Self-Reported Antiretroviral Adherence: Association with Maternal Viral Load Suppression in HIV-1-Infected Postpartum Women in Promoting Maternal and Infant Survival Everywhere (PROMISE)-Randomized, Open-label trial in Sub-Saharan Africa and India.

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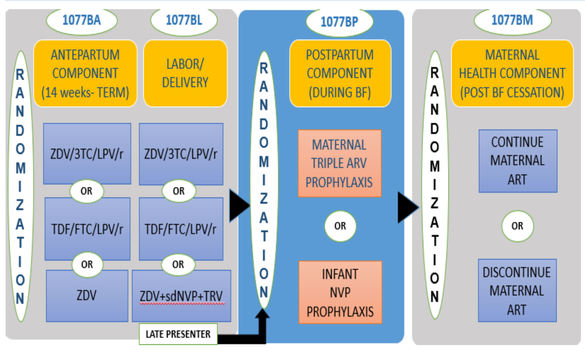
ABSTRACT # A-IAS2021-01071

Background

- Globally, almost 50% of the 38 million adults living with human immunodeficiency virus (HIV) are women[1].
- Option B+ antiretroviral therapy (ART) strategy has increased the number of HIV-positive women initiating lifelong ART since 2013.
- Adherence to ART among women remains a great concern especially during postpartum period[2].
- Poor adherence increases the risk of virologic failure, maternal HIV disease progression, mother-to-child transmission (MTCT) and emergence of antiretroviral drug resistance.
- Detecting suboptimal adherence to ART is important because adherence-enhancing interventions may improve viral response, maternal health and survival.

Methods

- **Study Design:** The PROMISE study was an open-label, randomized controlled, multi-component clinical trial conducted between June 2011 to September 2016 at 14 sites in seven countries: *India, Malawi, South Africa, Tanzania, Uganda, Zambia and Zimbabwe.*
- **Aim of PROMISE study**: To determine optimal antiretroviral (ARV) strategy to prevent vertical transmission of HIV and maintain maternal and infant health.



Postpartum Component (1077BP)

Key Eligibility:
1. Maternal CD4 > 350 cells/mm^3 or the country-specific threshold
2. Infant HIV-1 NAT negative, B.W. > 2kg

Randomization:

- 2431 mother-infant pairs were randomized at 6-14 days post delivery to two arms
- 1220 were in maternal ART (mART) arm and 1211 in infant nevirapine (iNVP) prophylaxis arm.
- Maternal ART: twice daily PI-Lopinavir/ritonavir + fixed dose-TDF/FTC preferred regimen.
- Infants in the mART arm also received NVP for 6 weeks.
- The randomized regimens were continued until 18 months postpartum , unless stopped earlier due to BF cessation, infant HIV-1 infection or toxicity.

Study Measures:

- Exposure Variable: Self-reported adherence to mART and to iNVP prophylaxis.
- Outcome of Interest: Maternal viral load (MVL) suppression

Study Evaluations:

Self-Reported Adherence	Week 1 (6-14 days postpartum), weeks 6, 14, 26, 50 and 74
Maternal Viral Load	

Definitions:

Self-reported Adherence:

- ***Dichotomous adherence* measure**- missing of any of the ART medication within a 4, 2 and 1 week period of each visit.
- ***Continuous adherence measure***- the proportion of missed doses (doses missed/total doses expected) within 3 days prior to each study visit.

Maternal Virologic Suppression:

- ***MVL*** < 1000 copies/ml at or after 24 weeks of being on ART

Methods contd.

Analyses

- Secondary analyses within the postpartum component
- Self-reported adherence using dichotomous and continuous measures was assessed.
- Overall dichotomous adherence measures between treatment arms were compared using a Chi-Square test.
- Time-to-event analyses were performed to explore the association between maternal adherence and maternal viral load (MVL) with both adherence measures as time-dependent predictors.
- The models analyzed the adherence measures as predictors of: time to first MVL ≥400 copies/ml and time to first MVL ≥1000 copies/ml after 6 weeks of randomization in mART arm.

Results

Baseline Characteristics[3]:

The median age at entry was 26 years [interquartile range (IQR) 23–30], 97% were in WHO Clinical Stage I, median CD4+ T-cell count was 686 cells/mm3 (IQR 553–869), and median MVL was 322 copies/mL (IQR 40-1422).

Table 1: Self-reported Adherence with Dichotomous Measures combined over all study visits using Chi-Square test

Adherence Measures	mART Arm (N=1220)	iNVP Arm (N=1211)	P-value
Did not miss any dose within last 4 weeks at any study visit	776 (65.82%)	987 (83.29%)	< 0.0001
Missed a dose within last 4 weeks during any study visit	403 (34.18%)	198 (16.71%)	
Did not miss any dose within last 2 weeks at any study visit	835 (70.88%)	1010 (85.23%)	< 0.0001
Missed a dose within last 2 weeks during any study visit	343 (29.12%)	175 (14.77%)	

Self-reported adherence to mART with the Dichotomous measure was lower than adherence to iNVP within 4 and 2 weeks prior to study visits

Table 2: Self-reported ART adherence with the Continuous measures

Study Visit Week		mART Arm (N=1220)	iNVP Arm (N=1211)	Total (N=2431)
Week 6	N	1,179	1,184	2,363
	Mean (SD)	0.069 (0.337)	0.058 (0.352)	0.063 (0.345)
	Median (Q1-Q3)	0 (0-0)	0 (0-0)	0 (0-0)
Week 14	N	1,123	1,139	2,262
	Mean (SD)	0.039 (0.221)	0.038 (0.286)	0.038 (0.256)
	Median (Q1-Q3)	0 (0-0)	0 (0-0)	0 (0-0)
Week 26	N	1,070	1,090	2,160
	Mean (SD)	0.049 (0.299)	0.041 (0.305)	0.045 (0.302)
	Median (Q1-Q3)	0 (0-0)	0 (0-0)	0 (0-0)
Week 50	N	851	888	1,739
	Mean (SD)	0.036 (0.284)	0.048 (0.344)	0.042 (0.316)
	Median (Q1-Q3)	0 (0-0)	0 (0-0)	0 (0-0)
Week 74	N	377	385	762
	Mean (SD)	0.086 (0.454)	0.060 (0.381)	0.073 (0.419)
	Median (Q1-Q3)	0 (0-0)	0 (0-0)	0 (0-0)

Proportion of doses missed in the 3 days prior to study visits was quite low in both arms

Results contd.

Table 3: Comparison of adherence for infants on NVP at Week 6 in both arms

Study Visit Week	Adherence Measures	mART Arm (N=1220)	iNVP Arm (N=1211)	P-value
Week 6 (N=2277)	Did not miss any dose within last 4 weeks	1072 (96.58%)	1109 (95.03%)	0.0664
	Missed a dose within last 4 weeks	38 (3.42%)	58 (4.97%)	
Week 6 (N=2277)	Did not miss any dose within last 2 weeks	1074 (96.76%)	1112 (95.29%)	0.0735
	Missed a dose within last 2 weeks	36 (3.24%)	55 (4.71%)	

Self-reported adherence to infant NVP is high in both arms.

Maternal Virologic Outcome

Table 4: Time-to-Event Analysis with Adherence as a Time-varying Predictor of MVL in mART arm

Parameter	Hazard Ratio (95% CI)	Standard Error	P-value
1st occurrence of MVL ≥400			
Missed dose within 4 weeks of visit	0.97% (0.75,1.25)	0.13104	0.8044
Missed dose within 2 weeks of visit	1.04 (0.78,1.39)	0.14853	0.8011
Missed dose within 1 week of visit	1.08 (0.74,1.58)	0.19315	0.6855
* Total doses missed / Total doses expected over past 3 days	1.58 (1.33,1.87)	0.08785	<.0001
1st occurrence of MVL ≥1000			
Missed dose within 4 weeks of visit	1.11 (0.83,1.48)	0.14750	0.4724
Missed dose within 2 weeks of visit	1.15 (0.83,1.60)	0.16873	0.3991
Missed dose within 1 week of visit	1.21 (0.80,1.86)	0.21628	0.3682
* Total doses missed / Total doses expected over past 3 days	1.66 (1.37,1.99)	0.09467	<.0001

Missing 1 full day of mART doses over the past 3 days prior to a study visit was associated with a 58% or 66% higher risk of having a MVL ≥400 or ≥1000 copies/ml, respectively.

Discussion

Strength:

- Self-reported adherence and viral load measures were taken as a part of randomized controlled PROMISE trial.
- Large sample size using same standardized methods.
- The collated adherence data from ethnically, geographically and socially diverse countries increases the generalizability of the study results.

Limitations:

- The preferred ART regimen used in our study, lopinavir/ritonavir, is no longer used as standard of care in pregnancy/postpartum.
- Newer Integrase inhibitor regimens are becoming standard of care in many settings.
- These regimens with higher efficacy, good tolerability and relatively higher barrier to drug resistance, will have improved adherence and lower risk of virologic failure in postpartum women.

Conclusion

- Postpartum women in mART arm were more adherent to providing nevirapine to their infants than taking ART for themselves.
- The self-reported missed mART doses were associated with increased risk of unsuppressed MVL.
- The findings also highlight the need for individual counseling and education regarding the importance of adhering to ART for mother's own health after delivery.
- Strategies and interventions to optimize postpartum maternal ART adherence are needed for long term benefits of ART use and sustained viral suppression.

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References:

1. UNAIDS – Global HIV and AIDS Statistics Update Fact Sheet.
2. AIDS 2012. 26(16):2039-2052.
3. J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2019 April 01.

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