External validation of the bilirubin-atazanavir nomogram for assessment of atazanavir plasma exposure in HIV-1 infected patients

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Introduction & Aim

Atazanavir increases bilirubin levels in a concentration dependent manner. Due to less costly and readily available assays, bilirubin has been proposed as a marker of atazanavir exposure. In this work a previously developed nomogram for detection of sub-optimal atazanavir exposure (based on an indirect bilirubin response PK/PD model [1]) is validated against an external patient population.

Conclusions

Bilirubin as a measure of atazanavir exposure in patients is a useful alternative to atazanavir plasma concentration monitoring. The low cost of bilirubin measurement may be of particular importance in resource limited settings. Further validation of the nomogram in 200 non-Scandinavian patients is ongoing.

Methods

External validation of the bilirubin-atazanavir nomogram

Baseline bilirubin measurements (n=76) together with one or more matching bilirubin and atazanavir steady state plasma concentrations (n=98) were available from 76 HIV-1 infected Norwegian patients. The data was retrospectively analyzed to assess if the bilirubin-atazanavir nomogram can predict suboptimal atazanavir exposure.

Bilirubin levels were plotted on the bilirubin-atazanavir nomogram **(Figure 1).** Bilirubin observations below the lower solid black line of the nomogram were identified as corresponding to atazanavir exposure below the minimum effective concentration (MEC) of 0.2 µmol/L. Observations correctly and incorrectly identified as below MEC were considered to be true positives (TP) and false positives (FP), respectively. Observations correctly and incorrectly identified as above MEC were considered to be true negatives (TN) and false negatives (FN), respectively.

Simulation based validation of the bilirubin-atazanavir nomogram

In order to evaluate if the nomogram can predict non-adherence it was applied to data from 1000 simulated patients of whom 10% were non-adherent to therapy. Three scenarios were simulated **(Figure 2)** using the previously developed PK/PD model [1]. Correctly and incorrectly identified non-adherent and adherent patients were labeled as TP, FP, TN and FN, respectively. The ability to detect non-adherence using the nomogram was compared to the use of atazanavir plasma measurements.

Table 1. Patient demographics and clinical characteristics

Characteristic	Value	Mean(±SD)
Number of patients	76	-
Male patients	59	-
Female patients	17	-
Number of atazanavir concentrations at steady state	98	
Number of bilirubin samples at baseline	76	-
Number of bilirubin samples at steady state	98	
Body weight (kg)	-	71.9 (13.9)
Age (years)	-	41.2 (10.2)
Bilirubin at baseline (µmol/L)	-	7.5 (3.7)
Bilirubin at steady state (µmol/L)	-	32.2 (19.1)
Atazanavir plasma concentration below MEC	4	-
CD4 cell count at baseline, (X 10^6 /µL)	-	268 (168)
Detectable viral load at baseline	61	-

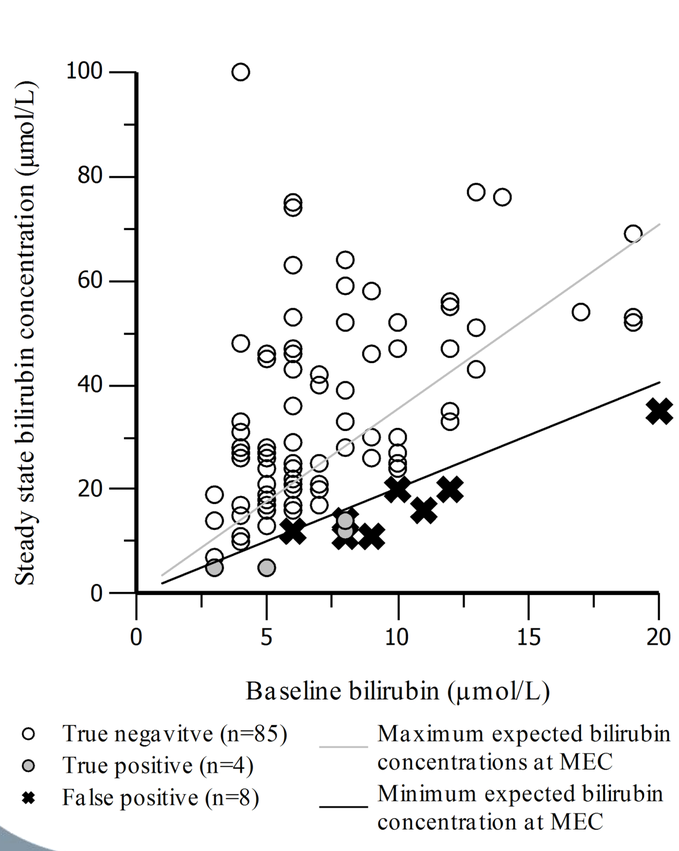

Figure 1. External validation of the bilirubin nomogram. MEC: minimal effective atazanavir plasma concentration (0.2 µmol/L).

Table 2. Summary of the bilirubin nomogram ´s predictive properties

Estimate	Value	95% CI
Sensitivity	1.0	(0.28-1.0)
Specificity	0.91	(0.84-0.96)
PPV	0.33	(0.10-0.65)
NPV	1.0	(0.94-1.0)
Accuracy	0.92	(0.84-0.96)

PPV: positive predictive value, NPV: negative predictive value, CI: Confidence interval

Refrences

Rekić, D., Clewe, O., Röshammar, D., Flamholc, L., Sönnerborg, A., Ormaasen, V., Gisslén, M., et al. (2011). Bilirubin-A Potential Marker of Drug Exposure in Atazanavir-Based Antiretroviral Therapy. *The AAPS journal*, *13*(4), 598-605. Springer New York.

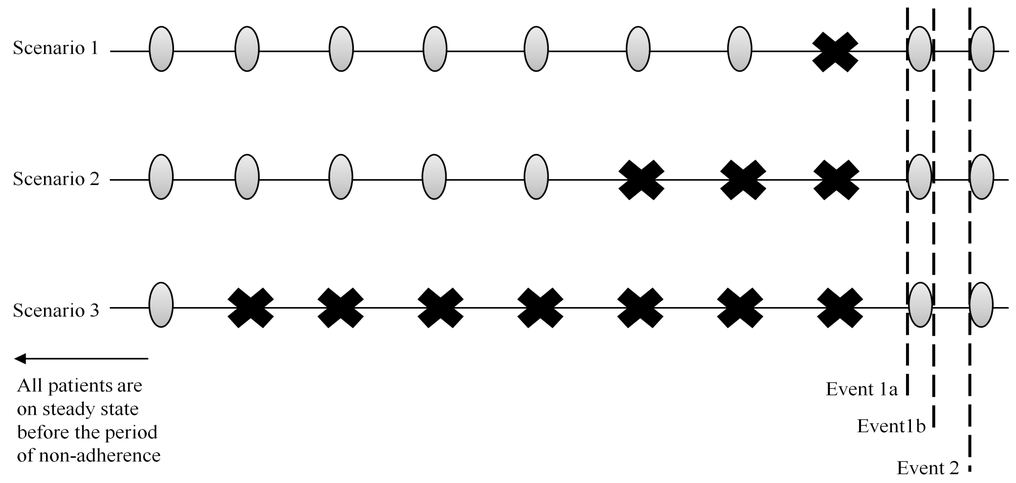

Figure 2. Study design for the simulation based validation. The crosses represent days of non-adherence to atazanavir while the ellipsoids represent administered doses. The dashed lines represent sampling/monitoring events. Event 1a: patients are monitored/sampled 24 hours after a period of non-adherence. Event 1b: patients are monitored/ sampled 1 hour after an undisclosed dose of atazanavir following a period of non-adherence. Event 2: patients are monitored/sampled 48 h after a period of non-adherence.

Results

External validation of the bilirubin-atazanavir nomogram

The nomogram identified 12 bilirubin observations as corresponding to atazanavir exposure below MEC, 4 of these were true positives and 8 were false positives. The nomogram identified 85 bilirubin observations as corresponding to atazanavir exposure over the MEC of which all were categorized as true negatives **(Figure 1).** Predictive properties (positive predictive value [PPV], negative predictive value [NPV], accuracy, sensitivity and specificity) of the nomogram are shown in **Table 2.**

Simulation based validation of the bilirubin-atazanavir nomogram

The predictive properties of the bilirubin nomogram and measured atazanavir concentrations in assessing treatment adherence are shown in **Figure 3**. Based on NPV, both the nomogram and atazanavir measurements showed good performance in detecting ongoing non-adherence (Event 1a). Performance decreased when attempting to detect past episodes of non-adherence. (Event1b and 2)

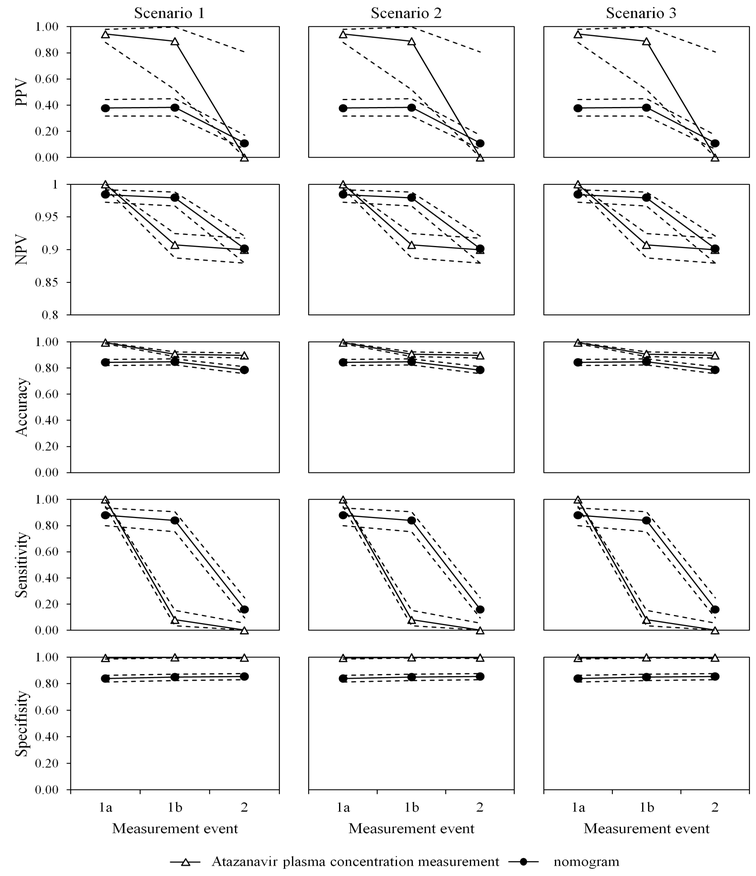

Figure 3. Summary of predictive properties of the bilirubin nomogram (circles) and atazanavir drug monitoring (triangles) based on simulations of 1000 virtual patients. The solid and dashed lines represent the estimated parameter and its 95% confidence interval, respectively. PPV: positive predictive value, NPV: negative predictive value. The scenarios and the events are explained in the methods section and in **Figure 2**.

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