Therapeutic Drug Monitoring of anti-TNF drugs

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Tumor Necrosis Factor

- Promotes the inflammatory response in
  - rheumatoid arthritis
  - ankylosing spondylitis
  - Crohn’s disease
  - ulcerative colitis
  - psoriasis

Inflammatory Bowel Disease (IBD)
Treatment of IBD

- Surgery
- anti-TNF biologicals
- cyclosporine
- steroids (short term)
- azathioprine/6MP (long term)
- 5-ASA (probiotics, antibiotics, alternative treatment)
Anti-TNF biologicals

Infliximab: Remicade®

- Normal treatment:
  - Induction: 5 mg/kg weeks 0, 2, 6 + azathioprine (first 6m)
  - Dosage: 5mg/kg
  - Dosing intervals: 8 weeks

- LOR
  - Dose escalation: 10 mg/kg
  - Reducing dosing intervals: every 4-6 weeks
  - Switch to adalimumab

UZ Leuven: > 1300 IBD patients treated with Remicade®
Anti-TNF biologicals

Adalimumab : Humira®

- Normal treatment:
  - Induction: 160/80 mg w 0, 2
  - Dosage: 40 mg
  - Dosing intervals: eow

- LOR
  - Dose escalation: 80 mg
  - Reducing dosing intervals: ew
  - Switch (back) to infliximab

UZ Leuven: > 600 IBD patients treated with Humira®
Anti-TNF biologicals

What is the true efficacy of the biologicals?

- Loss of response (LOR)?

- Up to 40% of CD patients treated do not have a clinically relevant response to the currently available anti-TNF agents.

- 30% to 50% of all patients achieve complete remission after 6 months of treatment assessed by various clinical scoring systems.

- 30% maintain a response for 12 months during continuous treatment.

Nielsen OH et al., J Intern Med 2011
• What is the true efficacy of the biologicals?
  – Acute infusion reactions
  – Delayed infusion reactions
  – Acute severe infusion reactions (ASIR)

- infusion reactions are associated with the formation of anti-drug-antibodies

Vande Castele et al. APT 2011; 34:394-407.
Towards a more effective treatment

- Maximize clinical benefit
- Minimize complications

“trough level adapted treatment scheme”
Measurement of trough levels

Trough level: dalspiegel

= lowest serum drug level
= level just taken before the periodically administered medicine

Picture adapted from Tracey D et al. Pharm & Ther, 2008
Infliximab serum level: ELISA

Cut off value (mean of 78 anti-TNF naïve patients samples + 1.96*SD): 0.3 µg/ml

< 0.3 µg/ml: undetectable

Higher limit of quantification (HLOQ) = 22.5 µg/ml

versus infliximab spiked in serum
Inter-individual difference in trough levels due to pharmacokinetic (PK) variability

Leuven IFX cohort

serum infliximab level (µg/ml)

weeks after start IFX

0 5 10 15 20 25

2 6 14 22 30 46 54
Trough level profiles of IBD patients receiving IFX therapy

- **Patient ID 139**
- **Patient ID 4757**
- **Patient ID 7676**
- **Patient ID 8177**
Measurement of trough levels

Which factors will influence trough levels?

- Pharmacokinetics (FcRn receptor) and pharmacodynamics (Fc\γ receptors)

- Remission *versus* flares

- Formation of antibodies (immunogenicity)

\[\text{Determination of antibodies towards IFX/ADM}\]
Anti-drug antibody (ADA) serum level

Anti-IFX ELISA: bridging assay

- Drug
- Serum with ATI
- Drug-HRP

Bridging ELISA

Cut off value (mean of 99 anti-TNF naïve patient samples + 1.96*SD) = 0.7 µg/ml; LOD = 1 µg/ml equivalent

< 1 µg/ml: undetectable ATI

Higher limit of quantitation (HLOQ)=20 µg/ml

*versus* polyclonal monospecific rabbit Ab
Anti-drug antibody (ADA) serum level

In the presence of high (> 1 µg/ml) IFX concentrations, ATI can not be detected because bridging assay requires bivalency.
Measurement of ADA levels

Anti-Drug-Antibodies (ADA)

- Neutralizing antibodies will decrease the functional anti-TNF concentration
- Antibodies can form immune complexes which can influence the clearance of the drug

Loss of response
- Antibodies can induce an allergic reaction at site of infusion or even an infusion reaction
Clearance of antibodies

- **Long half-lives:**
  - Chimeric mAbs: 10 – 14 days
  - Humanized / fully human mAbs: 10 – 20 days

- **Distribution:**
  - Mainly within the central compartment; Small volume of distribution
    $\approx 0.1 \text{ L/kg} \approx 4.5 – 6 \text{ L} (\approx \text{extracellular fluid volume})$
  - Mechanisms: Extravasation, diffusion, convection

- **Elimination:**
  - No renal or hepatic clearance but intracellular proteolytic catabolism after fluid-phase or receptor-mediated endocytosis
  - mAbs targeting soluble antigens often exhibit linear pharmacokinetic behavior / mAbs targeting cell surface antigens frequently exhibit nonlinear behavior due to receptor-mediated clearance (*Mould and Green, BioDrugs 2010 ; 24 : 23-39*)
Clearance of antibodies

- Antibody salvage and recirculation via the Brambell receptor (FcRn):

Trough level profiles of IBD patients receiving IFX therapy

Trough levels = black lines
antibodies towards IFX: red lines
TL of IFX is associated with:
- Clinical remission
- Lower CRP values
- Endoscopic healing


105 CD patienten/IFX

A

Remission (%) vs Serum Infliximab (ug/ml)

R² = 0.61
P < 0.001
Therapeutic drug monitoring (TDM)

Which are the reference values?

Reference values set at 3-7µg/ml for CD and UC patients

Test hypothesis

Trough level adapted infliximab treatment trial
Hypothesis and aim

• In patients suffering from Crohn’s disease (CD) or ulcerative colitis (UC) under IFX maintenance therapy, sustained good trough levels are associated with:
  ✓ Better response and remission rates
  ✓ More mucosal healing
  ✓ Less loss of response

• Aim was to investigate in a prospective manner the clinical outcome of individualised treatment with IFX based on trough levels: Trough level Adapted infliXImab Treatment (TAXIT) trial.

• Self-funded monocentric randomised controlled trial
  Eudract: 2011-002061-38
Methods: study outline

- Consecutive cohort of CD and UC responder patients on maintenance IFX
- Included between August 1st 2011 and October 27th 2011
- Clinicians and patients were blinded for TLI and ATI status

Screening

Optimization to have TLI between 3 and 7 µg/ml

Randomization

Control group treatment scheme based on symptoms and CRP

Active group treatment scheme based on TLI

1 year follow-up

Primary endpoint
Primary and secondary endpoints

- **Primary endpoint** was defined as clinical and biological (CRP < 5 mg/l) remission rates at one year after randomisation

- **Secondary endpoints**
  - Pharmacoeconomical cost of treatment in both groups
  - Proportion of patients with TLI within optimal interval
  - Proportion of patients needing to switch to adalimumab
  - The number of treatment adaptations in both groups
  - The number of adverse events in both groups
  - The number of infusion reactions in both groups
  - The number of disease flares in both groups
  - The median biologic activity (CRP-levels) in both groups
  - The total amount of IFX given in both groups
  - Mucosal healing assessed by endoscopy in both groups
TAXIT algorithm

TLI and ATI were measured with an in-house developed direct and bridging ELISA.
TAXIT algorithm

TLI measurement

- **undetectable TLI (TLI < 0.3 µg/ml)**
  - ATI measurement
    - **high ATI level (ATI > 8 µg/ml)**
      - STOP
    - **low ATI level (ATI < 8 µg/ml)**
      - dose increase (by 5 mg/kg) to max 10 mg/kg

- **TLI < 3 µg/ml**
  - 1) interval decrease (by 2 weeks) to min 4 weeks
  - 2) dose increase (by 5 mg/kg) to max 10 mg/kg

- **3 µg/ml < TLI < 7 µg/ml**
  - no dose adaptation

- **TLI > 7 µg/ml**
  - interval increase (by 2 weeks)
**TAXIT algorithm**

- **TLI measurement**
  - **undetectable TLI (TLI < 0.3 µg/ml)**
    - **ATI measurement**
      - **high ATI level (ATI > 8 µg/ml)**
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  - **3 µg/ml < TLI < 7 µg/ml**
    - no dose adaptation
  - **TLI > 7 µg/ml**
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TAXIT algorithm

TLI measurement

- undetectable TLI (TLI < 0.3 µg/ml)
  - ATI measurement
    - high ATI level (ATI > 8 µg/ml)
      - STOP
    - low ATI level (ATI < 8 µg/ml)
      - TLI measurement
        - TLI < 3 µg/ml
          - 1) interval decrease (by 2 weeks) to min 4 weeks
        - 3 µg/ml < TLI < 7 µg/ml
          - no dose adaptation
        - TLI > 7 µg/ml
          - interval increase (by 2 weeks)
      - dose increase (by 5 mg/kg) to max 10 mg/kg
TAXIT algorithm

TLI measurement

- undetectable TLI (TLI < 0.3 µg/ml)
  - ATI measurement
    - high ATI level (ATI > 8 µg/ml)
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  - no dose adaptation

- TLI > 7 µg/ml
  - interval increase (by 2 weeks)
Infliximab trough level (screening)

**Infliximab trough level (TLI)**

- undetectable TLI
- TLI < 3 µg/ml
- 3 µg/ml < TLI < 7 µg/ml
- TLI > 7 µg/ml

- 9%
- 26%
- 21%
- 44%

Vande Castele N. et al., ECCO 2012
Antibodies to infliximab (screening)

- 24 patients (9%) out of 275 had an undetectable TLI
- Of which 18 patients (75%) were ATI positive
- Median ATI level: 5.2 µg/ml eq. (IQR 2.8-9.1)
- 6 patients were excluded due to ATI > 8 µg/ml

**Infliximab trough level (TLI)**

- Undetectable TLI: 9%
- TLI < 3µg/ml: 21%
- 3 µg/ml < TLI < 7 µg/ml: 44%
- TLI > 7 µg/ml: 26%

Vande Casteele N. et al., ECCO 2012
275 pts screened

14/275 (4%) pts were excluded

115/261 (44%) pts: TLI within interval

Randomised to control or active group

14/275 (4%) pts were excluded

146/261 (56%) pts: TLI not within interval

10/146 (7%) pts could not be optimised

4/10 pts due to active disease

6/10 pts due to not willing to adapt

136/146 (93%) pts were optimised

Randomised to control or active group
Flowchart

Optimization phase

136 pts successfully optimised

- 68 pts (50%) dose escalated
  - 10 pts dose increase
  - 58 pts interval decrease
  - 65 pts interval increase
  - 26 pts 10-week interval
  - 6 pts 12-week interval

- 68 pts (50%) dose de-escalated
  - 3 pts dose decrease

10-week interval
12-week interval
Optimization of pts with TLI < 3 µg/ml (n=68)

Average of 2.0 adaptations per patient

IFX trough level

\[ P < 0.0001 \]

C-reactive protein

\[ P = 0.0008 \]

Harvey-Bradshaw index (n=36)

\[ P = 0.029 \]

Partial MAYO score (n=21)

\[ P = 0.80 \]

Vande Casteele N. et al., ECCO 2012
Optimization of pts with TLI > 7 µg/ml (n=68)

Average of 1.3 adaptations per patient

IFX trough level
P < 0.0001

C-reactive protein
P = 0.66

Harvey-Bradshaw index (n=43)
P = 0.19

Partial MAYO score (n=19)
P = 0.85

Vande Casteele N. et al., ECCO 2012
In our prospective cohort of responder patients on maintenance infliximab, only 44% had optimal TLI.

Dose escalation in patients with TLI <3 µg/ml results in a significant drop in CRP and Harvey-Bradshaw index.

Dose de-escalation in patients with TLI >7 µg/ml does not have an effect on CRP, Harvey-Bradshaw index or partial MAYO score.

The on-going controlled maintenance study will show whether long term adjustment of treatment based on IFX levels is the superior strategy in routine clinical practice.
Patients who develop ATI during treatment have a **worse prognosis**:

- **Hypersensitivity reactions**
  - Acute or delayed infusion reactions

- **Adverse events**
  - Deep venous thromboembolism?

- **Loss of clinical benefit**
  - Neutralising ATI
  - Non-neutralising ATI

\[\text{(Maser E.A. et al., 2006; Rutgeerts P. et al., 2005; Hanauer S.B. et al., 2004; Baert F. et al. 2003)}\]

\[\text{(Korswagen L.A. et al., 2011; Petitpain N. et al., 2010)}\]

\[\text{Direct effect on IFX binding capacity to TNF} \alpha\]

\[\text{Influences clearance rate of IFX} \]

\[\text{(Ducourau E. et al., 2011; Xu Z. et al., 2008)}\]
Study outline

• Retrospective study of 90 IBD patients:
  ➢ 64 Crohn’s disease and 26 ulcerative colitis
  ➢ Maintenance IFX, in follow-up at our IBD unit

• Loss of Response:
  ➢ An increase in symptoms with or without an increase of CRP followed by therapeutic intervention

• Hypothesis:
  ➢ can ATI be transient or do they always persist and inevitably lead to worse clinical outcomes?
90 IFX-treated IBD patients

33/90 (37%) patients did not develop ATI

ATI negative

57/90 (63%) patients did develop ATI

In 18/57 (32%) patients ATI disappeared

Transient ATI

In 39/57 (68%) patients ATI persisted

Sustained ATI
Transient vs. Sustained ATI and the risk for IFX discontinuation

IFX discontinuation due to loss of response or hypersensitivity

% of patients

69%

***

6%

Sustained ATI

Transient ATI
Predicting ATI formation through trough levels

- ATI were first detected after a median of **32 weeks** (transient ATI) or **22 weeks** (sustained ATI) after start of IFX.

- ATI positive patients already had **low IFX trough levels at week 6** after start of IFX: 5.2 µg/mL (IQR 0.6-13.6) versus 17.9 µg/mL (IQR 16.0-21.7) (P=.0003).

- Receiver operator curve (ROC) analysis of IFX **trough level at week 14** showed that patients
  - <3.1 µg/mL developed ATI with a likelihood ratio of 6.5
  - <0.95 µg/mL -> three-fold higher likelihood for IFX discontinuation
Conclusions

• Antibodies to IFX can be transient

• Low IFX trough levels during induction can be an indication for ATI development

• Patients who develop sustained ATI more often lose response to IFX

• Sustained ATI, in contrast to transient ATI lead to IFX discontinuation due to persistent loss of response and adverse events
https://pharm.kuleuven.be/biotech
Inlichtingen formulier

• **Welke tubes te gebruiken:**
  Serumtubes met clot activator en gel separator (bijvoorbeeld BD Vacutainer SST II Advance).

• **Hoe centrifugereren:**
  Het bloedstaal moet na afname afgecentrifugeerd worden (10 min – 1960 g) en het serum dient overgebracht te worden naar een nieuwe tube (minimum 200 µl).

• **Hoe bewaren en versturen:**
  Het serum wordt minstens 1 nacht op -20°C bewaard en vervolgens op icepacks of droog ijs naar het laboratorium gestuurd of via centraal klinisch labo UZ Leuven
Identificatie formulier

Met welk medicijn werd patiënt behandeld:
• Infliximab
• Adalimumab

Wat moet er bepaald worden:
• Enkel dalspiegels
• Dalspiegels en wanneer onder detectielimiet ook antilichamen
• Sowieso dalspiegels en antilichamen

Wie moet het resultaat krijgen
• Email adres of fax

Aan wie mag het factuur gestuurd worden
• Ziekenhuis
• patient
Standardization of assays

Round robin experiment

-Samples from UMC Groningen, The Netherlands (Buurman DJ, Sturkenboom MGG, Kleibeuker JH, Dijkstra G) BMD kit

-Samples from Sanquin Amsterdam, The Netherlands (Rispens T, van der Kleij D) Sanquin assay

-Samples from University Hospitals Leuven, Belgium (Vande Casteele N, Vermeire S, Gils A) Leuven assay
Type of samples

Clinical samples (n=36)

- Trough levels of IFX
  - Low
  - Intermediate
  - High

- Antibodies to IFX
  - Low
  - Intermediate
  - High

Quality control samples (n=26)

- Serum pool of healthy controls spiked with:
  - IFX
  - Antibodies to infliximab (ATI)
  - Antibodies to adalimumab (ATA)
Standardization of assays

infliximab levels

ELISA Leuven

ELISA from Sanquin

ELISA from BMD
Infliximab level results

A

Pearson r = 0.91
P < 0.0001

B

Pearson r = 0.83
P < 0.0001

C

Pearson R = 0.73
P < 0.0001

ICC  = 0.91
P < 0.0001

ICC  = 0.73
P < 0.0001

ICC  = 0.59
P < 0.0001
Standardization of assays

Antibodies toward infliximab levels

- ELISA Leuven
- RIA from Sanquin
- ELISA from BMD
Antibodies to infliximab

Conclusions:
- Good correlation between infliximab and antibody to infliximab assays
- BMD kit detected false positives in 18% of the samples
- RIA appears to be superior in detecting low level ATI

Comparison with other assays

Prometheus (US):

Fluid phase mobility shift assay to measure trough levels and to measure anti-drug antibodies

Comparison: 1230 serum samples: Pearson corr: 0.83

ELISA: has a lower sensitivity to detect ATI in absence of TL
Fluid phase assay: is able to detect ATI in presence of TL due to acid dissociation step

Neutralising vs non-neutralising antibodies

- **Non-neutralizing antibodies**: affect clearance by formation of immune complexes
- **Neutralizing antibodies**: affect clearance by formation of immune complexes + have a direct effect by neutralizing immediately the effect of the anti-TNF drug

**Bridging assay**: determines all antibodies that are bivalent

**Cell based assay**: measures functional effect
Neutralising *versus* non-neutralising antibodies

- Wolbink *et al.* (Amsterdam, Sanquin) have shown that all ADA raised towards adalimumab are neutralizing antibodies.

- We have seen that patients with antibodies towards infliximab (ATI) can have measurable adalimumab trough levels, antibodies do not cross-react.
Future projects

• Evaluation of TAXIT: last patient: april 2013!

• Development of alternative ELISA assay: using two MA that bind functional IFX/ADM

• Development of a rapid device: in framework of kennisplatform NANODIAG

• Pharmacometric analysis: sampling of peak and intermediate levels: Dried Blood Spots

• Development of assay to measure etanercept (Enbrel)

• Validation of assay to measure neutralizing antibodies: generating MA that inhibit IFX/ADM/ETN
Future projects
Future projects

• Evaluation of TAXIT: last patient: april 2013!

• Development of alternative ELISA assay: using two MA that bind functional IFX/ADM

• Development of a point of care device: in framework of kennisplatform NANODIAG

• Pharmacometric analysis: sampling of peak and intermediate levels: Dried Blood Spots

• Development of assay to measure etanercept (Enbrel)

• Validation of assay to measure neutralizing antibodies: generating MA that inhibit IFX/ADM/ETN
Monitor IFX trough level during induction phase

IFX trough level at week 14 >3µg/mL

In case of loss of response: measure IFX trough level

Continue IFX treatment

IFX trough level at week 14 <3µg/mL

Continue IFX trough level monitoring

IFX trough level <0.3µg/mL

Monitor TL and ATI on two consecutive visits

ATI levels decrease
IFX trough level >0.3µg/mL

Continue IFX treatment

ATI levels increase
IFX trough level <0.3µg/mL

Stop IFX treatment

When to measure TL: my personal advice
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Thank you for your attention

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IBD pathology

• Relapsing inflammation of the intestine characterised by flares and remission.

Crohn’s disease (CD) = transmural disease

Ulcerative colitis (UC) = mucosal disease
PK/PD modeling?

- **PK** = Pharmacokinetics: What the body does to the drug (ADME: Absorption / Distribution / Metabolism / Elimination)
- **PD** = Pharmacodynamics: What the drug does to the body (effect)

**Pharmacology**

- **Pharmacokinetics**
  - Dose
  - Concentration
- **Pharmacodynamics**
  - Effect
- **Pharmacometrics**
  - Efficacy
- **Clinic**

(From Jacqmin P., Conference in Lyon - December 10th 2012)

- Modeling: use of mathematical models to describe observed experimental / clinical data (simplified mathematical representation of the reality)
- No ideal model!
Specificities of mAbs PK

• Long half-lives:
  – Chimeric mAbs: 10 – 14 days
  – Humanized / fully human mAbs: 10 – 20 days

• High variability in drug exposure between subjects

• Absorption:
  – Less variability IV vs SC; SC more immunogenic?
  – Slow after SC injection ($t_{\text{max}}$: 2 – 8 days)
  – Bioavailability after SC administration is highly variable: 50 – 100%
  – Mechanisms of systemic absorption:
    • Convective transport through lymphatic vessels and into the blood
    • Diffusion across blood vessels

• Distribution:
  – Mainly within the central compartment; limited penetration inside cells (high molecular weight and hydrophilicity).
  “Small” volume of distribution $\approx 0.1 \text{ L/kg} \approx 4.5 – 6\text{L} (\approx \text{extracellular fluid volume})$
  – Mechanisms: Extravasation, diffusion, convection

• Elimination:
  – No renal or hepatic clearance but intracellular proteolytic catabolism after fluid-phase or receptor-mediated endocytosis
  – mAbs targeting soluble antigens often exhibit linear pharmacokinetic behavior / mAbs targeting cell surface antigens frequently exhibit nonlinear behavior due to receptor-mediated clearance (Mould and Green, BioDrugs 2010; 24: 23-39)
Specificities of mAbs PK (2)

- Antibody salvage and recirculation via the Brambell receptor (FcRn):

Specificities of mAbs PK (3)

- Many mAbs are likely to demonstrate Target Mediated Drug Disposition (TMDD): Interaction drug – target influences PK of mAbs
  - Rate of uptake and elimination of mAbs = function of:
    - Dose
    - Expression level of target
    - Kinetics of receptor internalization
    - Kinetics of intracellular catabolism

- Immunogenicity: Endogenous antibody response may alter the PK of the mAb: Half-life of the mAb decrease
  But… Complex and difficult to predict (depending on the number of antigenic sites…)

Optimization of pts with undetectable TLI (ATI positive at screening) (n=10)

Average of 5.1 adaptations per patient

IFX trough level
P < 0.0001

Antibodies to IFX
P = 0.008

Vande Castele N. et al., ECCO 2012
What we started to do…

• **PK analysis of the data from the study concerning UC patients:**
  First, with a limited number of patients (15 patients)

  – With WinNonlin (« classical » approach):
    • 1 compartment model

  • 2 compartment model not accurate: very high CV%...
  • Non compartmental analysis: Impossible to obtain estimates of the PK parameters (AUC etc…)

  – With NONMEM (population approach): First, without testing any covariate

  Need for more extensive data sets (concentration peaks and/or intermediate levels)

  Measurements from dry blood spots method ?
TAILORIX

• Randomized controlled trial investigating tailored treatment with IFX for active luminal CD

• **Primary objective:** can sustained steroid-free remission between w22 and w54 mucosal healing at 1 year be achieved using adjustment of dosing based upon trough level measurements?

• Multicentric study
TAILORIX

5 mg/kg at w0,w2,w6

from w14 onwards

Clinical relapse

10 mg/kg

Clinical relapse or TL decrease

7,5 mg/kg (1)
10 mg/kg (2)

Clinical relapse or TL decrease

10 mg/kg
76 IBD patients were included

- 31 patients (41%) continued infliximab therapy without any modification
- 39 patients (51%) had an intensification of infliximab therapy
- 5 patients (7%) had switched to adalimumab therapy
- 1 patient (1%) underwent surgery

Clinical response was observed in 27 patients (69%) with an intensification of infliximab therapy.
Trough levels

- no significant difference in mean infliximab trough level at inclusion in patients who responded to intensification of infliximab therapy (3.3 ± 4.1 μg/mL) as compared with patients who did not respond (2.3 ± 2.2 μg/mL, P = 0.85).

ATI levels

- 16/76 patients (22.4%) presented detectable ATI in the serum.
  - 10 ATI-positive patients had an intensification of infliximab therapy
  - 6 (60%) demonstrated a clinical response

After intensification of infliximab therapy the ATI concentration decreased in five patients.

But pariente et al. used kit of BMD which might detect false positives, ATI kit measures TL