VANDERBILT UNIVERSITY MEDICAL CENTER

FROM MOLECULE TO PATIENT

Understanding Immune-Mediated Drug Toxicities: *A Roadmap for Translation and Discovery*

John A. Oates Chair in Clinical Research
Professor of Medicine and Pharmacology
Vanderbilt University Medical Center

Professor & Director
Centre for Clinical Pharmacology and Infectious Diseases
Institute for Immunology and Infectious Diseases
Murdoch University

INSTITUTE FOR IMMUNOLOGY & INFECTIOUS DISEASES
Murdoch UNIVERSITY

ASCPT March 14, 2019: Applications of Immunopharmacogenomics

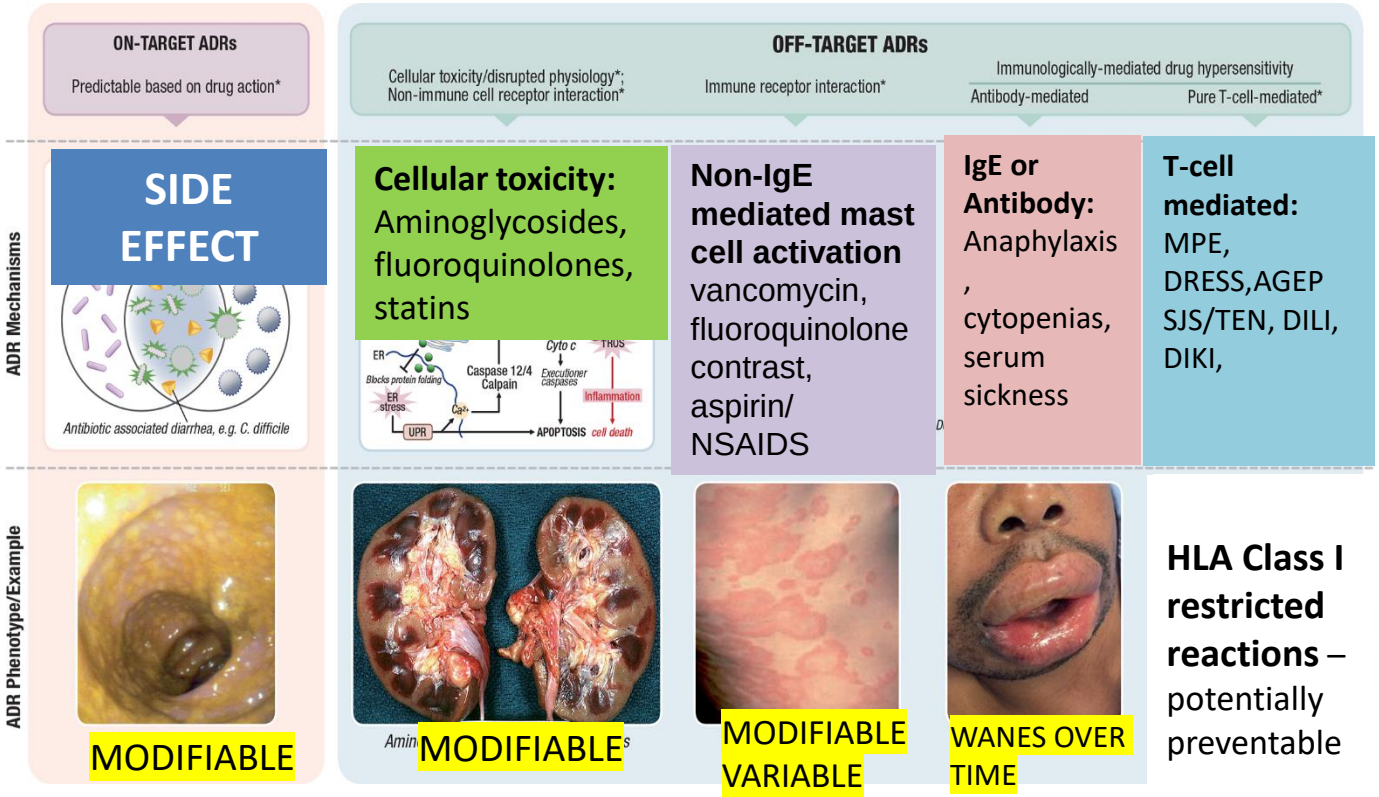
Disclosures

- Patent: Equity in IIID that has a patent for HLA-B*57:01testing for abacavir hypersensitivity
- Provisional patent: testing for vancomycin hypersensitivity

Key Messages

- HLA associations with severe T-cell mediated adverse drug reactions
- Translational road map successes
- HLA associations have helped define mechanisms
- ”Negative predictive gap”
  - Associations with many drugs/populations still to be defined
- “Positive predictive gap”
  - Why do only a small fraction of those carrying a risk allele develop disease
- HLA testing and its utility beyond screening
- What to look forward to

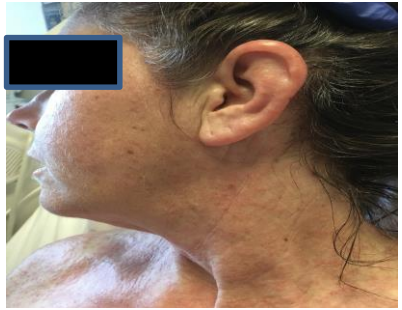
Classification of Adverse Drug Reactions

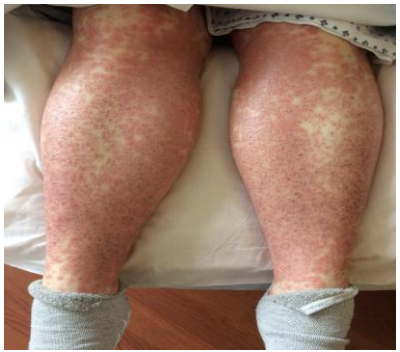


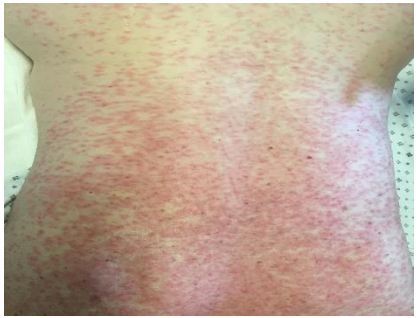
Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ Lancet 2019 Jan 12;393(10167):183-198

Case

- 48 year old woman otherwise healthy
- Donated blood and weeks later develops high fever and found to be bacteremic with E. coli and MRSA RUL infiltrate.
- Started vancomycin + levofloxacin
- 2 weeks later generalized rash, facial edema and fever
- Eosinophilia peak 1.7 and LFTs ALT 4 x ULN
- On high dose prednisone weaned over 5 months







Questions?

- What is the likely diagnosis?
- Is this drug related?
- Is there a most likely implicated drug and how you determine this?
- Can this be prevented or preempted?
- Would knowledge of genetic background help in the diagnosis?

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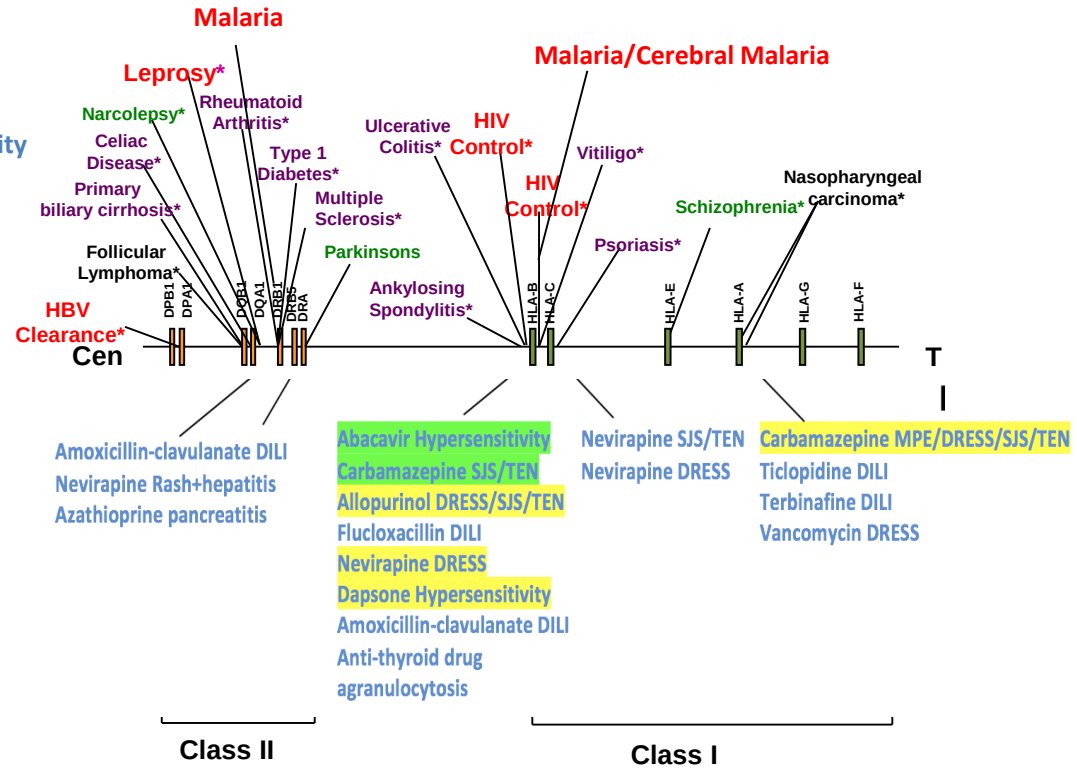
VARIATION IN HLA AND DISEASE ASSOCIATIONS

* Top Hit

1970s-2000s

Autoimmune
Cancer
Infectious Diseases
Neurology
Drug Hypersensitivity



2002-present

Amoxicillin-clavulanate DILI
Nevirapine Rash+hepatitis
Azathioprine pancreatitis

Abacavir Hypersensitivity
Carbamazepine SJS/TEN
Allopurinol DRESS/SJS/TEN
Flucloxacillin DILI
Nevirapine DRESS
Dapsone Hypersensitivity
Amoxicillin-clavulanate DILI
Anti-thyroid drug agranulocytosis

Nevirapine SJS/TEN
Nevirapine DRESS

Carbamazepine MPE/DRESS/SJS/TEN
Ticlopidine DILI
Terbinafine DILI
Vancomycin DRESS

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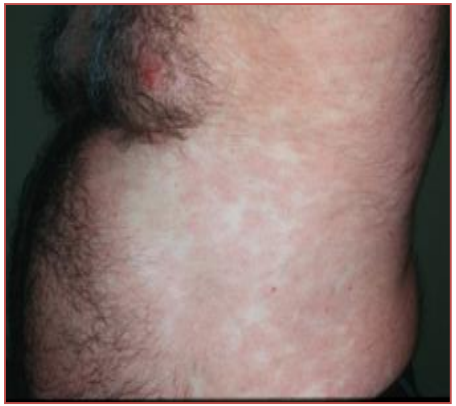
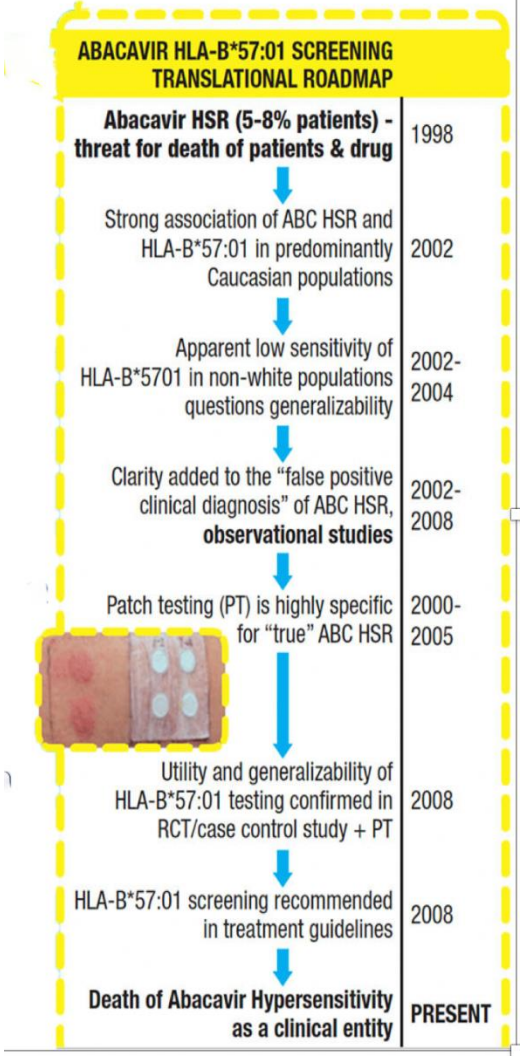
- Beyond – potential utility of HLA as adjunctive diagnostic test
- What to look forward to

HIV Drug Abacavir - HLA Translation "Death" of Hypersensitivity Syndrome

- 5-8% of patients developing fever, malaise and later rash average 8 days into treatment
- Symptoms disappear rapidly on stopping drug
- Hypotension, shock, death could occur rapidly on rechallenge
- Seen less commonly in those of non-European origin
- Warning card issued and used as clinical safety strategy until HLA-B*57:01 guideline based widespread screening





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ALTERED PEPTIDE REPERTOIRE MODEL (2012)

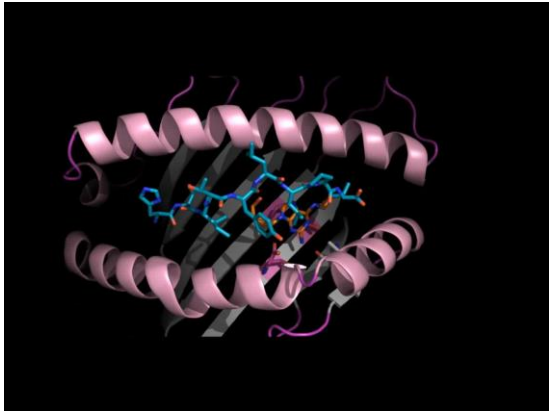
19 June 2012

PNAS

Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire

David A. Ostrov[a], Barry J. Grant[b], Yuri A. Pompeu[c], John Sidney[d], Mikkel Harndahl[e], Scott Southwood[d], Carla Oseroff[d], Shun Lu[a], Jean Jakoncic[f], Cesar Augusto F. de Oliveira[g], Lun Yang[h], Hu Mei[h], Leming Shi[h], Jeffrey Shabanowitz[i], A. Michelle English[i], Amanda Wriston[i], Andrew Lucas[j], Elizabeth Phillips[j], Simon Mallal[j], Howard M. Grey[d,1], Alessandro Sette[d], Donald F. Hunt[i], Soren Buus[e], and Bjoern Peters[d,1]

[a]Department of Pathology, Immunology and Laboratory Medicine, University of Florida College of Medicine, Gainesville, FL 32611; [b]Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI 48109; [c]Department of Chemistry, University of Florida, Gainesville, FL 32611; [d]Division of Vaccine Discovery, La Jolla Institute for Allergy and Immunology, La Jolla, CA 92037; [e]Laboratory of Experimental Immunology, Faculty of Health Sciences, University of Copenhagen, 2200 Copenhagen, Denmark; [f]Brookhaven National Laboratory, Upton, NY 11973; [g]Departments of Chemistry and Biochemistry, Howard Hughes Medical Institute, and Center for Theoretical Biological Physics, University of California at San Diego, La Jolla, CA 92037; [h]National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR 72079; [i]Department of Chemistry, University of Virginia, Charlottesville, VA 22901; and [j]Institute for Immunology and Infectious Diseases, Murdoch University, Perth 6150, Australia



28 June 2012

LETTER

doi:10.1038/nature11147

Immune self-reactivity triggered by drug-modified HLA-peptide repertoire

Patricia T. Illing[1,2], Julian P. Vivian[3], Nadine L. Dudek[2], Lyudmila Kostenko[1], Zhenjun Chen[1], Mandvi Bharadwaj[1], John J. Miles[4,5], Lars Kjer-Nielsen[1], Stephanie Gras[3], Nicholas A. Williamson[2], Scott R. Burrows[4], Anthony W. Purcell[2]*, Jamie Rossjohn[3,5]* & James McCluskey[1,6]*

17 July 2012

FAST TRACK

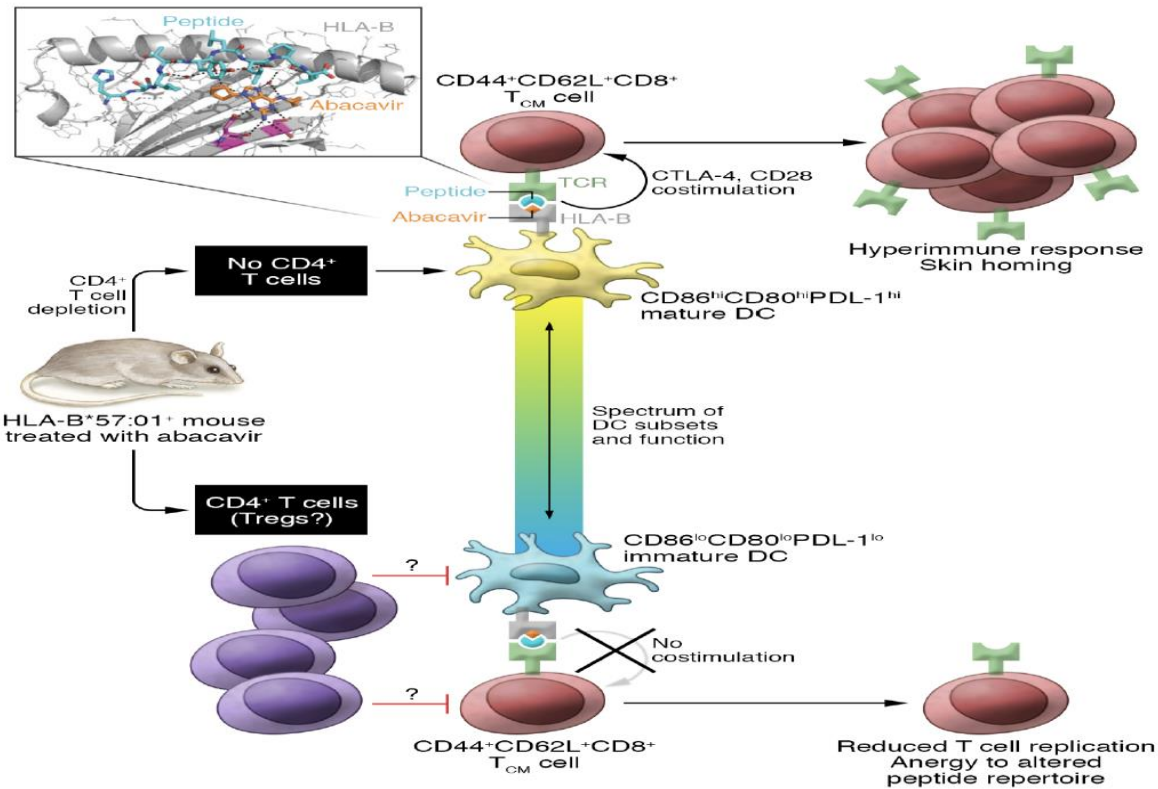
Abacavir induces loading of novel self-peptides into HLA-B*57:01: an autoimmune model for HLA-associated drug hypersensitivity

Michael A. Norcross[a], Shen Luo[a], Li Lu[a], Michael T. Boyne[b], Mary Gomartelli[c], Aaron D. Rennels[c], Janet Woodcock[d], David H. Margulies[e], Curtis Mcmurtrey[f], Stephen Vernon[f], William H. Hildebrand[f] and Rico Buchli[c]

PNAS 2012; 109(25):9959; Nature 2012;486(7404):554; AIDS 2012;26(11):F21

HLA-B*57:01+ Abacavir Tolerance: Further Insights (2018)

Abacavir alters repertoire of self-peptides presented to CD8+ T cells
In all HLA-B*57:01+



in the absence of CD4+ T-cell depletion dendritic cells remain in an immature state and there is tolerance to the altered peptide repertoire

Cardone et al 2018;128(7):2819–2832
Phillips E and Mallal S JCI 2018;128(7):2746–2749

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25.7 Million Africans Living with HIV

END TB

SOUTH AFRICA

POPULATION: 57 MILLION

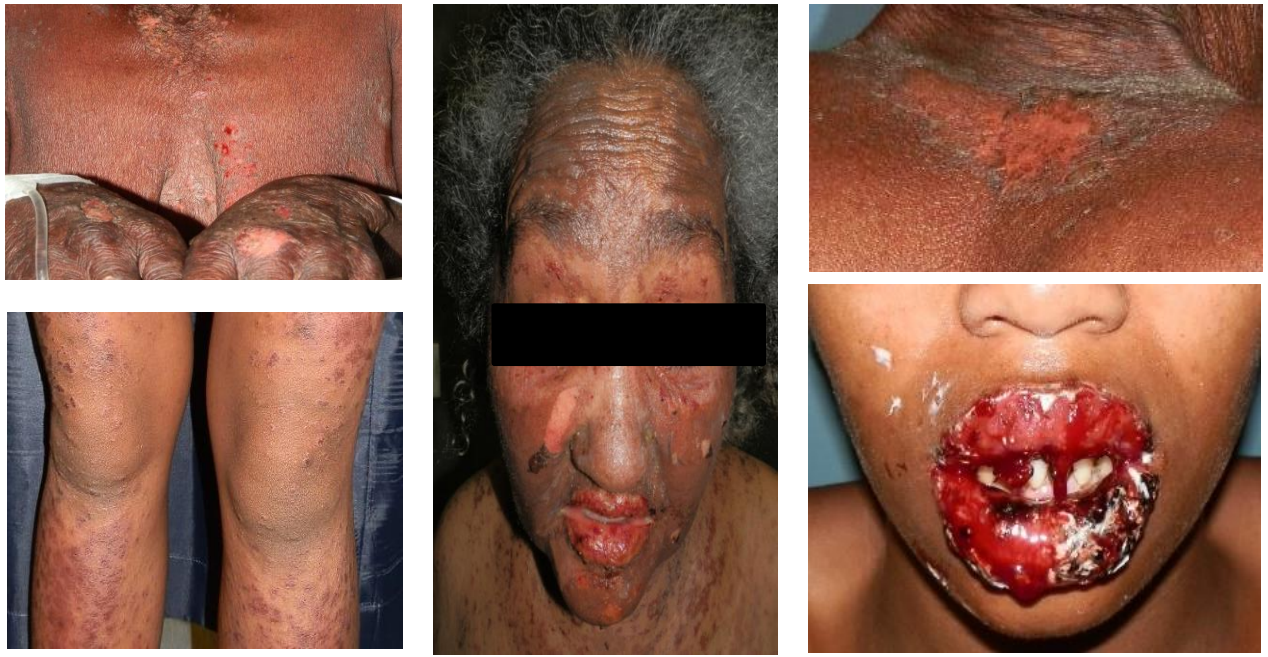
World Health Organization

WHO GLOBAL TB REPORT 2018

About 5000 new HIV infections (adults and children) a day | 2017

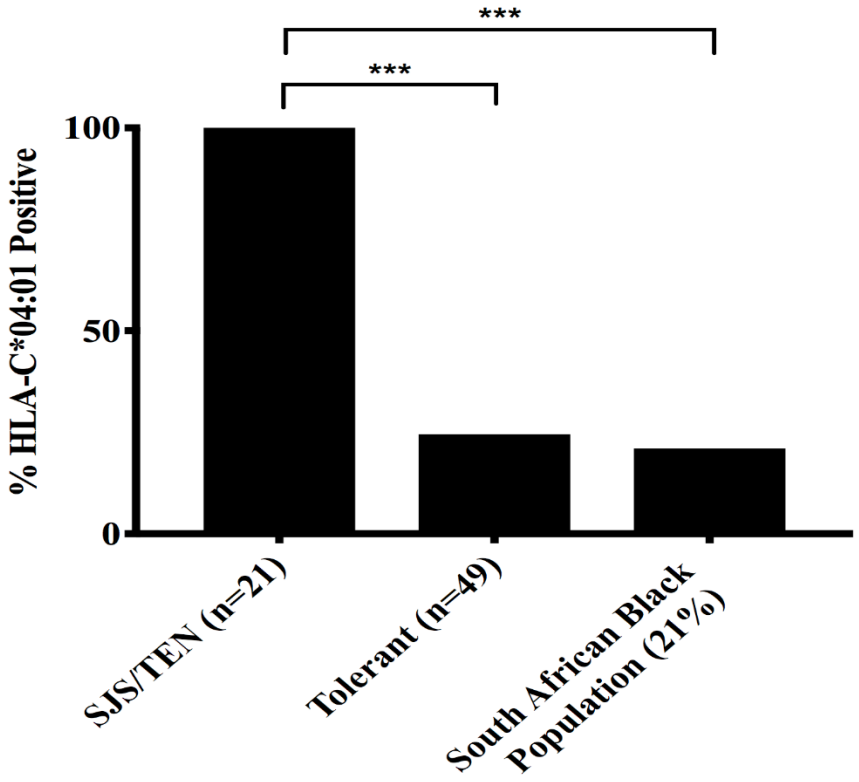
- About 66% are in sub-Saharan Africa
- About 500 are among children under 15 years of age
- About 4400 are among adults aged 15 years and older, of whom:
  - almost 43% are among women
  - about 33% are among young people (15–24)
  - about 19% are among young women (15–24)

Severe Immune Mediated ADRs are the Limiting Toxicity of Nevirapine



Nevirapine Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis in South Africa

HLA-C*04:01 is a Risk Allele for Nevirapine SJS/TEN



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HLA: Global Implications for Translation

Drug	HLA Allele	Population	OR	PPV	NPV	Number to test to prevent 1*
Abacavir	B*57:01	European <1% Africa/Asia	960	55%	100%	13
Allopurinol	B*58:01	Asia 10-15% African 5-8% American 4% African European 1-6%	>800	3%	variable	250
Carbamazepine SJS/TEN	B*15:02	Southeast Asian <1% European <1% African	>1000	3%	variable	1000
Dapsone DRESS/DIHS	B*13:01	East Asians 0% Europeans 0% African	20	7.8%	variable	84
Flucloxacillin	B*57:01	European <1% Africa/Asia	81	0.14%	variable	14000

*in populations of high prevalence

Not all patients with an HLA risk allele develop disease
"Positive Predictive Gap"

Abacavir Hypersensitivity Syndrome

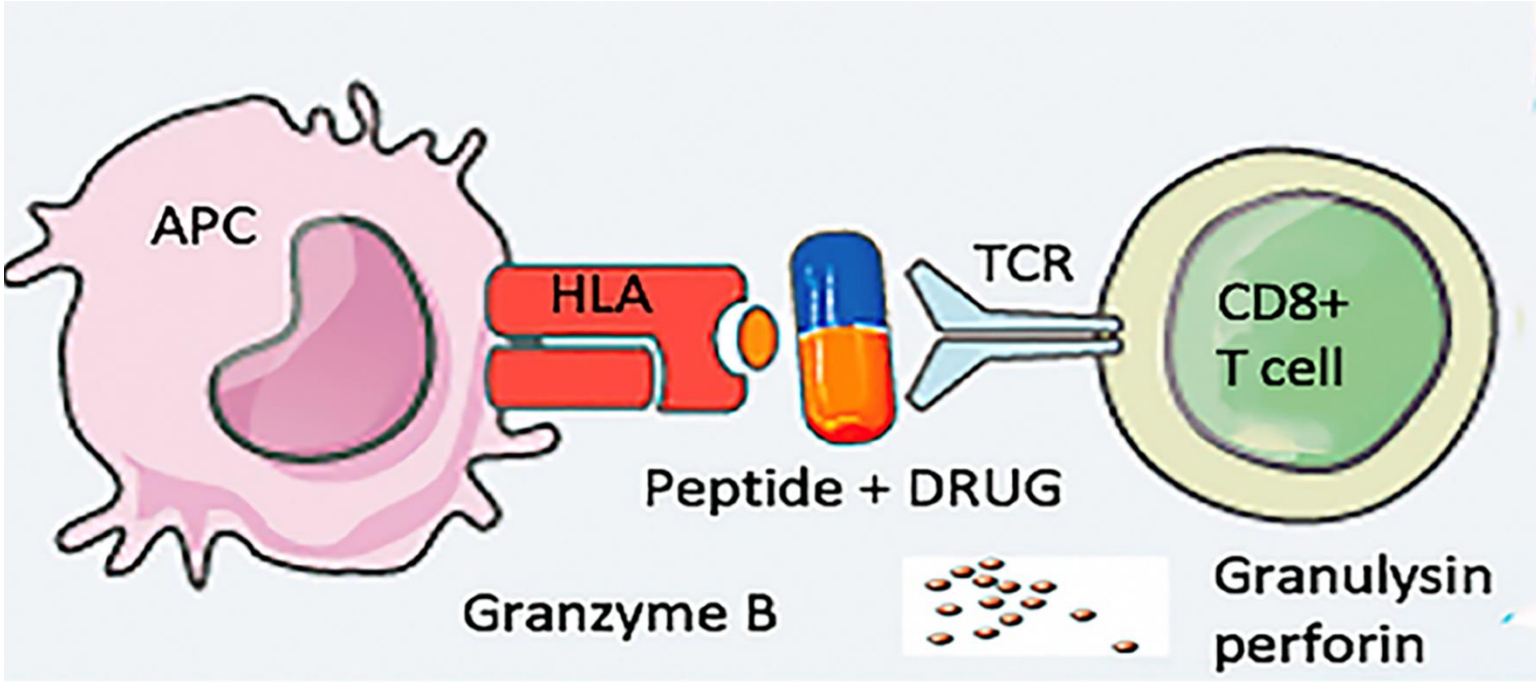
55% of HLA-B*57:01

Allopurinol DRESS or SJS/TEN*

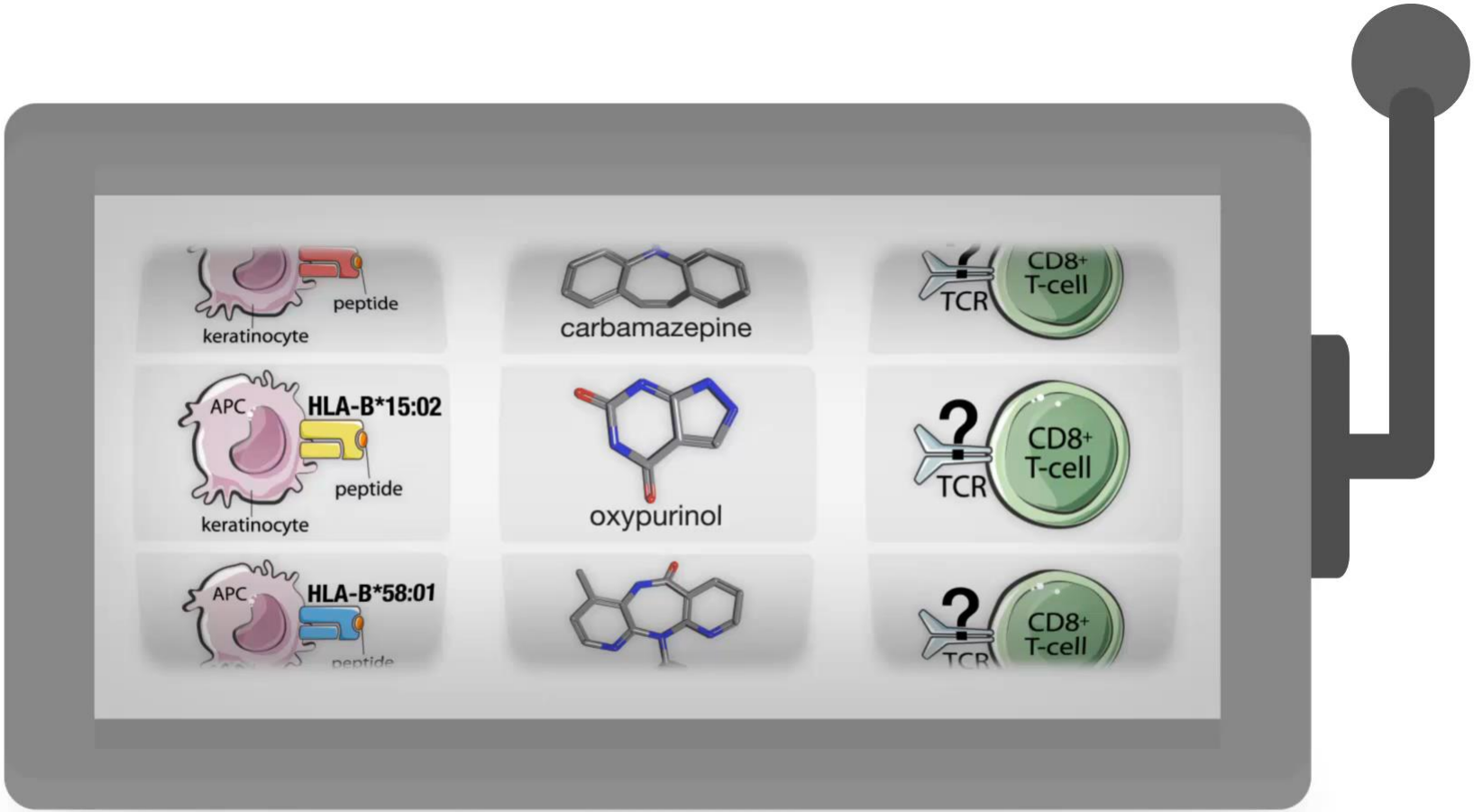
3% of those carrying HLA-B*58:01

*Drug reaction with eosinophilia and systemic symptoms
Stevens-Johnson syndrome/toxic epidermal necrolysis

Drug Interacts with HLA Protein on Antigen Presenting Cell which Activates T cells

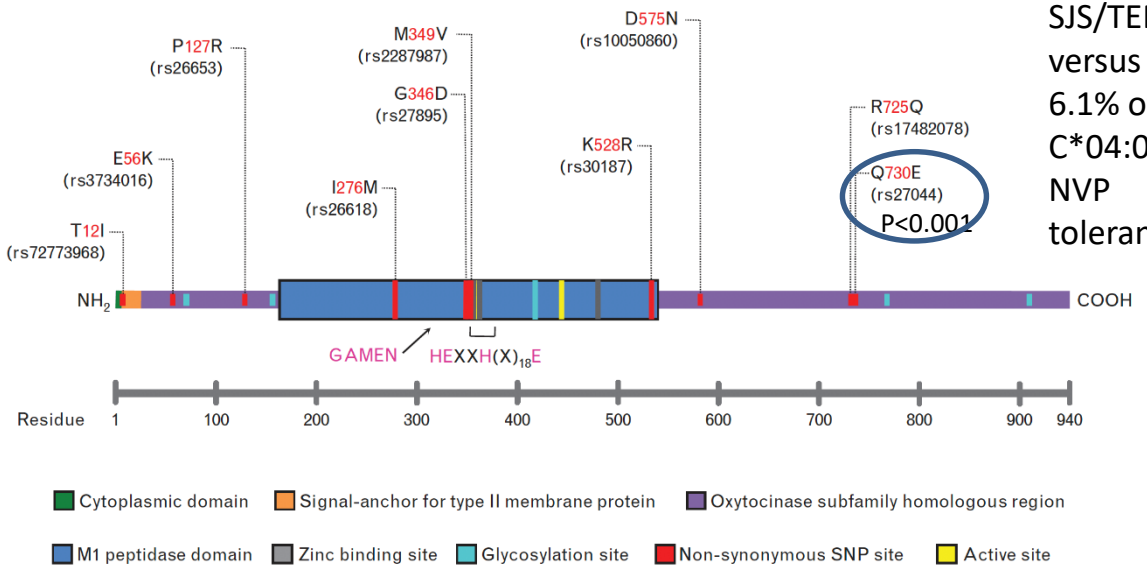


Adapted from Peter *et al*. J Allergy Clin Immunol Pract. 2017; 5(3):547-563.


peptide
keratinocyte
carbamazepine
TCR
CD8+
T-cell
APC
HLA-B*15:02
peptide
keratinocyte
oxypurinol
?
TCR
CD8+
T-cell
APC
HLA-B*58:01
?
TCR
CD8+
T-cell

Role of Antigen Processing in HLA-C*04:01 Carriers

ERAP-1 (chromosome 5)

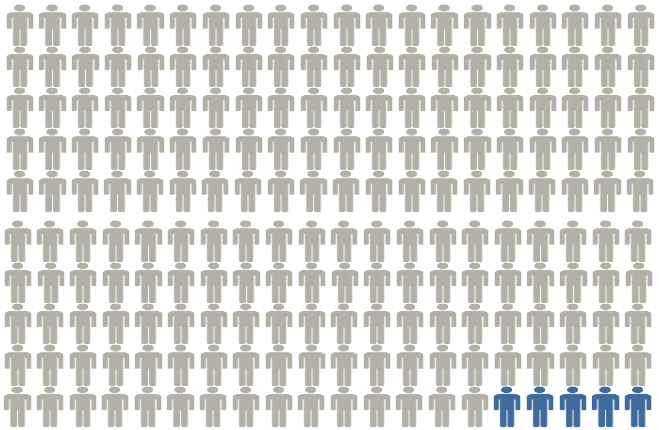


86% of C*04:01 SJS/TEN versus 6.1% of C*04:01+ NVP tolerant

- Altered trimming activity
- HLA-B*27+ spondyloarthropathies

Nevirapine HLA-C*04:01 Implementation Considerations

HLA-C*04:01 carriers



1000 patients starting on nevirapine

100 would carry C*04:01+rs27044C

5 would develop nevirapine SJS/TEN

Therefore 100 needed to screen to prevent one case of NVP SJS/TEN

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Case

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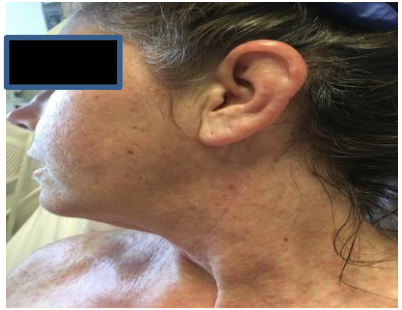
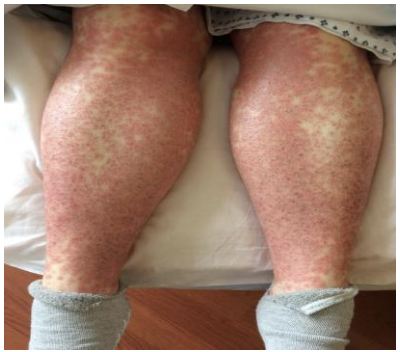
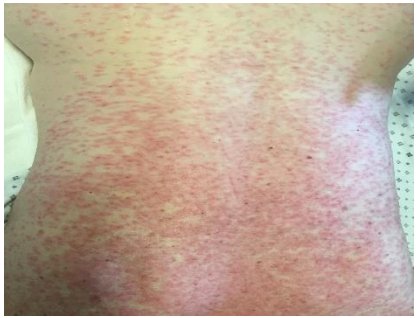






Drug Rash with Eosinophilia and Systemic Symptoms

ACUTE

- **Fever**
- Facial edema
- **Extensive rash (>50% BSA)**
- **Organ (liver, kidney)**
- **Hematology (eosinophilia, atypical lymphocytosis)**
- **Lymphadenopathy**
- **Supportive pathology**

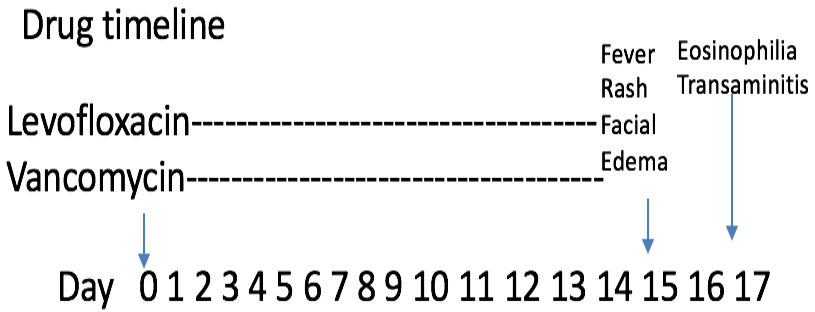
Weeks to years

- EBV/CMV/HHV-6 reactivation
- Relapse
- Autoimmune thyroiditis
- Other autoimmune manifestations (lupus, diabetes

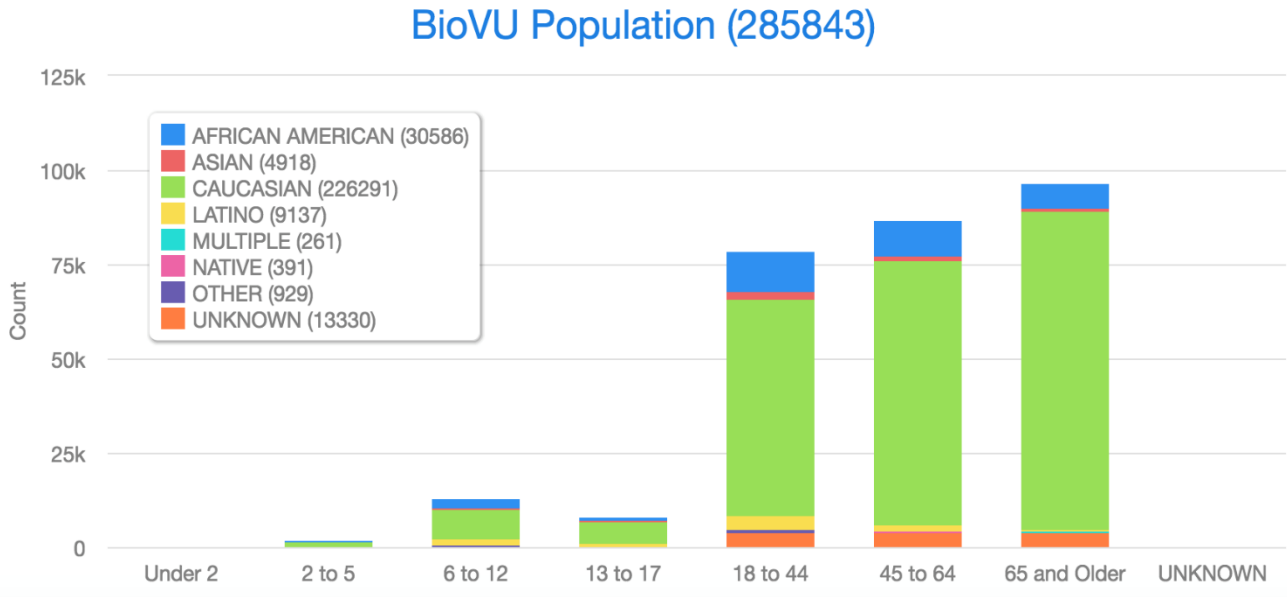
10% Mortality secondary to organ failure or complications of immunosuppression

Drug Reaction with Eosinophilia and Systemic Symptoms

- What is the most likely drug?



- Can this reaction be prevented or preempted?
- Could knowledge of genetics help in causality assessment in DRESS occurring on multiple antibiotics

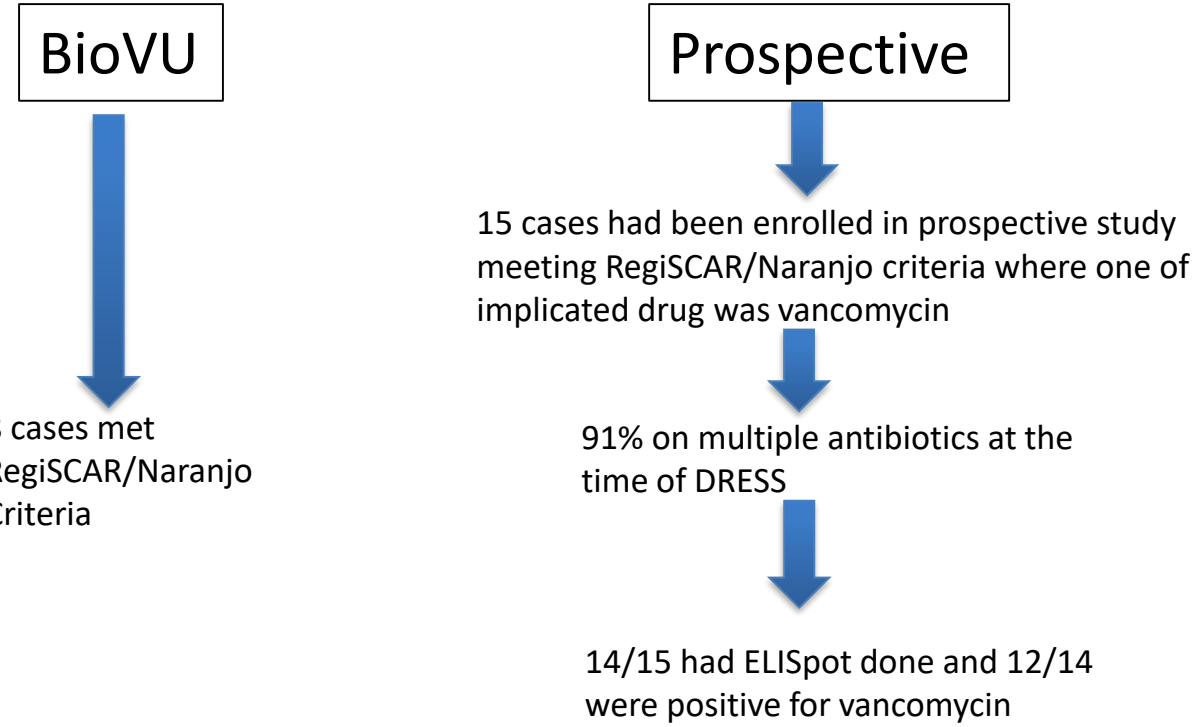


-8 cases out of 174 both met criteria (RegiSCAR $\geq$ 4 for DRESS and had DNA or typing available)

-6/8 carried the same HLA class I allele; this same allele present in <7% of population

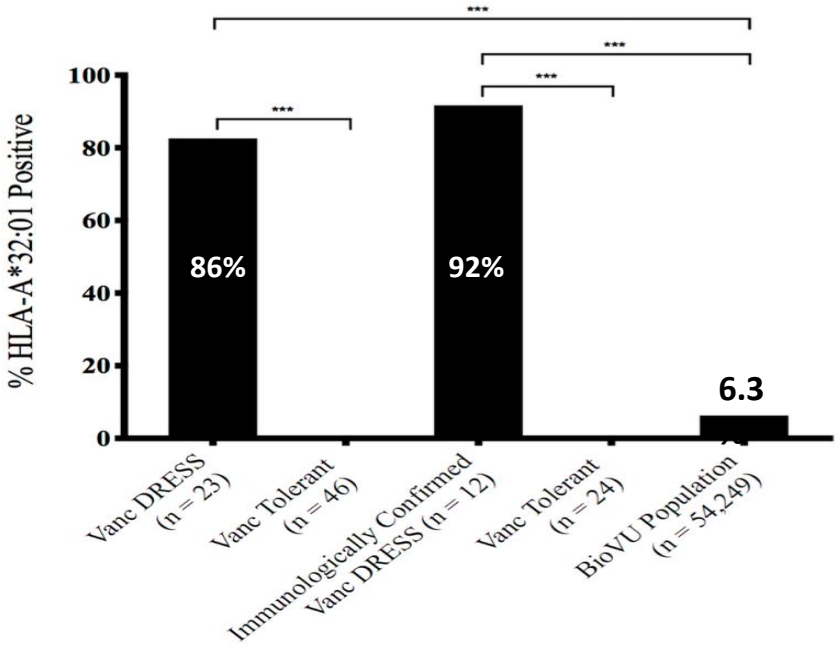
Vancomycin DRESS: Prospective Study

- Three centers (VUMC, Institute for Immunology & Infectious Diseases (Perth Hospitals) and Austin Hospital (Melbourne)
- Adults developed DRESS 2009-2018
- RegiSCAR criteria probable $\geq$4 and Naranjo $\geq$5
- PBMCs, DNA and skin collected
- HLA ABC DR DQ DP typing on all cases
- γ-interferon ELISpot done on all cases acutely, follow-up, multiple time points when possible to all possible implicated drugs



23 cases matched age, race and sex 2:1 with vancomycin tolerant controls from BioVu (with available imputed HLA typing) defined as ≥5 weeks of vancomycin with therapeutic trough levels

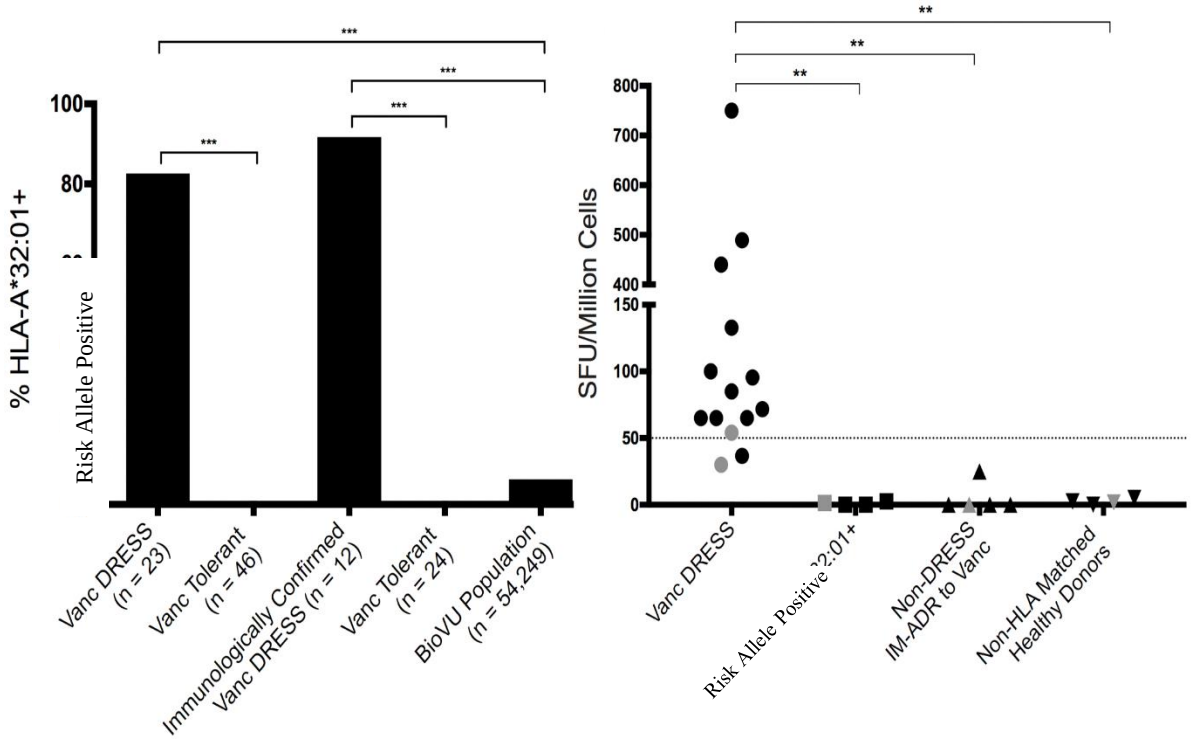
HLA-A*32:01 is Strongly Associated With Vancomycin DRESS



P= 1 x 10^{-8} conditional logistic analysis; Bonferroni control for multiple comparison

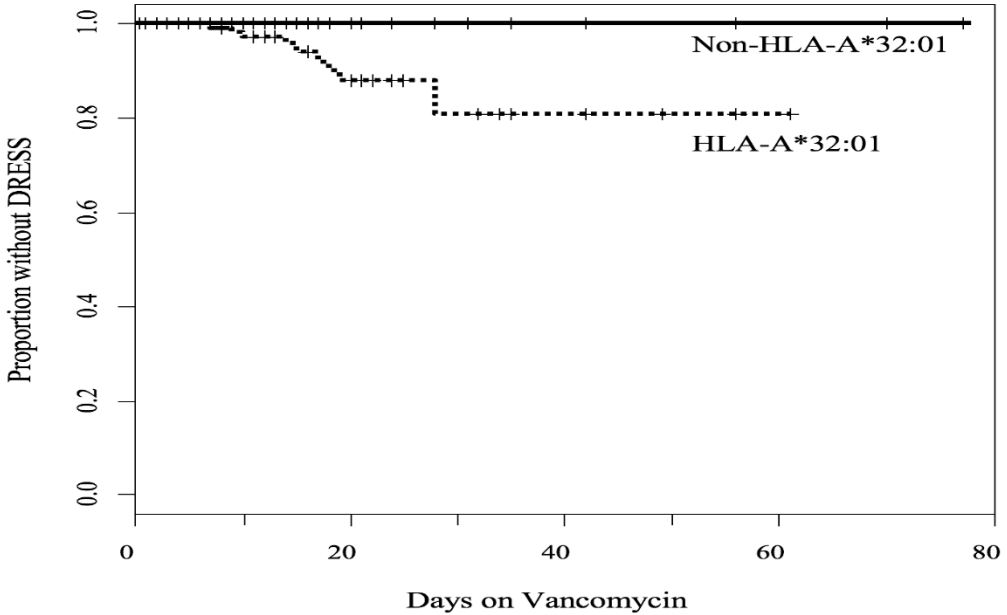
Konvinse et al J Allergy Clin Immunol. 2019 Feb 15 [Epub ahead of print]

92% (11/12) of the Vancomycin ELISpot Positive Cases Carried the Risk Allele



Konvinse et al J Allergy Clin Immunol. 2019 Feb 15 [Epub ahead of print]

Survival Analysis in BioVu



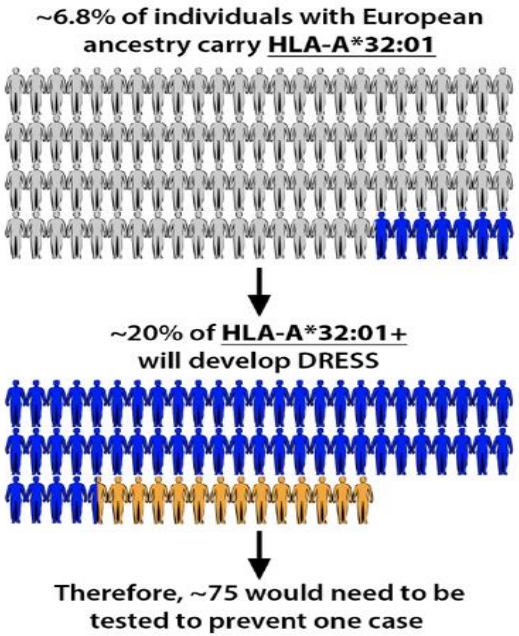
Numbers on Vancomycin:

137	99	41	18	16	5	HLA-A*32:01
137	104	50	32	28	4	Non-HLA-A*32:01

*approximately 20% of patients carrying HLA-A*32:01 developed DRESS by 4 weeks

Konvinse et al J Allergy Clin Immunol. 2019 Feb 15 [Epub ahead of print]

HLA-A*32:01 and Vancomycin DRESS Implications for Translation



-**SCREEN** – for emergent use not practical but DRESS latency ≥2 weeks

-PREEMPT- intervene early if patient at risk

-DIAGNOSIS – adds to causality (with clinical and functional assessments)

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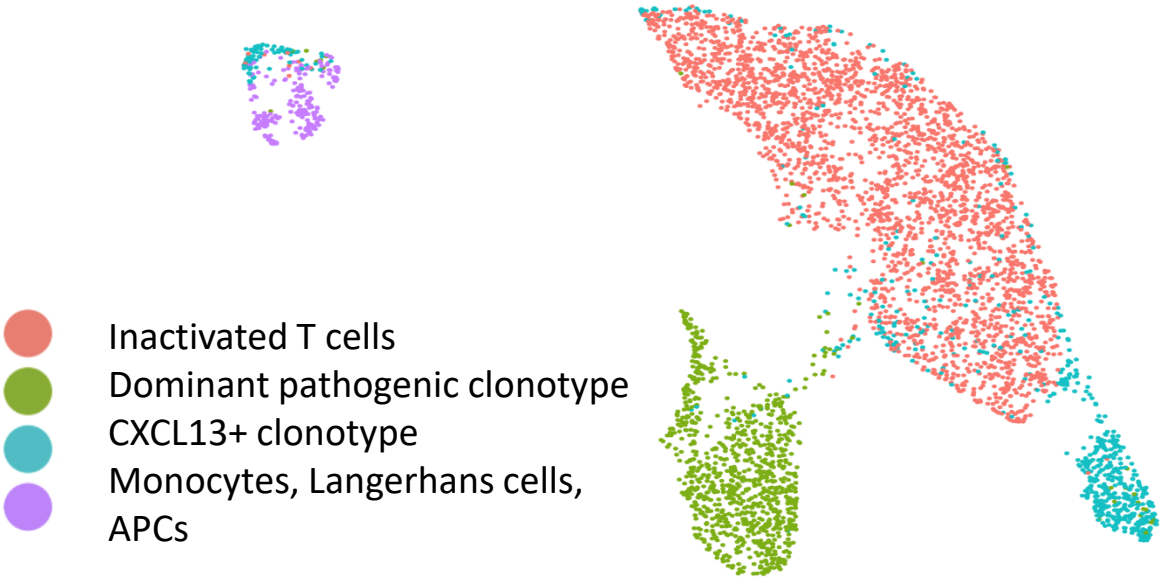
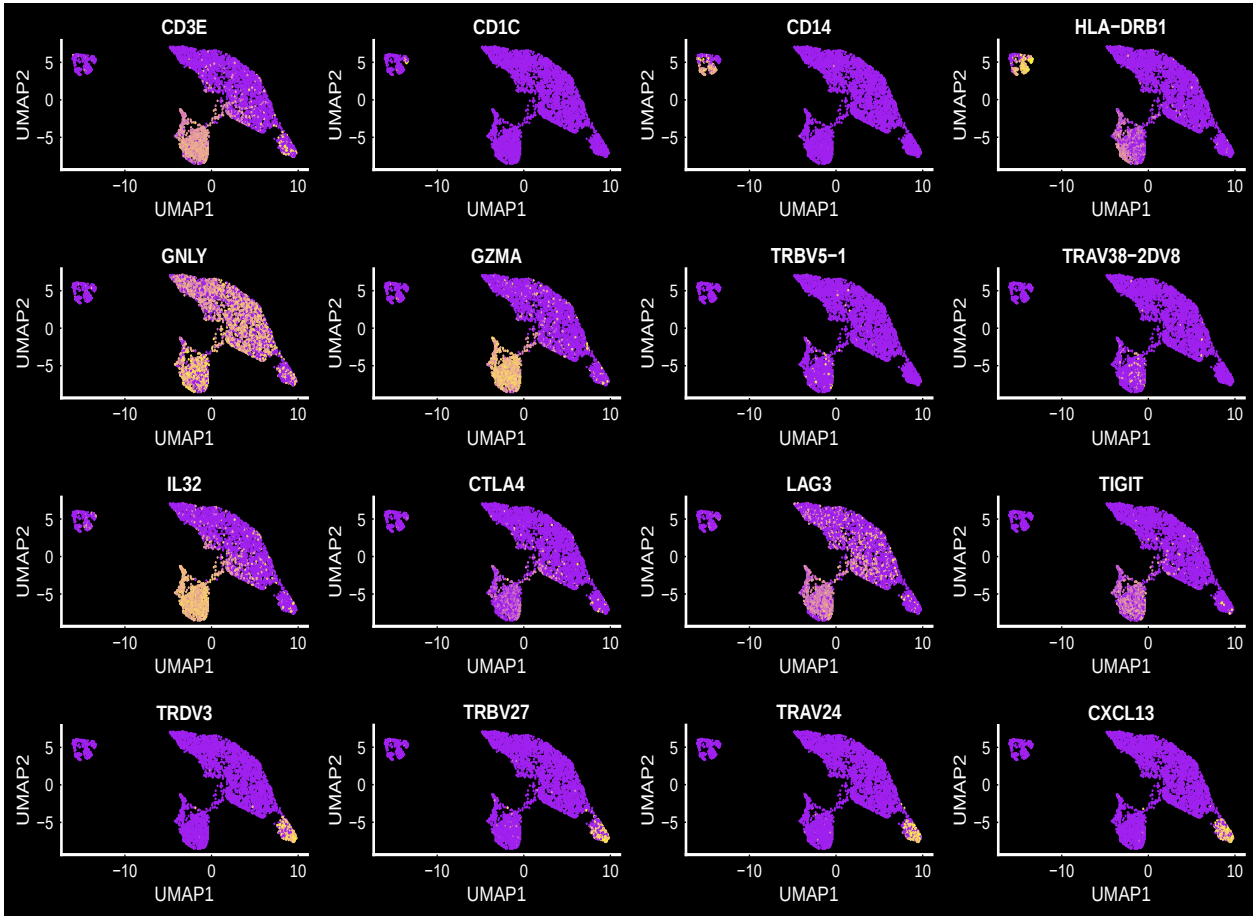
HLA-B*58:01 + allopurinol SJS/TEN
Blister Fluid Clusters




CD3E
CD1C
CD14
HLA-DRB1
GNLY
GZMA
TRBV5-1
TRAV38-2DV8
IL32
CTLA4
LAG3
TIGIT
TRDV3
TRBV27
TRAV24
CXCL13
UMAP1
UMAP2
5
0
−5
−10
0
10

Granulysin as Biomarker for Earlier Diagnosis of SJS/TEN

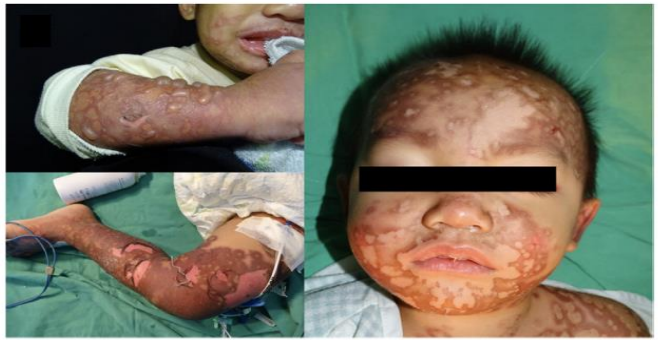


FIGURE 1 | Multiple reddish macules, patches and tense bullae with atypical target lesions over the face, neck, trunk and limbs of patient. Written informed consent was obtained from the mother of the patient for publication.

Positive rapid granulysin test in child with vancomycin SJS/TEN

Lin et al Frontiers Pediatrics 2018:6

Rapid immunochromographic test for granulysin

Syndrome	Blister fluid granulysin concentration
SJS/TEN	High: 100 ng/mL
Bullous fixed drug eruption	High: 100 ng/mL
Bullous erythema multiforme	Moderate: 50 ng/mL
Hand-foot-and-mouth disease bullae	Low: 10-20 ng/mL
Chemotherapy hemorrhagic bullae	Low: 10-20 ng/mL
Pemphigus	Negative: <5 ng/mL
Bullous pemphigoid	Negative: <5 ng/mL
Acute generalized exanthematous pustulosis	Negative: <5 ng/mL

Chung et al,[180] Su et al,[186] and unpublished data (Chung W.-H., MD, PhD, March 2017).

White KD, et al J Allergy Clin Immunol Pract. 2018 Jan - Feb;6(1):38-69

A New Era of Precision Drug Hypersensitivity

- The right drug to the right patient at the right time without drug safety concerns
- Not just prediction and prevention but early diagnosis and diagnosis
- Phenotypes, clinical diagnoses, mechanisms, risk stratification and treatment will increasingly be driven by what we find at a cellular and molecular level.

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CANADA

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