Overview of HIV Research Findings at BHP

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Research Questions

- Discontinuation of PI-based or NRTI-based HAART for PMTCT – impact on development of HIV Drug Resistance Mutations.

- HIV Drug Resistance mutations in patients failing Tenofovir-based HAART in Botswana.

Discontinuation of PI or NRTI-based HAART for PMTCT – impact on development of HIV Drug Resistance Mutations

Background

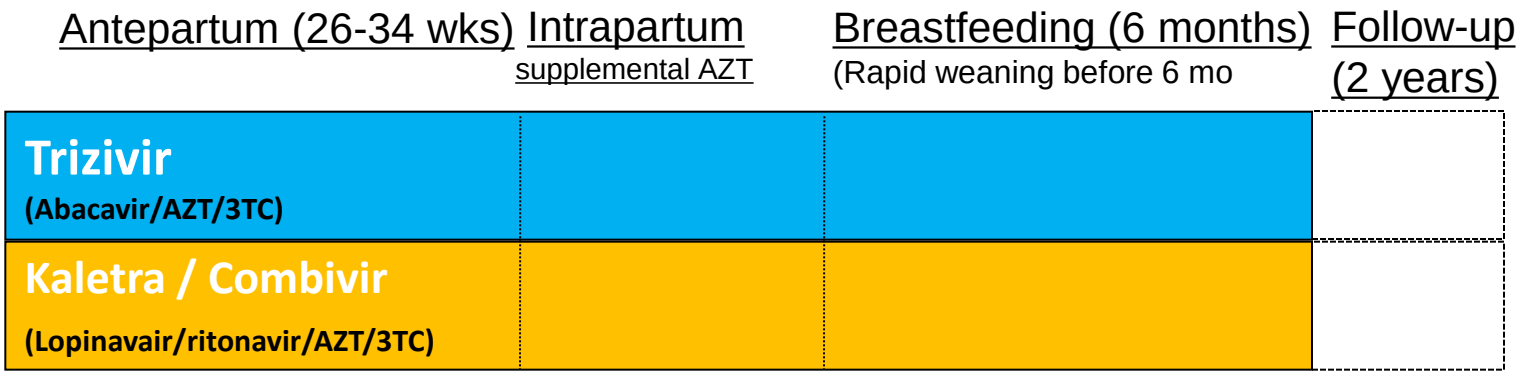
- The use of ART for prevention of vertical transmission of HIV is one of the biggest success in HIV prevention
- In Botswana, before the era of use of ART for PMTCT, 35.7% of HIV infected mothers would transmit the virus to their infants. (Montano M et al. JID Aug 2003)
- A recent PMTCT trial conducted in Botswana documented 1.1% HIV transmission. (Shapiro R et al NEJM 2010)
- The most recent WHO guidelines for PMTCT prescribe the use of HAART in all pregnant women starting at 14 weeks of pregnancy and for the whole duration of the breastfeeding period.
- Post breastfeeding, the mothers who do not qualify for HAART for their own health then stop HAART

Background Continued

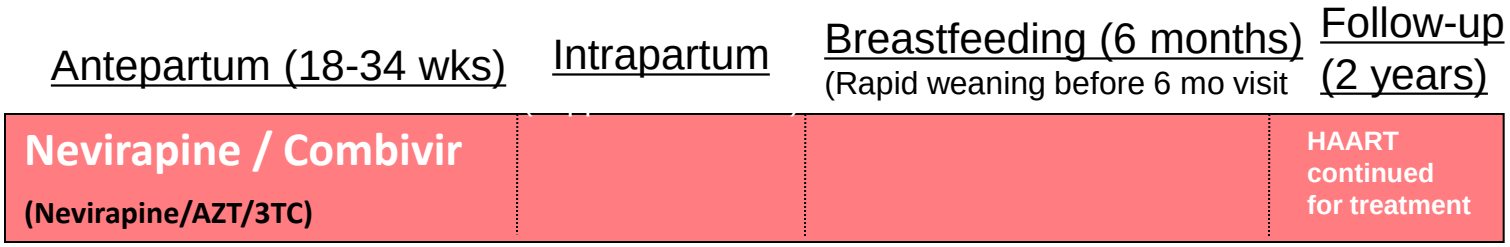
- Previous studies on the use of ART for PMTCT despite their success have been tainted by the development of drug resistant HIV strains.
- Previous studies on HIV treatment interruption have also shown association with development of drug resistant HIV strains.
- It is therefore of great interest to determine if the women who went on HAART for PMTCT develop any resistance once they stop HAART and they have viral rebound.

Materials and Methods

560 women with CD4 $\geq$ 200 cells/mm^3 randomized to:



170 women with CD4 < 200 cells/mm^3 or AIDS enrolled observationally:



Infants received single-dose NVP at birth and AZT x 1 month

1.1% overall transmission through 6 months

Materials and Methods

- The Mmabana Study randomised 560 treatment naïve women (285 women on NRTI based arm and 275 on PI based arm) to initiate HAART for PMTCT at 26-34 weeks gestation.
- AZT+3TC+LPV/r(combivir and kaletra) – PI arm and AZT+3TC+ABC(Trizivir) – NRTI arm.
- All the women had baseline CD4 counts >= 200 cells/mm^3 and breastfeed.
- HAART was stopped at 6 months or when they stopped breastfeeding
- We measured HIV viral load among 85 women at 7 months postpartum, 4 weeks after stopping HAART.

Materials and Methods continued

- Of the 85 women, 48 had viral loads >5000 copies /mL.
- Of the 48, 25 were from the NRTI arm whilst 23 were from the PI arm.
- Population sequencing of a segment of the HIV-1 pol was conducted using an in-house HIV drug resistance genotyping assay for all the 48.
- Sequences were analyzed for known ART resistance mutations using the Stanford HIV Drug Resistance Database

Results

- No clinically significant ART resistance mutations were detected one month post-treatment in the 48 samples genotyped by population sequencing
- All sequences were subtype C

Site of mutation	Minor resistance mutations detected	Frequency of mutation (%)		Frequency in treatment naïve HIV-1C patients[21] (%)	Drugs with potentially reduced susceptibility[21]
		PI Arm AZT+3TC+ LPV/r	NRTI Arm AZT+3TC+ ABC		
Protease	L10I	0/23 (0.0)	1/25 (4.0)	(2.1)	All PIs except TPV/r, DRV/r
	L10V	1/23 (4.3)	0/25 (0.0)	(1.4)	All PIs except TPV/r, DRV/r
	Q58E	1/23 (4.3)	0/25 (0.0)	(0.3)	NFV, ATV/r, DRV/r
	A71V	1/23 (4.3)	0/25 (0.0)	(0.2)	All PIs except TPV/r, DRV/r
	A71T	2/23 (8.7)	1/25 (4.0)	(1.0)	All PIs except TPV/r, DRV/r
	T74S	2/23 (8.7)	0/25 (0.0)	(9.7)	NFV
Reverse Transcriptase	V118I	0/23 (0.0)	2/25 (8.0)	(2.1)	All NRTIs
	E138A	2/23 (8.7)	2/25 (8.0)	(5.0)	All NNRTIs

Conclusions

- The two regimens used yielded no detectable major drug resistance mutations in our population
- The frequency of minor drug resistance mutations was no different from treatment naïve patients with HIV-1 C.
- Safety and effectiveness of the ARVs used and very good adherence among study participants could explain the lack of resistance mutations.

HIV Drug Resistance mutations in patients failing Tenofovir-based HAART in Botswana

Background

- In Botswana, ART reaches more than 96% of those who need it resulting in 50% decline in deaths due to HIV/AIDS while orphans due to AIDS fell by 40% between 2003 and 2007
- Botswana adopted the 2008 WHO guidelines and uses Tenofovir-based ART for treatment naïve adults and adolescents
- The triple regimen includes: Tenofovir (TDF) + Emtricitabine (FTC) and Nevirapine (NVP) or Efavirenz (EFV)
- BHP then started a study evaluating the efficacy and tolerability of Tenofovir and Emtricitabine (Truvada®) as the NRTI for first line HAART in adults in Botswana (Bomolemo study)
- Bomolemo study enrolled 300 adults following them for 24 months and this has offered a unique opportunity to evaluate the development of resistance in tenofovir- based regimens in a subtype C setting

Background Continued

- V106M that confers high-level resistance against NNRTIs is more prevalent among HIV-1C while HIV-1B preferentially selects for the V106A mutation
- In a study on the development of K65R between HIV-1B and HIV-1C, K65R was found in 4/30 of patients with HIV-1C but none in 26 subtype B patients
- K65R is a signature mutation for tenofovir but also seen in patients failing stavudine(d4T) and didanosine (DDI)
- In Botswana, a study discovered K65R in 30% of patients who failed a ddI/d4T- based regimen (Doulla-Bell et al 2005)

Objectives of the study

- To determine the prevalence of resistance mutations in HIV-1C infected adults who failed a tenofovir- based regimen

- To determine the prevalence of baseline drug resistance mutation in baseline samples of patients who failed a tenofovir- based regimen compared to those who maintained viral suppression

Baseline samples

No.	Patient ID	Gender	Viral Load	Log10 VL	CD4 count	Baseline Mutations
1	B003267-9	F	336000	5.526339277	145.23	None
2	B007362-5	F	572000	5.757396029	69.86	None
3	B007388-1	F	634000	5.802089258	8.53	None
4	B007126-1	F	750000	5.875061263	55.07	None
5	B007326-9	M	750000	5.875061263	6.49	None
6	B007422-9	F	53800	4.730782276	16.11	None
7	B007130-0	F	637000	5.804139432	7	None
8	B007296-0	F	367000	5.564666064	109.25	None
9	B007331-4	F	15400	4.187520721	100.16	-
10	B007427-9	F	750000	5.875061263	73.66	None
11	B007387-5	F	97600	4.989449818	21.70	None
12	B007429-1	F	750000	5.875061263	142.93	None
13	B007322-5	F	573000	5.758154622	209.62	None
14	B007345-3	F	70800	4.850033258	123.50	None
15	B007394-2	M	259000	5.413299764	22.42	-
16	B007129-9	F	18600	4.269512944	262.58	-
17	B007135-0	F	745000	5.872156273	67.93	None
18	B007220-9	M	750000	5.875061263	6.04	None

RESULTS

- From the 18 failure samples, 17 were successfully

Patient ID	Viral Load	Major Mutations
B003267-9	29000	K65R
B007362-5	51400	K65R, K103N, Y181C
B007388-1	10600	K65R, K103N
B007126-1	70700	K65R
B007326-9	153000	K65R, Y181C
B007422-9	30100	K65R, M184V, Y181C
B007130-0	6660	K65R, M184V, Y181C
B007296-0	91800	None
B007331-4	3580	K65R
B007427-9	750000	K65R
B007387-5	58200	None
B007429-1	367000	K65R
B007322-5	85500	K65R
B007345-3	7990	K65R
B007394-2	1160	K65R
B007129-9	2580	K65R
B007135-0	165000	K65R, M184V, Y181C
B007220-9	750000	-

15/17(88%) K65R

2/17(12%) K103N

3/17(18%) M184V

5/17(29%) Y181C

9/17(53%) K65R alone!

DISCUSSION & CONCLUSION

- 88% of patients failing treatment had K65R detected by bulk sequencing
- This result add to growing evidence that there is an increased prevalence of K65R in patients failing tenofovir based regimens
- Since K65R confers resistance to numerous NRTIs like ddI, ABC,3TC & D4T patients failing the tenofovir- based regimen and harboring the K65R mutation should be switched into alternative drug classes
- AZT is the only NRTI that can be used
- 56% of the switch from NNRTI containing HAART is done unnecessarily!
- Need for drug resistance testing for patients failing 1st line therapy

Thanks!