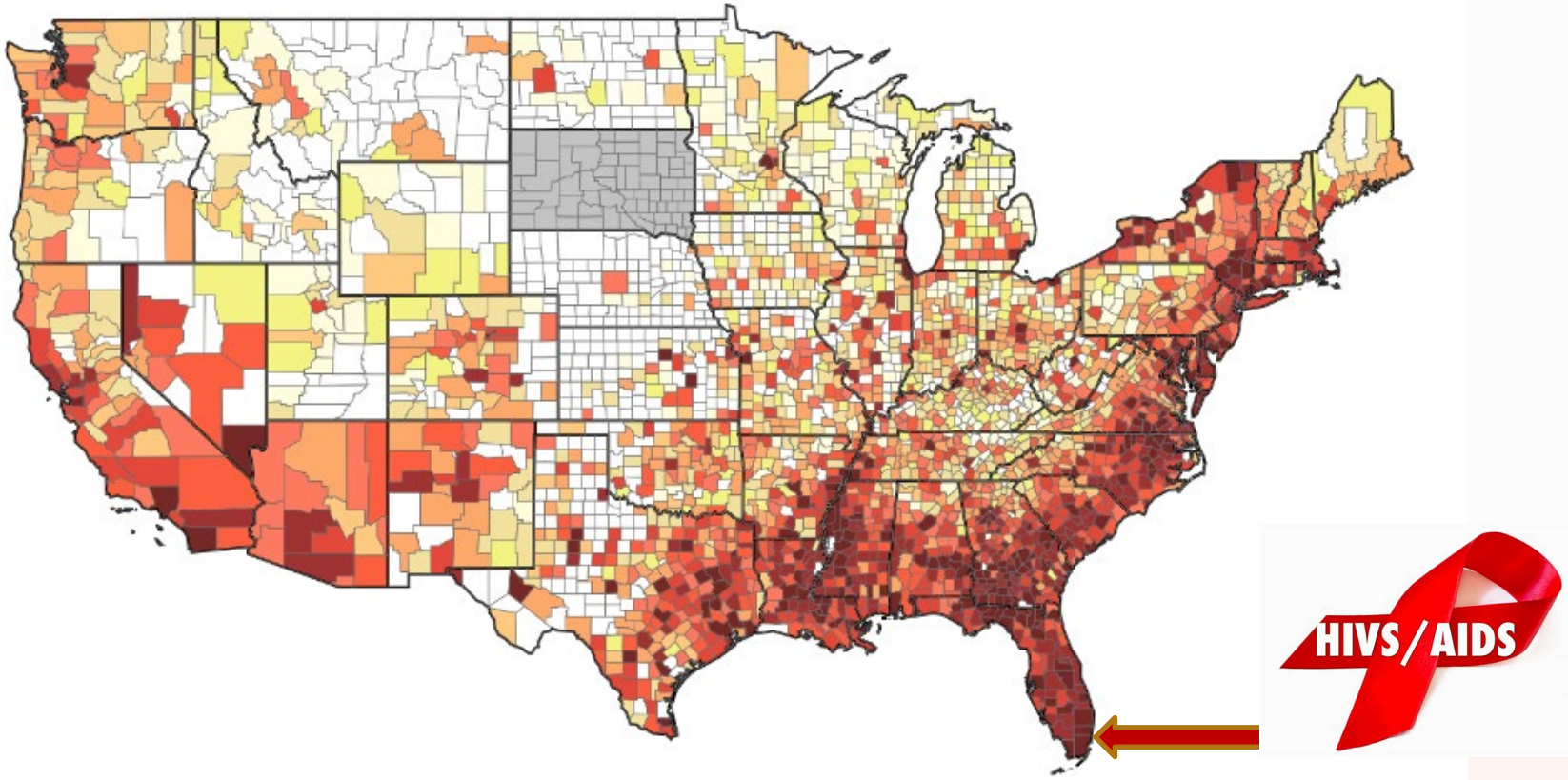
Halperin J, Butler I, Conner K, Myers L, Holm P, Bartram L, et al. Linkage and Antiretroviral Therapy Within 72 Hours at a Federally Qualified Health Center in **New Orleans**. AIDS Patient Care and STDs. 2018 Feb 1;32(2):39–41.

Colasanti J, Sumitani J, Mehta CC, Zhang Y, Nguyen ML, Del Rio C, et al. Implementation of a Rapid Entry Program Decreases Time to Viral Suppression Among Vulnerable Persons Living With HIV in the **Southern United States**. Open Forum Infect Dis. 2018 Jun;5(6):ofy104.

Ford N, Migone C, Calmy A, Kerschberger B, Kanters S, Nsanzimana S, et al. Benefits and risks of rapid initiation of antiretroviral therapy. AIDS. 2018 Jan 2;32(1):17–23**. (Across studies**)

Hoenigl M, Chaillon A, Moore DJ, Morris SR, Mehta SR, Gianella S, et al. Rapid HIV Viral Load Suppression in those Initiating Antiretroviral Therapy at First Visit after HIV Diagnosis. Sci Rep. 2016 06;6:32947. **(San Diego)**

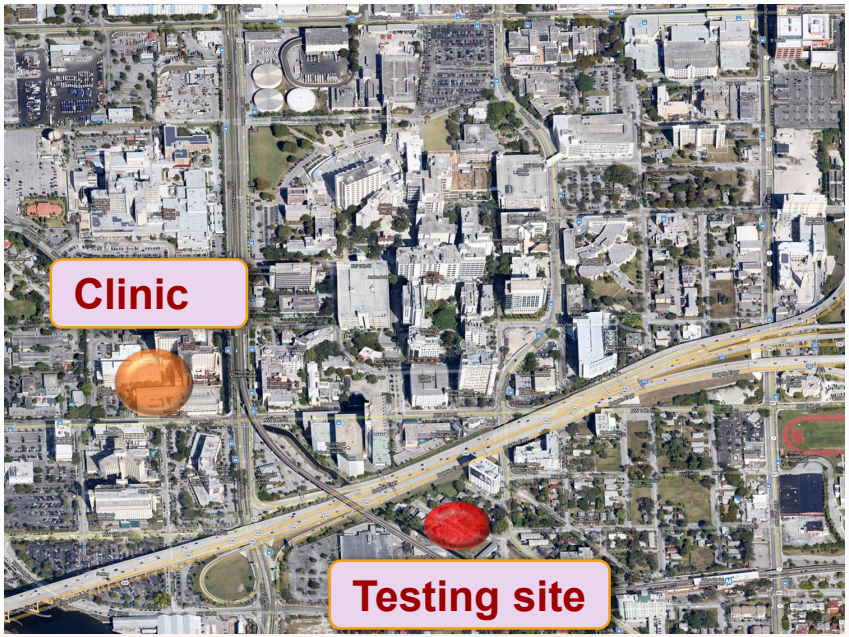
Test and Rapid Response Miami



United States HIV Prevalence 2015
Source: AIDSVu (www.aidsvu.org), Emory University, Rollins School of Public Health [accessed April 10, 2018].

Test and Rapid Response Miami- Treatment Setting
University of Miami/Jackson Memorial Hospital Medical Center/DOH

- Largest single-site HIV clinic in Florida
- 3200 HIV+ individual patients annually
- ~23% of the estimated 14,000 HIV (Miami)
- Minorities: 57.9% Black; 36.4% Hispanic
- Women: 37.6%
- Older population
  ~75% > 40
  ~50% > 50
- Interdisciplinary treatment
- Collaborations with the Miami HD

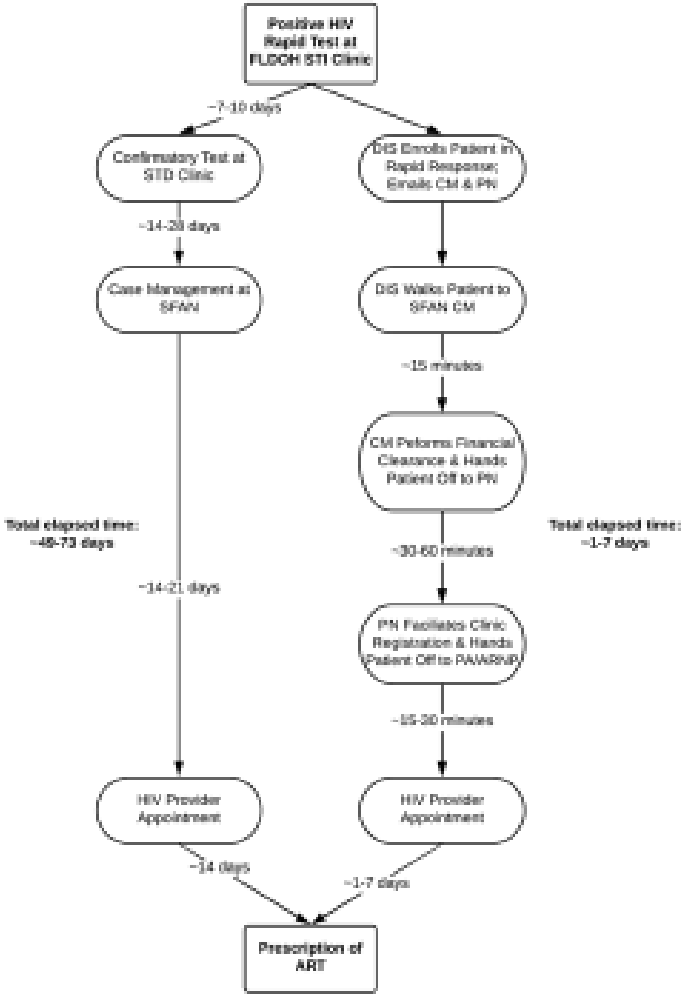


Pilot Program: Miami UM/JMMC Clinic March 2016
Statewide Guidance Issue September 2016
Miami Department of Health, testing agencies, funding agency, pharmacy, clinical settings

Traditional Linkage to Care vs. Test and Rapid Response Treatment Initiative

Time elapsed from a positive rapid HIV test to receipt of ART:

- Traditional Linkage Method: 49-73 days
- Test and Rapid Response Treatment: 1-7 days



UNIVERSITY OF MIAMI
MILLER SCHOOL of MEDICINE

Referral and Linkage Process Miami Dade

Before Rapid ARV

- Pt. tests for HIV
- Returns in 10 days for results.
- Referred to provider agency.
- Case management appointment given 2 weeks (or more) away.
- Case manager assesses for financial eligibility & ADAP; refers to Doctor; appointment given for 2 weeks (or more) away.
- Doctor orders labs, patient is scheduled for return appointment in 2 weeks.
- Doctor writes script at return appt.
- Pt. takes script to pharmacy.

Up to 3 months or more

After T&T

- Pt. tests for HIV; preliminary results positive.
- Pt accepts Test and Treat.
- Pt. is escorted to case management agency where eligibility is established.
- Pt. is seen by doctor and labs done.
- Doctor writes script.
- Medical case manager escorts Pt. to on site pharmacy to obtain 30 day supply of medication.

< 7 days (most same or next day)

Test and Rapid Response Treatment Process

- 4 organizations collaborated to contribute to patient care:
  - Florida Department of Health (FLDOH)
  - South Florida AIDS Network (SFAN)
  - Jackson Memorial Medical Center (JMMC)
  - University of Miami-Division of Infectious Diseases (UM-ID)

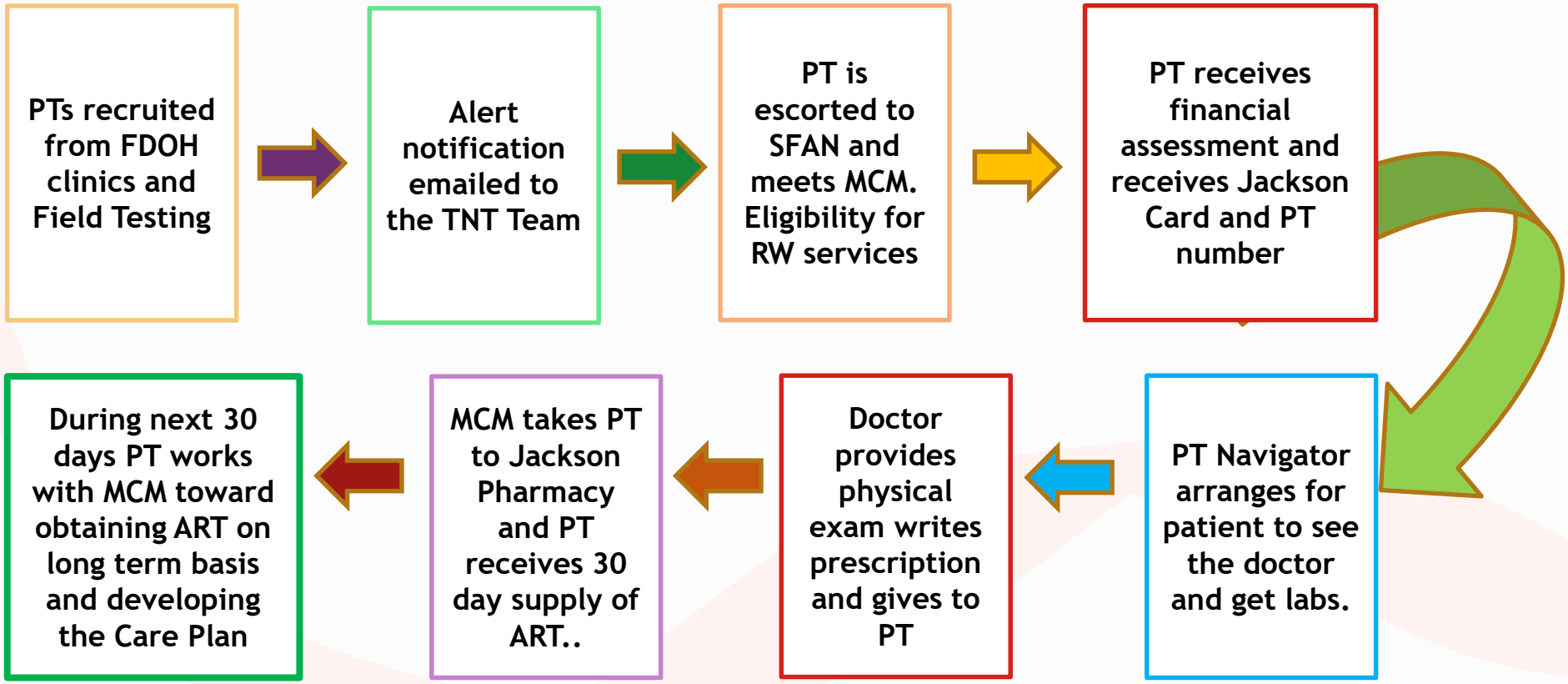
- FLDOH made funds available to provide the first 30 days of medication to the patients
  - Greatly reduced the time elapsed in the traditional linkage process

- The Ryan White Part A added a billing code to allow the first medical visit and laboratory work
  - Established immediate patient eligibility to immediately see the doctor, receive a prescription and, get baseline laboratory work.

- SFAN and UM-ID provided protected time for case management and medical staff

- JHS performed laboratory tests

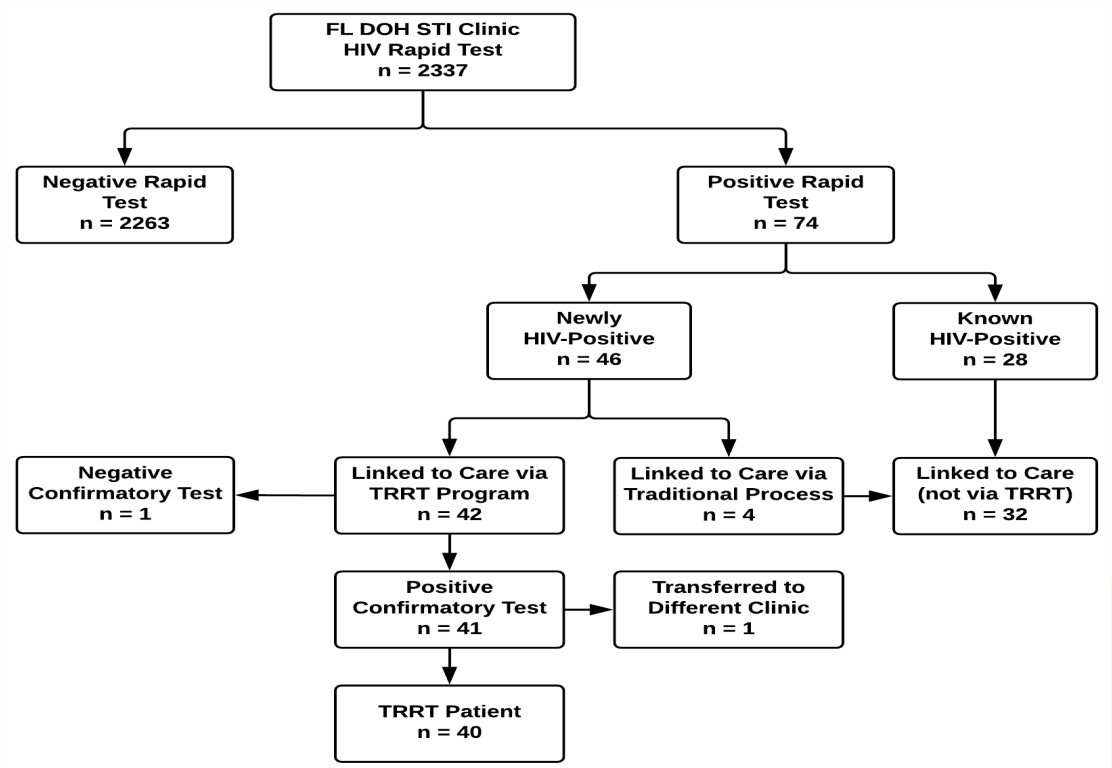
General Process



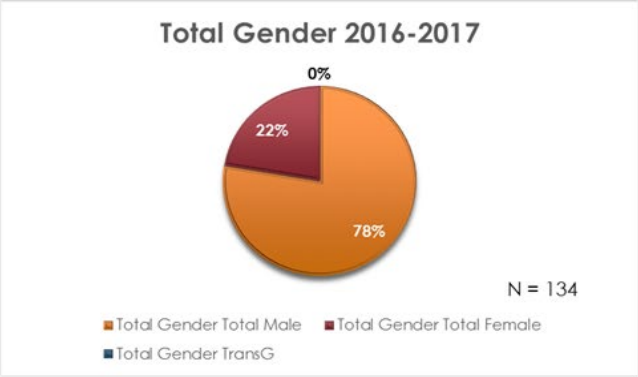
The Miami Experience

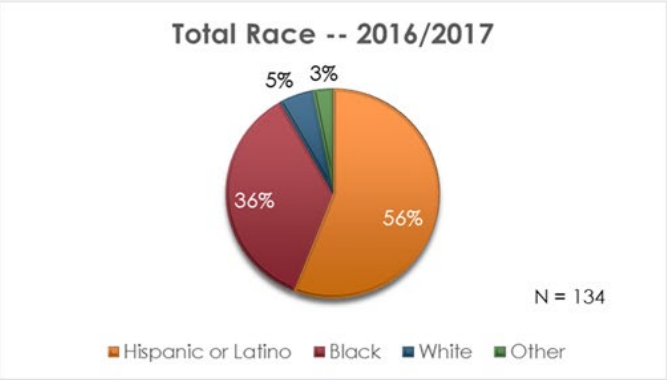
Implementation of an Immediate HIV Treatment Initiation Program in a Public/Academic Medical Center

First Year Acceptability

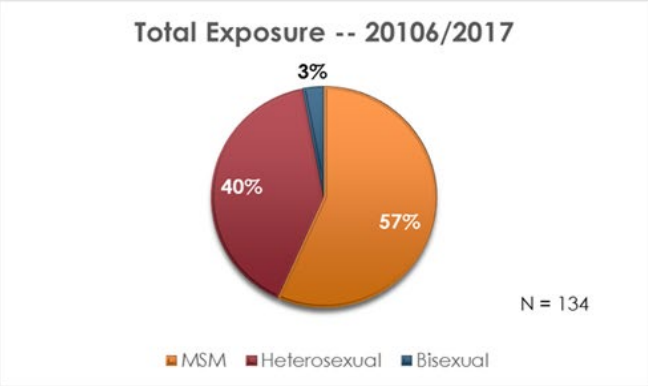


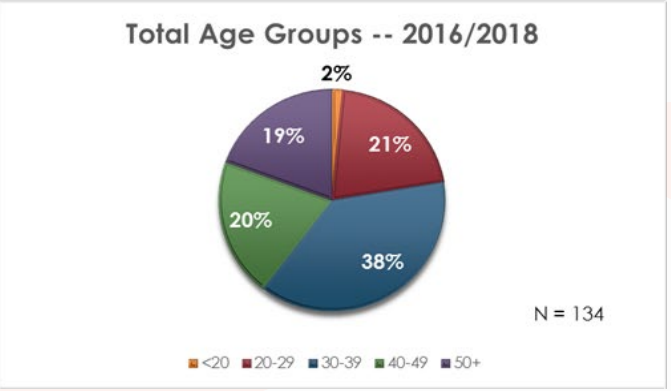
The Miami Experience
Demographics First 2 years



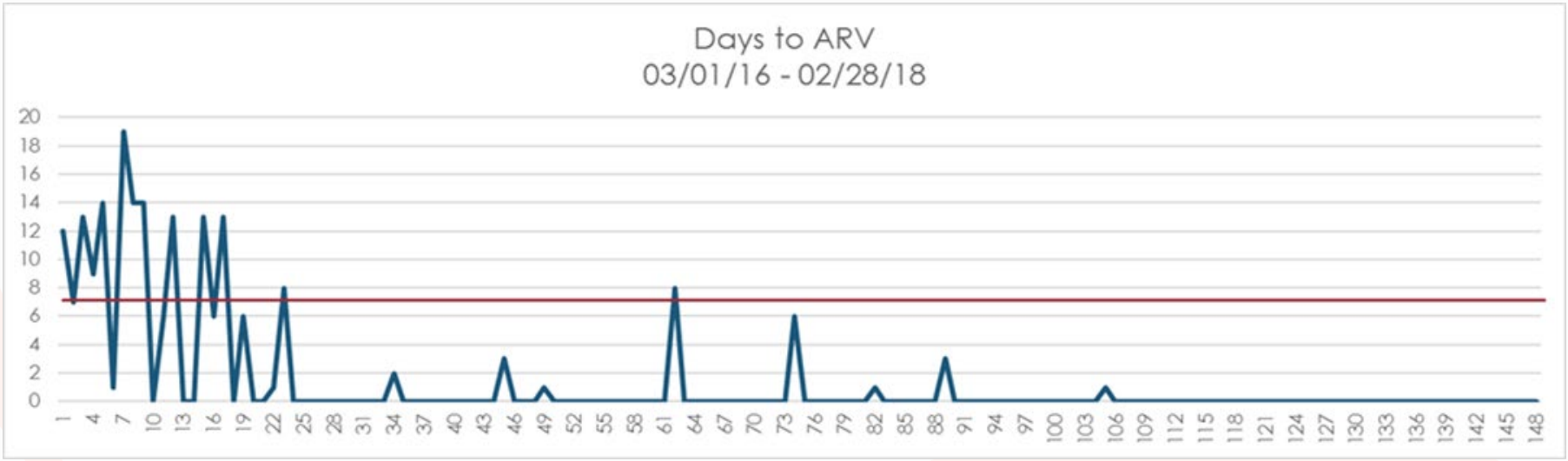


22% of the new cases had AIDS





Reduced time to ART



Improved Clinical Outcomes – 2 years

Over 90% received ART within 7 days

Virological suppression (<200 copies/mL)

92% suppressed within 70 days of testing (average 50 days)
97% suppressed within the first 12 months

97% retention

CD4 T-cell count (24% had AIDS at diagnosis)

Fast CD4 T-cell count improvement at 3 months when compared with historical data

327.77 $\pm$ 242.5 cells/mm^3 vs 597.78 $\pm$ 322.5 cells/mm^3

Increase over 1 year

Baseline = 452 cells/mm^3 12 months = 668 cells/mm^3

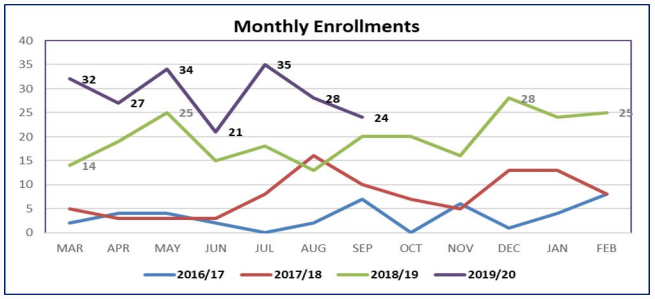
Under review

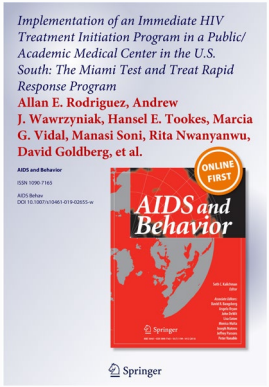
Program Implementation Highlights

- Pre planning -coordination of services among different co-located services handling initial testing, financial administration, clinic registration, navigation of the patient in the first visit, HIV provider availability, first visit clinical evaluation, next day reviews of labs and a subsequent clinic visit within two weeks.
- Our program in partnership with the Florida Department of Health did not require financial enrollment on the day of the positive HIV test
- Patient Clinic navigator's coordination of new patient care between case management, the clinic, and dispensing pharmacies allowed for the patient to transition into the existing patient flow involving sustained regular visits, labs, ART dispensation, and follow-up

The Miami Test and Treat Rapid Response Program

The Miami Test and Treat Rapid Response Program : Present: Accomplishments/Publications





- 460 patients
- 2 Navigators representing our demographics

Test Miami
Exceptional performance award
December 2018

- Rodriguez AE, Wawrzyniak AJ, Tookes H, Vidal M, Alcaide ML, Kolber MA, et al. HIV treatment initiation program in a public/academic medical center: The Miami Test and Treat Rapid Response Program Posters at UM Research Day and Miami Winter Symposium 2019
- Rodriguez AE, Wawrzyniak AJ, Tookes H, Vidal MG, Manasi SP, Nwanyanwu R, Goldberg D, Freeman R, Villamizar K, Alcaide ML, Kolber M. Implementation of an immediate HIV treatment initiation program in a public/academic medical center: The Miami test and treat rapid response program. AIDS and Behavior. In Press. doi: 10.1007/s10461-019-02655-w. October 2019, Volume 23, Supplement 3, pp 287–295
- Poschman K, Spencer EC, Goldberg D, Villamizar KA, Adams T, Beal JA. Impact of HIV test and treat initiative in antiretroviral-naive patients in Miami-Dade County, Florida. CROI; 2019; Seattle, WA.

AETC AIDS Education & Training Center Program Southeast

Immediate Initiation of Antiretroviral Therapy in the Outpatient Clinic

Management Recommendations

Optimal implementation of a rapid ART program should include:

- Efficient and reliable identification of all persons with new HIV diagnosis (for example, referral from testing sites via a single point of contact such as a dedicated pager or specific staff person).
- Activation of a "rapid" multidisciplinary team (social work, eligibility/insurance specialist clinician) that can mobilize quickly to see the patient on a same-day basis.
- Capacity to provide follow-up care within 1-2 week.

Appropriate patients to offer immediate ART include

- Individuals with confirmed new diagnoses of HIV infection.
- Persons with suspected acute HIV infection whose HIV diagnosis may not yet be confirmed (eg, the HIV antigen or antibody test results may be negative at the time of evaluation).
- Persons with positive results of rapid HIV antibody tests, before confirmatory test results are available, if the pretest probability of HIV infection is high (after counseling, immediate ART is offered with the understanding that, if confirmatory test results are negative, the patient would stop ART and start pre-exposure antiretroviral prophylaxis, if appropriate).
- Chronically infected patients who have never received ART.
- Chronically infected patients who return to care after being out of care and off ART, if they have a known wild-type virus or their viral resistance pattern is predictable (these persons may require individually-tailored regimens).

The Immediate ART Clinic Intake Visit

- Obtaining sufficient information from the history to determine whether immediate ART is indicated, whether the patient is willing to start ART, and what medications to use
- Beginning education about HIV, ART (eg, possible benefits of early ART, adherence), and preventing transmission to others
- Engaging the patient in committing to return to clinic for follow-up appointments
- Assistance with insurance enrollment or optimization

Recommended Laboratory Tests at Immediate ART Intake Visit

- Confirmatory HIV testing (if needed)
- HIV viral load
- CD4 cell count
- HIV genotype, including integrase genotype
- HLA-B*5701
- Metabolic panel (creatinine, electrolytes, glucose, liver function tests)
- Hepatitis A IgG
- Hepatitis B sAb, cAb, Ag
- HCV IgG
- STD testing: serum RPR or VDRL, chlamydia and gonorrhea NAAT
- tests (urine, pharynx, rectum, depending on sites of sexual exposure)
- Pregnancy test (if indicated)
- Consider: lipids, G6PD, toxoplasma IgG

Follow Up visit

- Phone check-in with a social worker, nurse, or clinician 2-3 days after the intake appointment
- Clinic follow-up appointment at 1-2 weeks
- At the follow-up appointment, clinicians should review baseline laboratory results with the patient, evaluate ART adherence, screen for side effects, and provide further counseling and education

Recommended Immediate ART Regimens for Naïve Patients

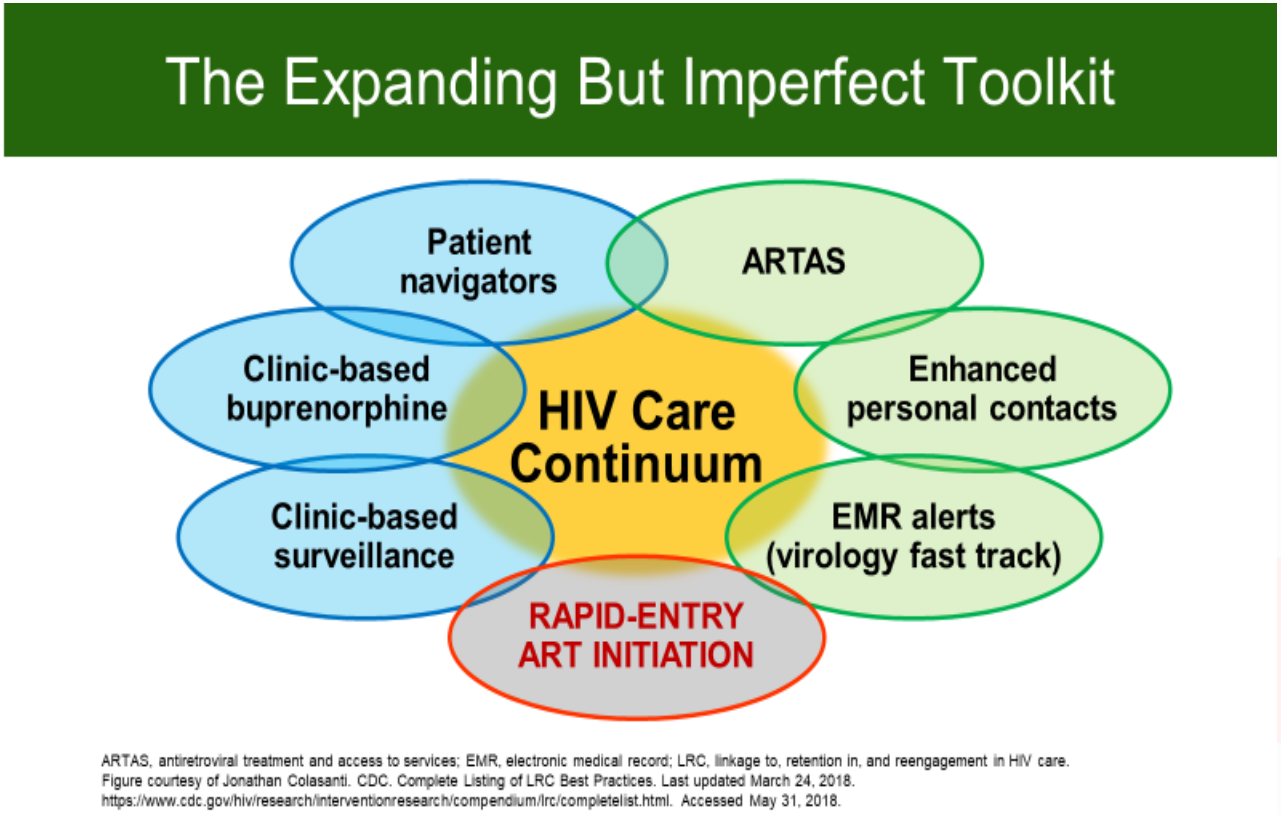
- **Preferred regimens**
  - Bictegravir/tenofovir alafenamide/emtricitabine (Biktarvy)
  - Dolutegravir* (Tivicay) + tenofovir alafenamide/emtricitabine (Descovy) or tenofovir disoproxil fumarate/ emtricitabine (Truvada) or tenofovir disoproxil fumarate/lamivudine
- **Alternative regimens**
  - Darunavir (Prezista)/cobicistat/tenofovir alafenamide/emtricitabine(Symtuza)
  - Darunavir + ritonavir + tenofovir alafenamide/emtricitabine (Descovy) or tenofovir disoproxil fumarate/ emtricitabine (Truvada) or tenofovir disoproxil fumarate/lamivudine

Recommended Immediate ART Regimens for patients that had been taking antiretroviral prophylaxis as pre- or postexposure prophylaxis (PrEP or PEP) at the time of HIV infection or since becoming infected with HIV

- Take a careful history to determine the last time the patient took PrEP or PEP medications.

- If we have concern that resistance to the antiretrovirals may have developed, we generally start a reinforced ART regimen consisting of an integrase inhibitor (dolutegravir or bictegravir) + boosted darunavir + a tenofovir/emtricitabine or tenofovir/lamivudine formulation while awaiting the results of the genotype assay.

Rapid ARV as one tool among many that may help us improve the HIV care continuum



ARTAS, antiretroviral treatment and access to services; EMR, electronic medical record; LRC, linkage to, retention in, and reengagement in HIV care.
Figure courtesy of Jonathan Colasanti. CDC. Complete Listing of LRC Best Practices. Last updated March 24, 2018.
https://www.cdc.gov/hiv/research/interventionresearch/compendium/lrc/completelist.html. Accessed May 31, 2018.

Concluding Comments

What We Know

- Rapid entry/initiation of ART is safe
- Rapid entry/initiation improves
  - Time to viral suppression
  - Viral suppression at 12 months
  - Retention in care at 10−12 months (domestic and international studies)
  - Survival at 12 months (international studies)
  - **Remaining question:** *Longitudinal retention plus viral suppression at 12 months?* The outcomes from existing cohorts certainly look promising
- Rapid entry/initiation is acceptable to patients and uptake is good
- Rapid entry/initiation is feasible in a variety of settings
- Population-level data demonstrate that HIV incidence decreases as the proportion of individuals virally suppressed increases

Remaining questions, future steps

- Which populations will benefit most from this approach?
  - Difficult-to-retain populations?
  - Late-stage vs early-stage disease?
- What is the effect on transmission within communities?
- What are the long-term benefits that rapid approaches bring
  to the HIV care continuum?
  - Longitudinal retention and viral suppression?
- What are the best implementation approaches?
  - Global vs domestic?
  - Ryan White vs FQHC vs insured populations?

Thank you

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