Immune Tolerance:
Eradication of allo-antibodies: international data.

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University of Manchester

ITI: The main practical questions.

- Can we predict success?
- When should we start?
- What product should we use for ITI?
- How do we define success?
- When should we stop?
- Is it cost effective?

Proposed Predictors of Success

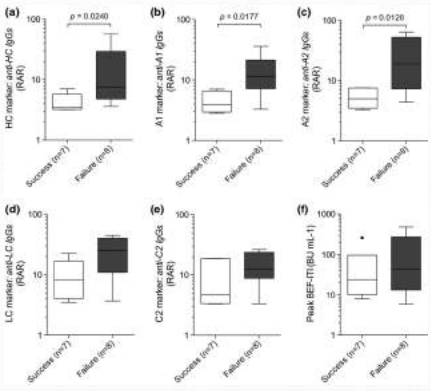
- Inhibitor titre: Peak historical <200 BU, starting titre <10 and peak on ITI[1,2,3].
- Anti-A2, Anti-A1, Anti-HC[4] (RAR).
- Low-risk FVIII Genotype[5]
- Age at start of ITI[1,6].
- Interval ≤5 years from inhibitor diagnosis to ITI[1,2].
- Bleed-rate on ITI[7]?
- Product type?

1.)Mariani G and Kroner B. Haematologica 2001;86:1186-93. 2.) Dimichele DM and Kroner B. Thromb. Haemost. 2002; 87:52-7. Hay C and Dimichele DM. Blood 2012; 119:1335-44. 4.) Lapalud P et al. J T&H 2015;13:540-47. 5.) Coppola A et al. J T&H 2009;7:1809-15. 6.) Mauser-Bunshotten EP, Blood 1995;86:983-88. 7) Kreuz W, et al. Haemophilia 2016;22:87-95

Anti-A2 and anti-A1 domain antibodies as predictors of ITI outcome

- Success correlates with: -
  - Anti-Heavy Chain (p=0.024)
  - and Anti-A2 (p=0.0128)
  - and Anti-A1 (p=0.0177)
  - But not anti-light-chain or anti-C2
- N=18.

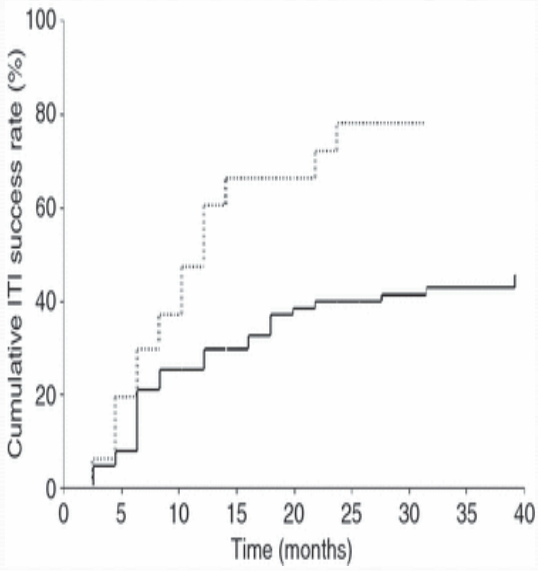
Relative Antigenic Reactivity



Lapalud P et al. J T&H 2015;13:540-47 **Journal of Thrombosis and Haemostasis**

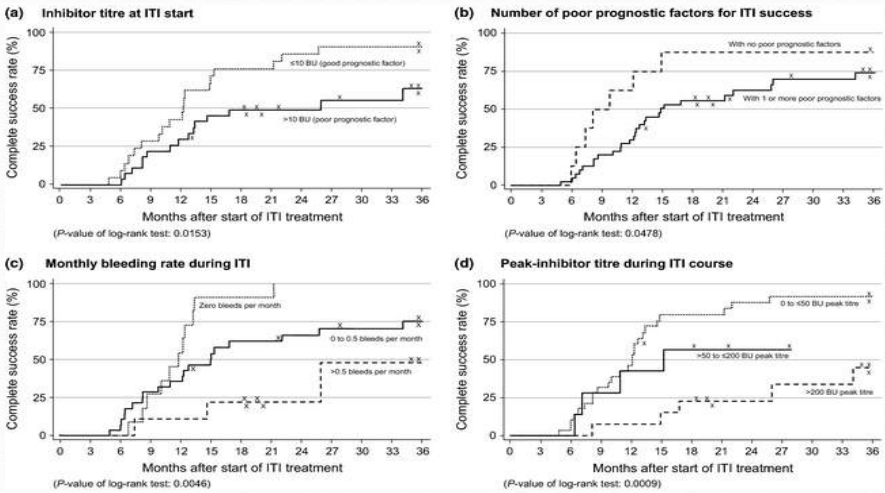
FVIII gene mutations and outcome of ITI

- Success correlates with low-risk factor VIII mutations[5].
- High –v- low; 47% -v- 81% success (p=0.01).
- N= 86, 81% high-risk, 49 with intron-22 inversion.



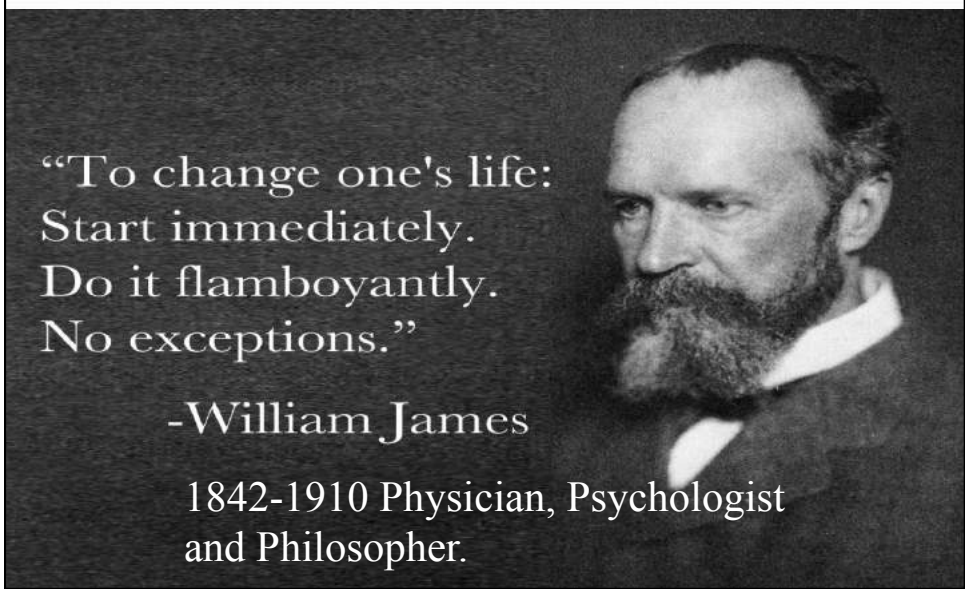
Coppola A et al. J T&H 2009;7:1809-15. **Journal of Thrombosis and Haemostasis**

OBSITI Study: Predictors of Success



Kreuz W, et al. Haemophilia 2016;22:87-95

When to start? William James' View:



Should ITI be deferred until <10 BU?

- ***Pros: -***
  - Starting titre ≤10 BU predicts success ($p < 0.001$[1,2])
  - ITI outcome unaffected by wait of ≤ 5 years (NAITR)[1,2].
  - Uniformly good results when ITI is deferred until inhibitor ≤ 10 BU[3,4,5].
  - Median 6 months to decline to <10 BU in the IITI study[6].
- ***Cons: -***
  - Starting when titre <10 may not be the same as *waiting* for it to decline.
  - *May* suffer joint damage whilst waiting to start.
  - Treatment during this interval may be very costly, especially prophylaxis.
  - Physician-need to *""get on with it"!*

1.) Mariani G and Kroner B. *Haematologica* 2001 (86): 1186; 3.) DiMichele DM et al. *Thromb Haemost* 2002 (87): 52. 3) Smith et al, *T&H* 1999:81:35-38. 4.) Rocino et al, *Vox Sang* 1999:77;65-69. 5.) Mauser-Bunshotten et al. *Blood* 1995;86:983-88. 6.) Hay and DiMichele, *Blood* 2012; 119:1335-44.

ITI deferred until <10 BU: Outcome.

Author	n	Dose	Success
Mauser-Bunschotten[1]	27	Low**	83%
Smith et al[2]	11	Interm.*	100%
Rocino et al[3]	22	Int/High***	82%

* Intermediate-purity pdFVIII

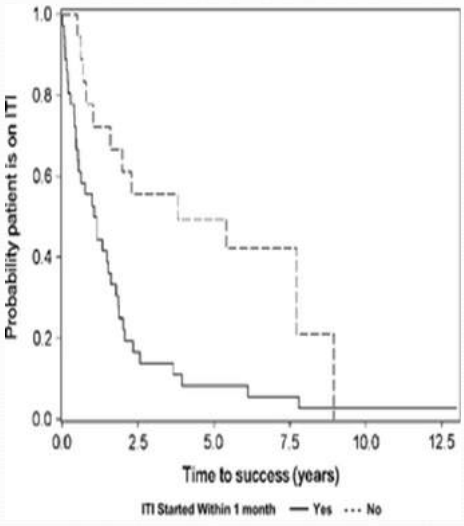
** High-purity pdFVIII/rFVIII.

*** Solely rFVIII. Proportion of poor-risk patients.

1.) Mauser-Bunshotten et al. *Blood* 1995;86:983-88. 2.) Smith et al, *T&H* 1999:81:35-38.
3.) Rocino et al, *Haematologia 2006;91(4) 558-61*

Early versus late start of ITI.

- Observational retrospective study.
- 32/39 high responders successful and 7/39 failed.
- 23/39 started <1 mth after inhibitor detection
  - No correlation with starting titre.
- 11/39 started >6 mths after inhibitor detection.
  - 64% success.
  - Delayed starters older
  - Are groups are comparable?



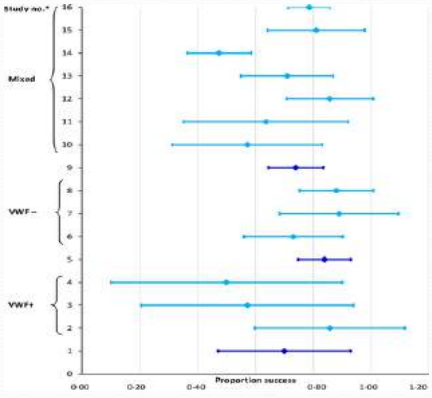
What product to use for ITI?

Effect of von Willebrand factor on ITI haemophilia A: a systematic review.

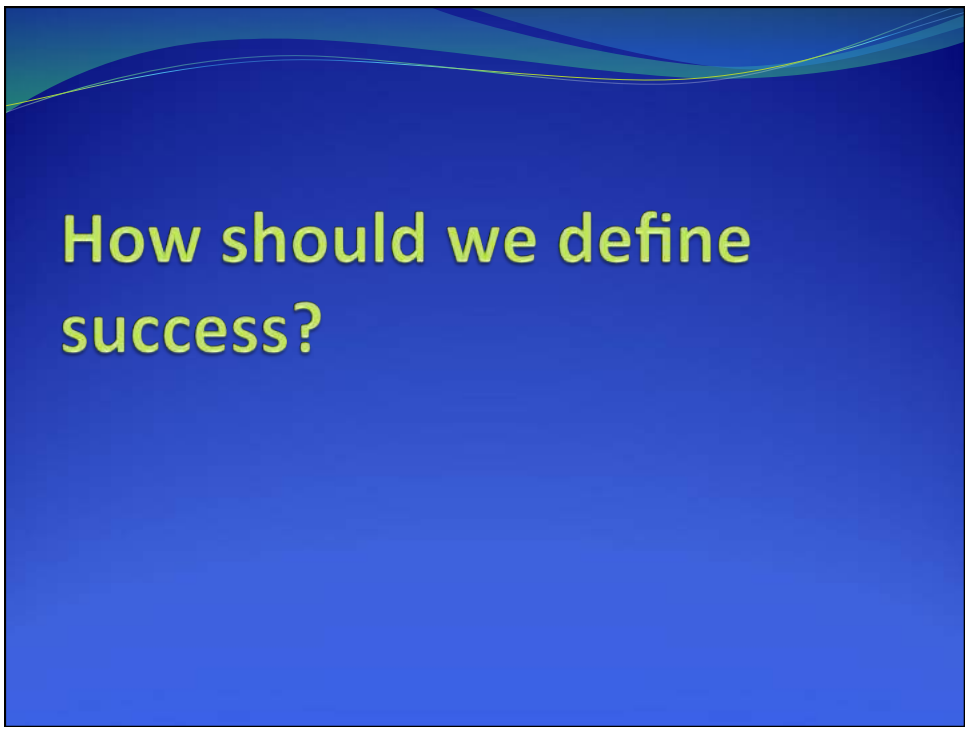
ITI by Product-Type.

- 26 studies inc. 1284 pts.
- Pooled meta-analysis of 13 studies.
- Pooled proportion of success:
- VWF+ve: -
  - RR 0.70 (95% CI 0.52-0.89)
- VWF –ve: -
  - RR 0.84 (95% CI 0.75-0.93)
- Mixed: -
  - RR 0.74 (95% CI 0.65-0.84)

Proportion of success (95% CI) of studies by FVIII product.



Van Velzen AS, Peters M, van der Bom J, Fijnvandraat K. British Journal of Haematology 2014;166:485-495



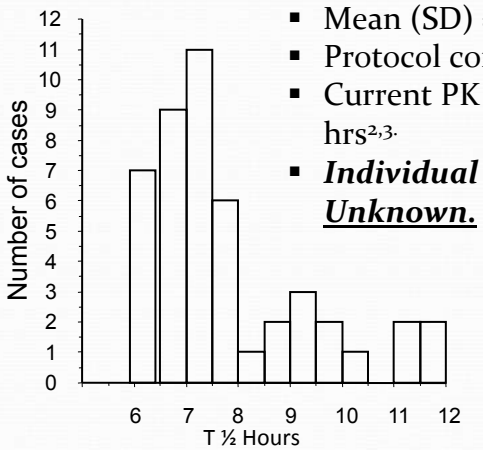
Agreed Definitions: Success, Failure and Partial Success.

As agreed at the ISTH VIII and IX SSC, Toronto June 2015: -

- Success: Restoration of normal PK.
  - Recovery >66% *and* ½-life ≥7 hrs[1,2.]
  - Or measurable FVIII trough 48 Hrs after 50 IU/kg[4.]
- Partial response:
  - Stable clinical response to factor VIII, without an anamnestic rise in inhibitor with abnormal PK[1,4].
- Failure:
  - Failure to achieve tolerance or partial response, with no specified time-limit.

1.) Hay and DiMichele, *Blood* 2012; 119:1335-44; 2.) Blanchette et al J *T&H* 2008, 6; 1319-26; 3.) Bjorkman et al *Blood* 2012; 119: 612-8; 4.) Collins et al, *UKHCDO* Inhibitor Guidelines BJ Hamatol 2013;160:153-70.

Distribution of factor VIII half-life at the time of tolerance (IITI Study).

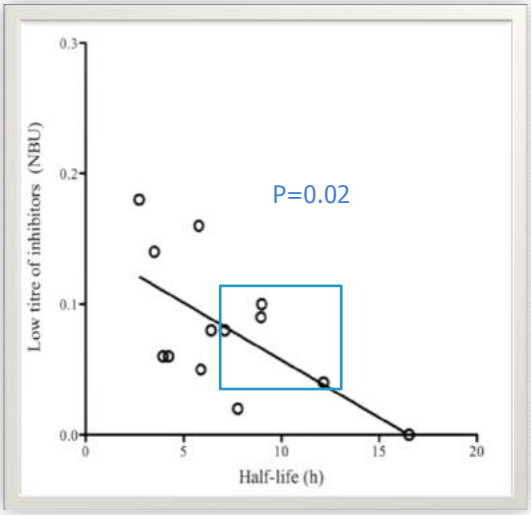


- Mean (SD) = 7.81(1.54), n=46.
- Protocol consensus min. 6 hrs[1].
- Current PK data suggest min. 7 hrs[2,3].
- ***Individual patient norm: <u>Unknown.</u>***

1.) Hay and DiMichele, *Blood* 2012; 119:1335-44; 2.) Blanchette et al *J T&H* 2008, 6; 1319-26; 3.) Bjorkman et al *Blood* 2012; 119: 612-8

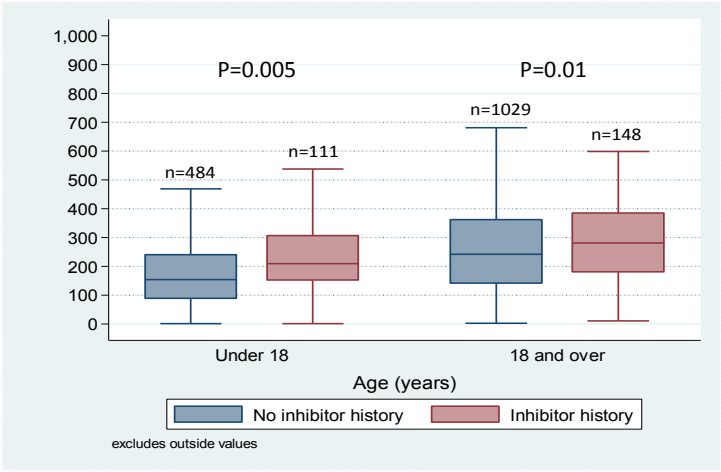
Correlation between LTA and ½-life

- The lower limit of detection of LTA is 0.04 BU/ml.
- The lower limit of normal for ½-life in children is 7 hrs
- 4/13 subjects, with a ½-life ≥ 7hrs have an LTA >0.04 BU.
- Likely they have not "normalised" their half-life to their personal norm and have low-level inhibitors.



Dardikh M, et al. Low titre inhibitors undetectable by the Nijmegen assay reduce factor VIII ½-life after ITI. *J T&H* 2012; 10(4): 706-8.

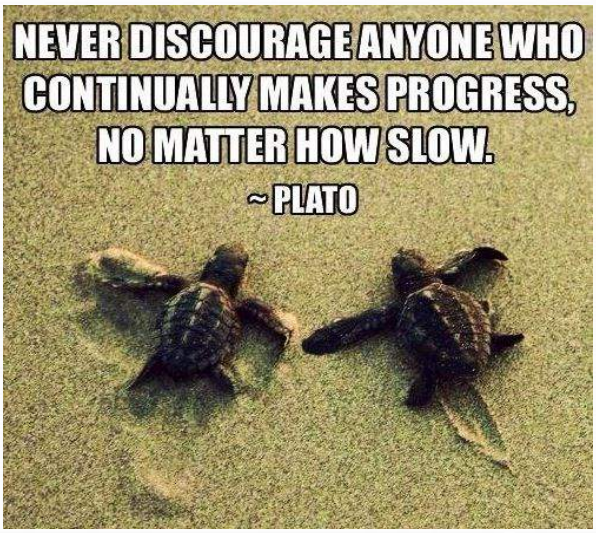
Factor VIII usage (IU/yr.) remains high in "tolerised" children.



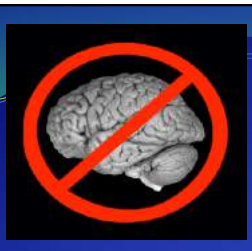
Hay et al. 2015 UKHCDO Annual Report © UKHCDO 2015

When to stop?

When to stop ITI? Plato's view:



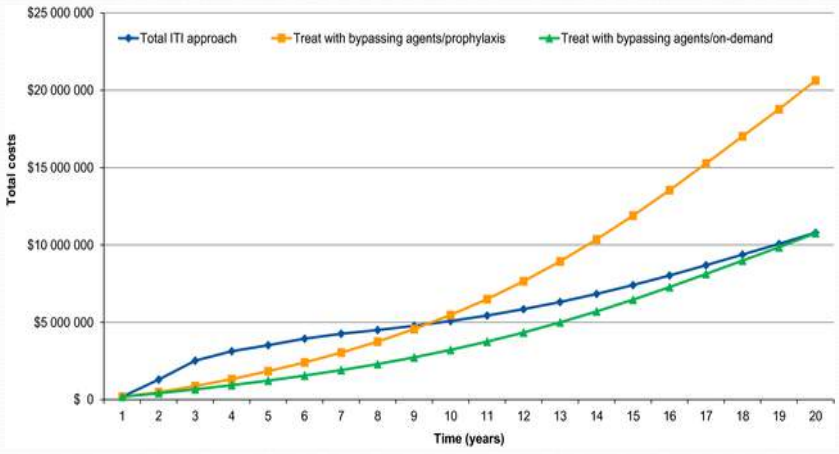
Is ITI cost-effective?



Does ITI save money and morbidity? A Decision-Analytical Model.

- Lifetime estimate of cost, morbidity and life expectancy
  - ITI –v- treatment on demand –v- bypass prophylaxis.
  - Assuming: -
    - ITI dose: 200 IU/kg. + Novoseven 180 ug.kg/day prior to start.
      - Novoseven prophylaxis for 2 yrs before ITI.
    - Novoseven dose from Fenoc study (109 ug/kg 2hrly).
    - Feiba Prophylaxis 85 u/kg thrice weekly (Leisinger NEJM 2011).
- All costs were extremely high, because of the worst-case assumptions made and unit cost estimate.

Cost analysis of ITI –v- Bypass prophylaxis –v- on-demand.



Earnshaw SR. et al. Haemophilia 2015, 21(3);310-319.


…er.. I would just like to say er… Thank you for your attention!