Maintaining the Third 90
Clinical Research from Rakai

Steven J. Reynolds, M.D., M.P.H., F.R.C.P.(C)
Senior Clinician
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Associate Professor of Medicine Johns Hopkins University
90-90-90
An ambitious treatment target to help end the AIDS epidemic

THE TREATMENT TARGET

90% diagnosed
90% on treatment
90% virally suppressed
Outline

• VL monitoring, evidence from RHSP

• Switching to second line ART

• Implications on HIV transmission and ultimately maintaining the third 90
The Slow Death of Immunologic Monitoring

September 12, 2008 Vol. 22 No. 14
Evaluation of the WHO Criteria for Antiretroviral Treatment Failure among Adults in South Africa
Mee et al.

March 27, 2009 Vol. 23 No. 6
Failure of Immunologic Criteria to Appropriately Identify Antiretroviral Treatment Failure in Uganda
Reynolds et al.

August 2009 Vol. 14 No. 8
Diagnosis of Antiretroviral Therapy Failure in Malawi: Poor Performance of Clinical and Immunological WHO Criteria
Van Oosterhout et al.

October 2009 Vol. 14 No. 10
Accuracy of WHO CD4 Cell Count Criteria for Virological Failure of Antiretroviral Therapy
Keiser et al.

August 1, 2009 Vol. 49 No. 3
Misclassification of First-Line Antiretroviral Treatment Failure Based on Immunological Monitoring of HIV Infection in Resource-Limited Settings
Kantor et al.

July 6, 2016
Positive Predictive Value of the WHO Clinical and Immunologic Criteria to Predict Viral Load Failure among Adults on First, or Second-Line Antiretroviral Therapy in Kenya
Waruru et al.
WHO HIV Treatment Guidelines 2003-present

2003
1) Clinical monitoring
2) CD4 monitoring if available
3) VL monitoring not recommended due to cost/complexity

2006
1) Clinical monitoring
2) CD4 monitoring needs to be expanded and not seen as a luxury
3) VL monitoring if available

2009
1) Clinical monitoring
2) CD4 monitoring
3) VL monitoring to confirm suspected treatment failure
4) Encourage expansion of viral load monitoring

2013
1) Routine VL monitoring recommended as preferred method to identify treatment failure
Switching to Second Line Therapy
Despite the increased availability of viral load monitoring, many programs in sub-Saharan Africa are switching individuals late after first failure detected.
Delayed Switching Even with Routine VL Monitoring

- Rakai program results 2004-11 revealed significant delays in switching to second line (median time to switch 8.1 months)
- Switching rates influenced by stage of disease

![Graph showing proportion switched to second line over time since failure on first line ART (years) for different viral load levels.](image)

- Viral load ≤ 5,000 copies/ml
- Viral load = 5,000-10,000 copies/ml
- Viral load > 10,000 copies/ml

p<0.001
Mortality in patients NOT switched to second-line ART was 11.9%, compared to 1.2% among those switched (p = 0.009)
Mortality Increases As Treatment Switch is Delayed

Petersen et al., AIDS 2014
HIV Transmission
Viral Load is the Main Driver of Transmission

**Transmission rate per 100 person-years**

- **<400**: 3500-9999
- **400-3499**: 3500-9999
- **10,000-49,999**: ≥50,000
- **≥50,000**: ≥50,000

**HIV-A RNA (copies/ml)**

**All subjects**

- **Male-to-female transmission**
  - **<400**: 400-3499
  - **3500-9999**: 3500-9999
  - **10,000-49,999**: 3500-9999
  - **≥50,000**: ≥50,000

**Female-to-male transmission**

- **<400**: 400-3499
- **3500-9999**: 3500-9999
- **10,000-49,999**: 3500-9999
- **≥50,000**: 3500-9999

**Quinn et al. New England Journal of Medicine 2000**
ART and HIV Transmission

HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy

Steven J. Reynolds\textsuperscript{a,b}, Frederick Makumbi\textsuperscript{c}, Gertrude Nakigozi\textsuperscript{d}, Joseph Kagaayi\textsuperscript{d}, Ronald H. Gray\textsuperscript{e}, Maria Wawer\textsuperscript{e}, Thomas C. Quinn\textsuperscript{a,b} and David Serwadda\textsuperscript{c}

- 42 HIV transmissions occurred 459.4 person years among couples not on ART, incidence:
  - 9.2/100 py (95% CI 6.59-12.36)

- No HIV transmissions occurred over 53.6 person years during periods when index partner was on ART

Reynolds AIDS 2011, 25;473
Antiretroviral therapy works

U=U

Undetectable Equals Untransmittable
ART also prevents Hepatitis B Transmission

39 Hepatitis B transmissions occurred 3342 person years among HIV positive individuals not on ART:
- 1.17/100 py (95% CI 6.59-12.36)

Hepatitis B incidence reduce by 75% among those receiving ART; NO incident cases among individuals receiving Tenofovir
Viral Load Monitoring and Differentiated Care

- 12 months after ART initiation:
  - 90% had VL < 400 copies/ml
  - 3% 400-1000 had copies/ml
  - 2% had 1001-2000 copies/ml
  - 5% had > 2000 copies/ml

- Viral load measurement at 12 months post-ART initiation predicted patients at high risk of subsequent virological failure.
Conclusions

• VL monitoring can help us maintain the third 90

• Implementation challenges need to be addressed to maximize the benefit of VL monitoring

• Acting on VL can improve patient care, clinical outcomes and our ability to control the epidemic
MY VIRAL LOAD IS UNDETECTABLE.

I AM CONTROLLING THE VIRUS!