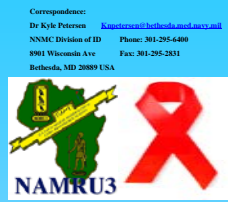


Use of Bilirubin as a Surrogate Marker of Medication Adherence to Atazanavir Based ART



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Abstract

Background: Poor adherence to anti-retroviral therapy (ART) is the most important factor contributing to virologic failure and HIV resistance. Using biochemical markers like mean copysaic volume (MCV) to monitor adherence is simple and inexpensive. Increased MCV has a sensitivity of 80% and specificity of 44% for adherence to zidovudine (AZT) or stavudine (d4T) based regimens, but many were once-daily regimens lack AZT or d4T, limiting use of MCV as a marker of adherence. Atazanavir (TAZ) raises bilirubin (Bil) in 83% of patients. We explored the use of bilirubin as a marker of adherence in TAZ containing regimens.

Methods: Retrospective chart review of 92 patients on TAZ-based ART to determine Bil, CD4, and viral load (VL) before start of ART and at subsequent follow-ups. Durability of Bil rise at subsequent follow up and effect of ritonavir on Bil were also studied.

Results: 83 patients met criteria for inclusion. Mean age was 40, 69% were male; baseline CD4 was 303, and median VL 16,000 copies/mL. Median baseline Bil was 0.5. Patients had taken a median of 6 ARV agents previously. Median 1st follow-up occurred at 45 days. There was a mean decrease in VL at 1st follow-up of 1.6 log (95% C.I. 1.0-2.1). Bil increased by a median of 0.7 using a 2-log drop as a marker for successful suppression. 43% of patients were suppressed at 1st follow-up. Association of Bil increase with successful viral suppression showed a statistically significant difference in Bil rise among responders compared to non-responders (2-sample Wilcoxon rank-sum, $p = 0.001$). Median Bil increase (IGR) for patients achieving successful viral suppression was 0.5 ($0.5 - 1.3$), compared to 0.2 ($0.1 - 1.3$) for those not achieving viral suppression. With a 2-log drop in viral load, Bil levels had various sensitivity & specificities as shown in table 1.

Table 1: Sensitivity and specificity of bilirubin elevation at varying levels

Cut-point	Sensitivity	95% C.I.	Specificity	95% C.I.
≥0.2	94	81-99	34	21-49
≥0.5	78	61-90	53	38-68
≥0.9	67	49-81	68	53-81
≥1.4	44	28-62	72	57-84

There were no differences in gender, CD4 count, % previous number of medications that an individual was on in the past, or viral load in those that demonstrated viral suppression compared to those that did not. Ritonavir boosted regimens did not achieve significantly more successful viral suppression nor increase in bilirubin. In the 43 patients with 3 complete f/u visits, bilirubin remained elevated on average >1.5 mg/dL in those suppressed suggesting durable effect.

Conclusions: Our results suggest that Bilirubin increase > 0.5 may be a good marker for adherence to atazanavir (Sensitivity 78%, Specificity 53%). Further studies are required including a larger population cohort, longer follow up and determination of confounders such as Gilbert's disease to confirm the use of Bilirubin increase to measure atazanavir adherence.

Background

- Adherence to medications is the most important predictor of HIV resistance and virologic failure
- Measurement of adherence is difficult, expensive or unreliable by current methods (e.g. patient self-report, MEMS Caps, Drug levels)
- MCV is a reliable marker of adherence (sensitivity of 80% & specificity of 44%) in AZT or d4T regimens, it is cheap and readily available in most clinic settings.
- IASUSA guidelines for 2004 feature the following NNRTI backbones
 - With a NNRTI: AZT or TDF and 3TC or FTC
 - DDI and FTC
- With a PI: ABC and 3TC, DDI and 3TC, DDI and TDF, D4T and 3TC, AZT and ABC
- Only 33% of NNRTI and 20% of PI based regimens would be able to utilize MCV as an adherence marker

Background

- Clearly other cheap easily used adherence markers need investigation
- Atazanavir is a novel protease inhibitor with IB evidence rating for IASUSA initial PI based regimen
- Manufacturer's data shows Bilirubin elevation in 83% of patients administered Atazanavir
- We hypothesize bilirubin might be a surrogate marker of adherence for Atazanavir based PI regimens
- Bilirubin is a cheap laboratory test and readily available in most HIV clinic settings, including in the developing world

Methods

- We conducted a retrospective chart review of 92 patients taking atazanavir-based ART to determine bilirubin level, CD4 count, and viral load before initiation of therapy and at subsequent follow-ups.
- We attempted to assess whether viral load decreased with initiation of atazanavir concurrent with a statistically significant increase in bilirubin, durability of bilirubin at subsequent follow up and effect of ritonavir boosting on bilirubin.
- We defined suppression as >2 log drop in VL at first f/u visit
- We performed surveillance for confounders such as number of previous drugs ("drug experience")
- There were no known patients with Gilbert's syndrome, AIDS cholangiopathy or cholecystitis 83 pts met criteria with at least 1 f/u visit

Table 1 Demographics

Characteristic (N = 83)		
Age in years, mean (range)	40	(21 – 69)
Male gender, n (%)	69	(83)
# of Rx's in past, median (IQR)	6	(4-9)
Baseline CD4 count, median (IQR)	303	(199-476)
Baseline CD4 %, mean (95% C.I.)	19	(11 – 24)
Baseline VL copies, median(IQR)	16K	(0.4– 100K)
Baseline bilirubin, median (IQR)	0.5	(0.3 – 0.7)
1 st visit follow-up in days, median (IQR)	49	(26 – 98)

Results

Figure 1. Changes in bilirubin in patients with and without viral suppression at 1st follow-up visit

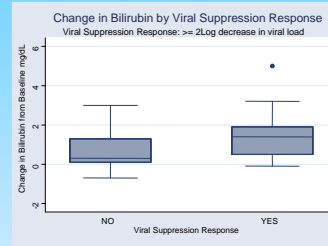
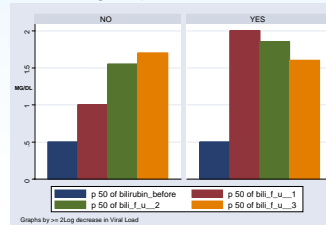


Table 2. Bilirubin sensitivity and specificity as a surrogate for viral suppression.

Cut-point mg/dL	Sensitivity	95% C.I.	Specificity	95% C.I.
≥0.2	94	81 – 99	34	21 – 49
≥0.5	78	61 – 90	53	38 – 68
≥0.9	67	49 – 81	68	53 – 81
≥1.4	44	28 – 62	72	57 – 84

Figure 2: Change in bilirubin by follow up for those with <and >2 log drop in viral load at first f/u



Results

- Mean time to follow up visit was 76, 128 and 186 days for visits 1, 2, & 3. 48 of 83 patients had 3 complete follow ups in our data set
- There was no association with baseline CD4 %, previous # of meds or baseline viral load between those who were or were not suppressed at first f/u
- There was no association with increased viral suppression or increased bilirubin by ritonavir boosting
- Figure 1 shows significant bilirubin difference between those who did or did not achieve 2 log suppression of HIV at first f/u (2 sample Wilcoxon rank-sum $p=0.002$)
- Median bilirubin in those suppressed at first f/u was significantly increased at 1.4 mg/dL (0.5-1.9) while in non suppressed patients it was 0.2 mg/dL (0.1-1.3)
- 12 "outlier" patients at first f/u had no viral suppression, but >1 mg/dL rise in bilirubin. 8 had never taken meds before 4 had avg. of 6-11 meds previously
- Table 2 demonstrates sensitivity and specificity for a 2-log drop in viral load at various elevations in bilirubin. Sensitivity fell as bilirubin increased, but specificity rose. The optimal cut-point of 0.5 mg/dL had a 78% sensitivity and 53% specificity for suppression
- Figure 2 shows virally suppressed patients had an initial spike in bilirubin with subsequent decline, but bilirubin remained over 1.5 even at third follow-up in most Patients
- Non-suppressed patients had a different pattern of bilirubin elevation with gradual increase over time.

Conclusions

- Possible explanations for increase in non-suppressed patient's bilirubin include resistant virus, or partial compliance as well as non HIV diseases of the biliary system such as Gilbert's syndrome
- The continued climb in bilirubin in non-suppressed patients indicates elevated bilirubin might be sensitive to even partial compliance
- Sensitivity and specificity of bilirubin might be even superior to our observations if it were to be correlated with viral suppression at 2nd or 3rd follow-up based on the trends in table 2
- Bilirubin elevation remains a durable predictor of adherence out to 245 days in our study
- Bilirubin is an adequate marker for adherence in atazanavir based regimens, approaching the sensitivity and specificity of the MCV for AZT- and d4T-based regimens.

References

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