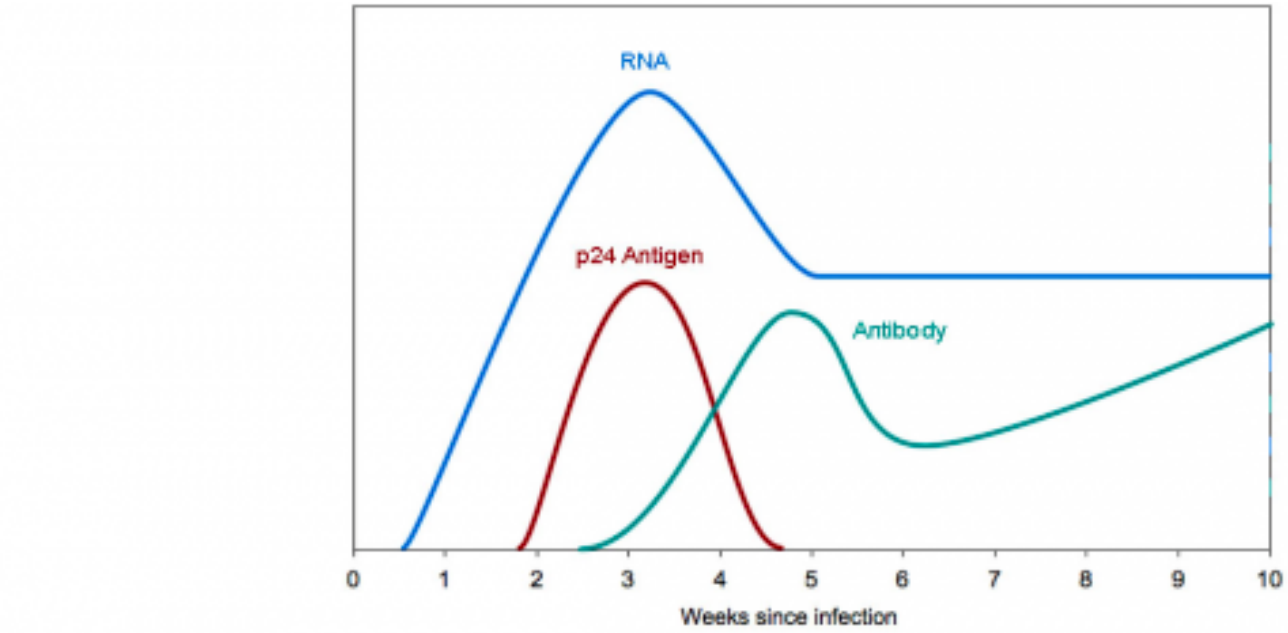
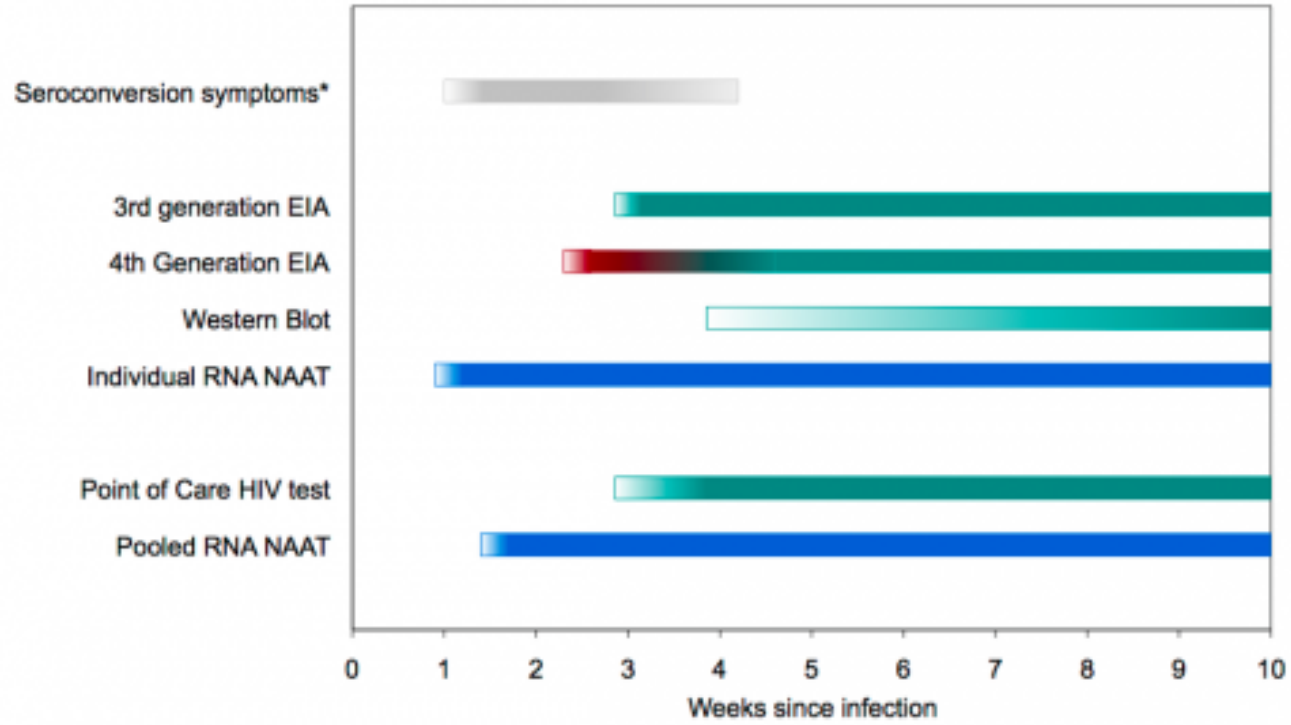
HIV Transplantation

Detangling Antiretrovirals and Immunosuppression

Elmi Muller


RNA
p24 Antigen
Antibody
0
1
2
3
4
5
6
7
8
9
10
Weeks since infection


Seroconversion symptoms*
3rd generation EIA
4th Generation EIA
Western Blot
Individual RNA NAAT
Point of Care HIV test
Pooled RNA NAAT
0
1
2
3
4
5
6
7
8
9
10
Weeks since infection

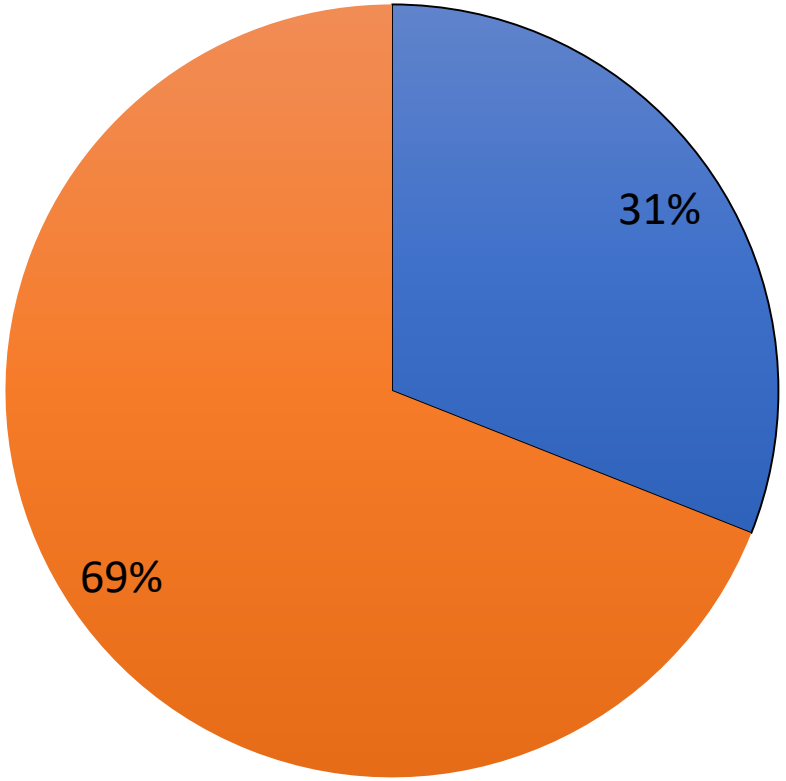
When should we start ART?

- Two seminal randomised controlled trials that addressed the optimal timing of ART in HIV-infected patients with high CD4+ counts:
  - strategic timing of antiretroviral therapy (START)
  - TEMPRANO ANRS 12136 (early antiretroviral treatment and early isoniazid prophylaxis against tuberculosis in HIV-infected adults)
- Significant individual clinical benefit from starting ART immediately in patients with CD4+ counts higher than 500 cells/µL rather than deferring until a certain lower CD4+ threshold or clinical indication was met.

The following investigations are recommended prior to initiating ART:

- alanine transaminase (ALT)
- full blood count (FBC) if AZT being considered: avoid AZT if haemoglobin (Hb) is < 8 g/dL
- serum creatinine / CrCl: avoid TDF if CrCl is < 50 mL/min; other nucleoside reverse transcriptase inhibitors (NRTIs), except abacavir (ABC), require dose adjustment if CrCl is < 50 mL/min
- HBsAg
- CD4+ count
- baseline VL
- syphilis serology
- serum cryptococcal antigen test in patients starting ART at a CD4+ count < 100 cells/µL (to screen for early cryptococcal disease and to initiate pre-emptive treatment if positive)
- Symptom screen for TB (cough, weight loss, fever, night sweats). If any are present then send sputum for Xpert and TB culture, and if CD4+ < 100 cells/µL then send urine for lipoarabinomannan (LAM) assay.

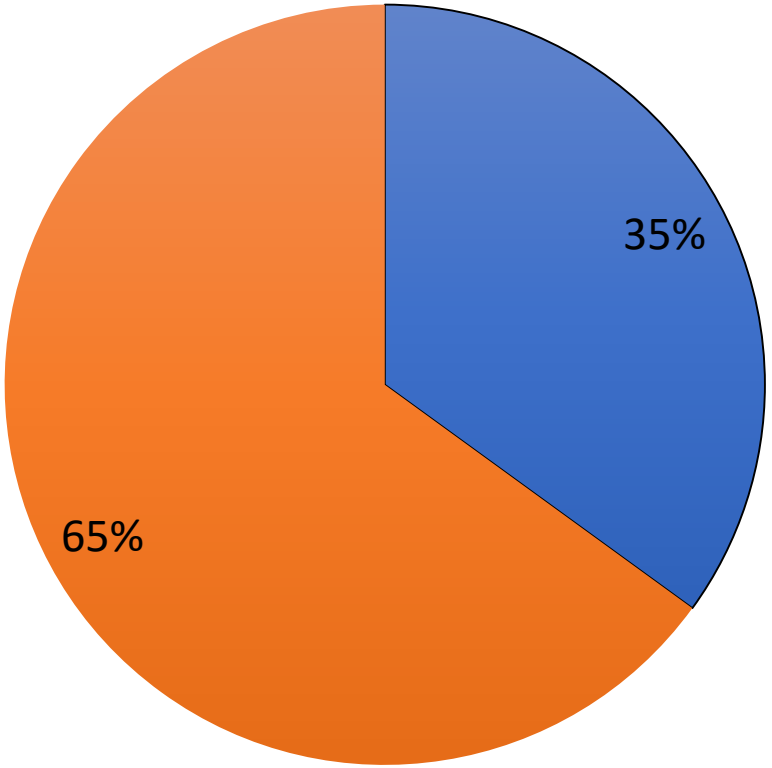
Access to ART in South Africa (2012)



31% of South Africans have access to ART

Johnson LF, Mossong J, Dorrington RE et al. Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies. PLoS Med. 2013;10(4):e1001418.

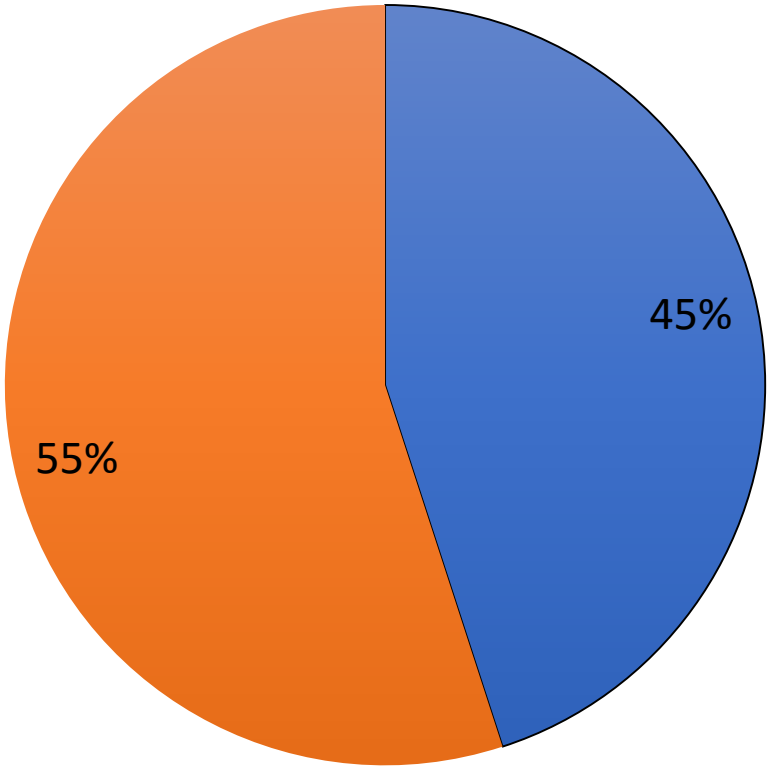
Access to ART in South Africa (2012)



35% of females with HIV in South Africans have access to ART

Johnson LF, Mossong J, Dorrington RE et al. Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies. PLoS Med. 2013;10(4):e1001418.

Access to ART in South Africa (2012)



45% of South African children between 0 and 14 have access to ART

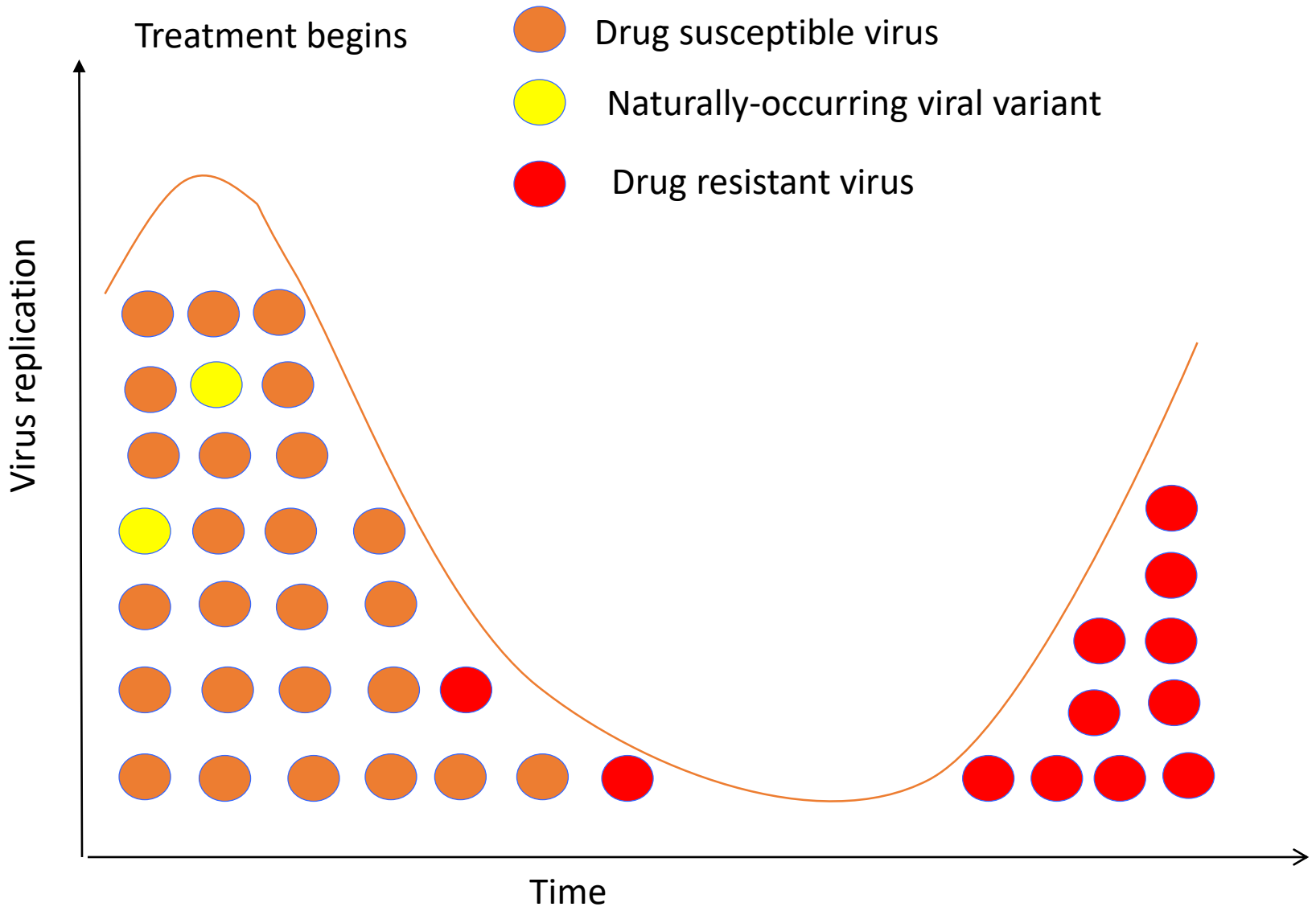
Johnson LF, Mossong J, Dorrington RE et al. Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies. PLoS Med. 2013;10(4):e1001418.

ART Resistance Rates in South Africa

- HIV Subtype C is the predominant viral subtype in South Africa
- Most patients who fail second-line ART in South Africa, have resistance rates less than 5%

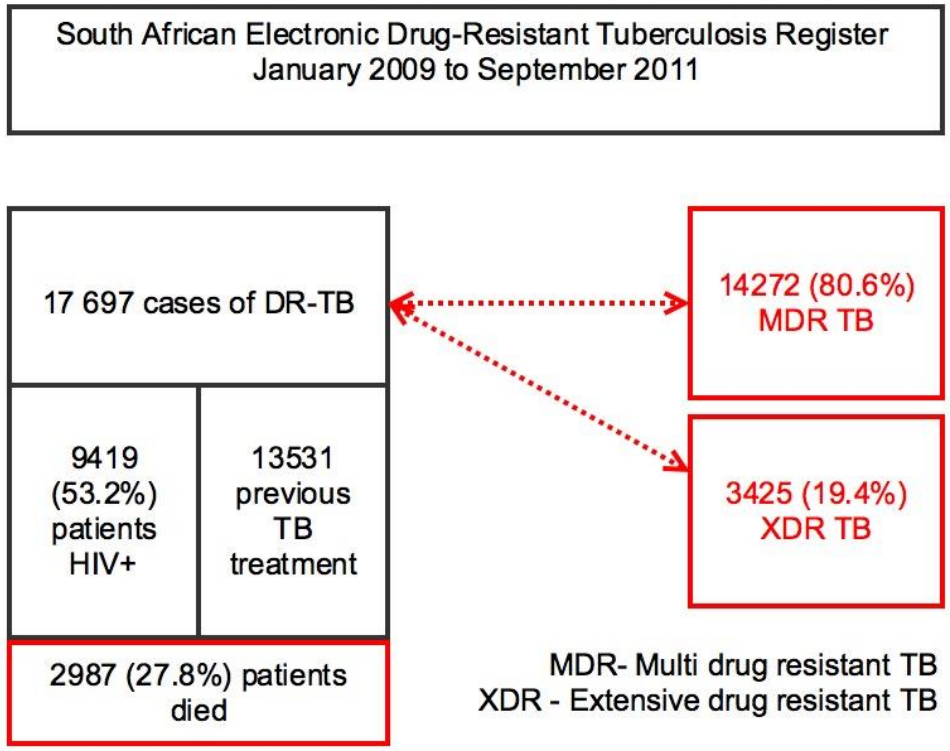
Jacobs GB et al AIDS Res Hum Retroviruses. 2008;24(7):1009-12.
Parboosing R et al Journal of medical virology. 2011;83(9):1508-13.
Nwobegahay J etal Journal of medical virology. 2012;84(12):1839-43

Anti-retroviral drug resistance



Screening Donors: Opportunistic infections

1. Tuberculosis
2. Bacterial sepsis
3. Fungal sepsis



In 53.2% of patients with drug resistant tuberculosis, a diagnosis of HIV is present as well

HIV Drug interactions

Clinical TRANSPLANTATION

The Journal of Clinical and Translational Research

SPECIAL ISSUE: TRANSPLANT INFECTIOUS DISEASES

Solid organ transplantation in the HIV-infected patient: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

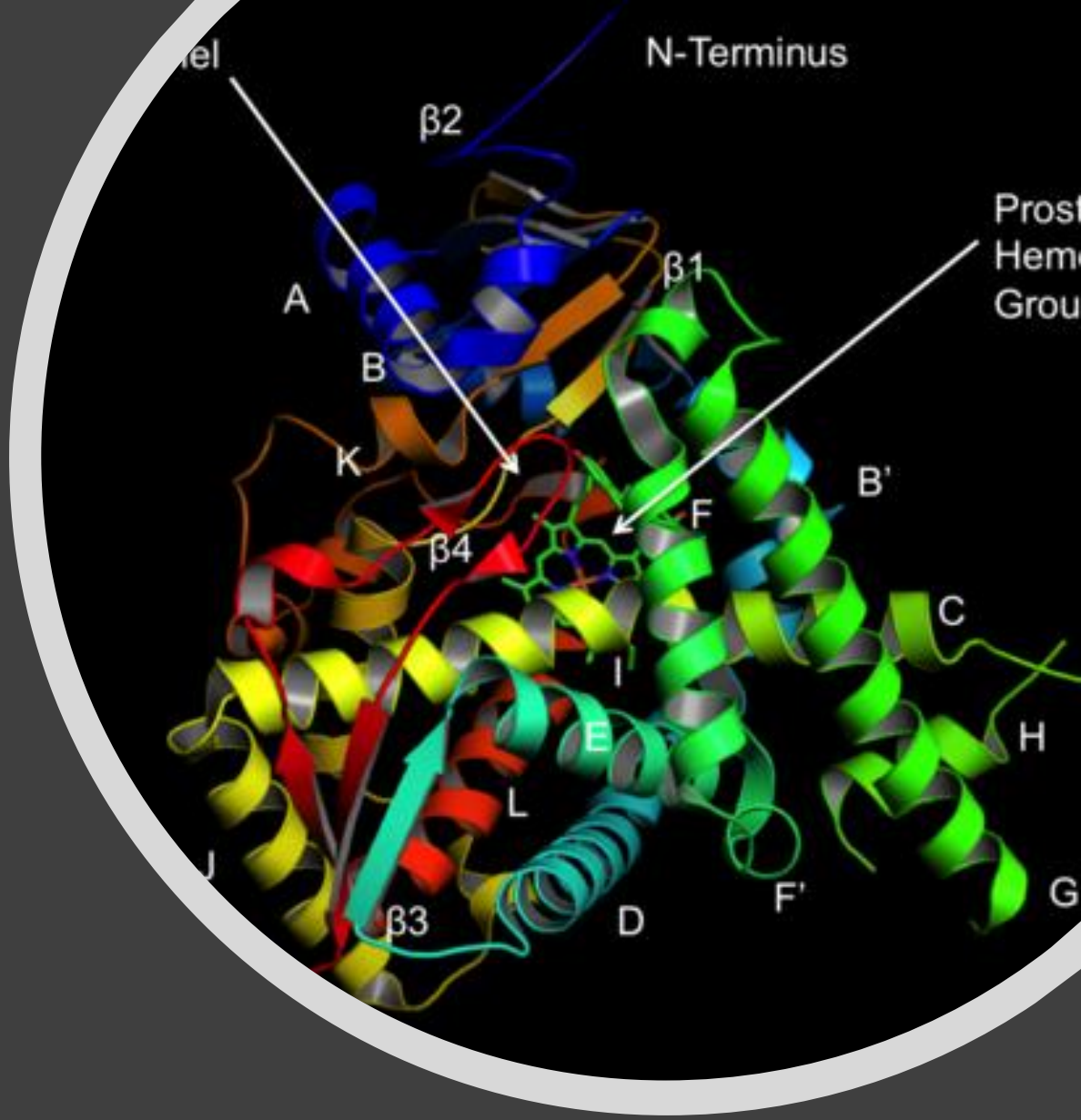
Emily A. Blumberg ✉, Christin C. Rogers, on behalf of the American Society of Transplantation Infectious Diseases Community of Practice

First published: 17 February 2019 | https://doi.org/10.1111/ctr.13499 | Cited by: 1

PDF TOOLS SHARE

Cytochrome P450

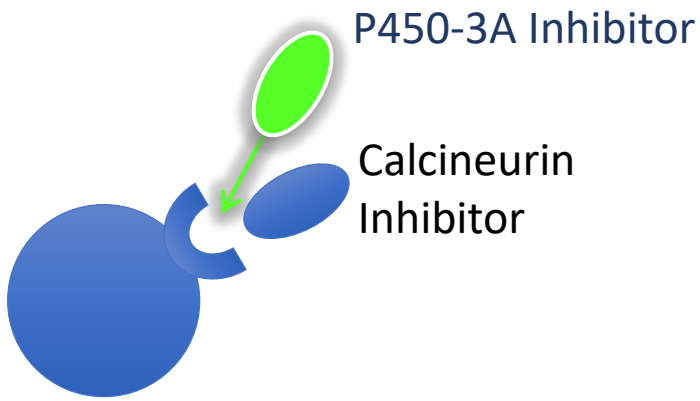
- Key issue in terms of drug interactions



Cytochrome P450-3A

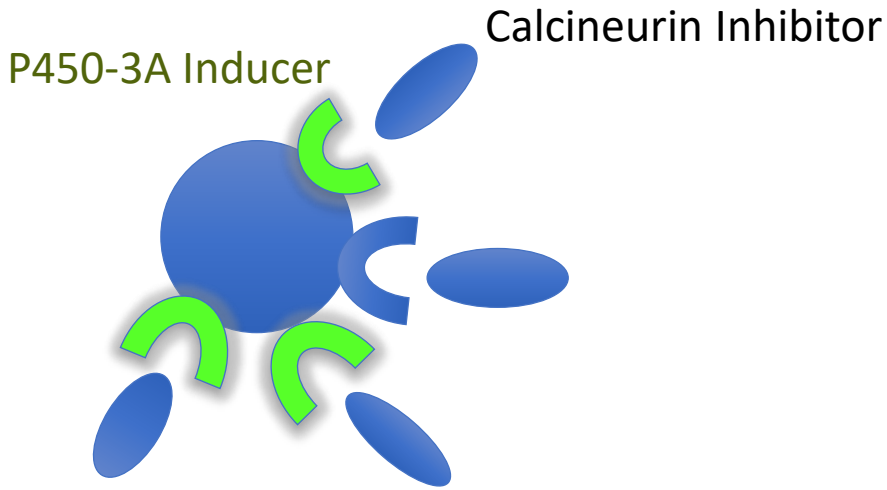
Inhibitors

- Decrease the metabolism of substrates and generally lead to increased drug effects



Inducers

- Increase the metabolism of substrates and generally lead to decreased drug effects

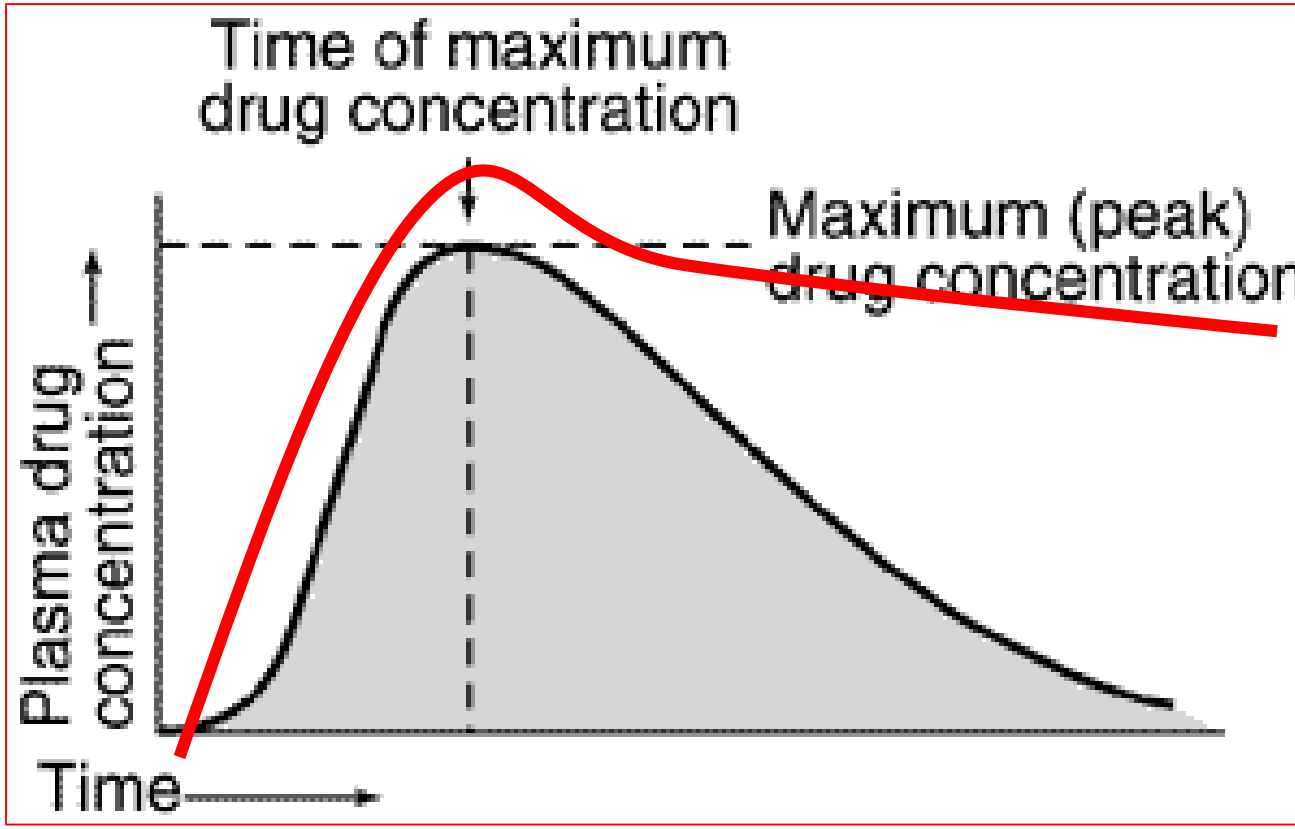


Effect of ARV's on Cytochrome P450-3A

Inhibitors

STRONG	Ritonavir (Protease Inhibitor)
	Ketokonazole
MODERATE	Fluconazole
WEAK	Cimetidine
UNSPECIFIED	Isoniazid

5 fold increase in plasma AUC
>80% decrease in clearance



Antiretroviral therapy at start of transplant

ART_reg_0	Freq.	Percent	Cum.
Abacavir/Lamivudine/Nevirapine	1	1.96	1.96
Abacavir/Lamivudine/Rilpivirine	1	1.96	3.92
Abacavir/Zidovudine/Lopinavir-Ritonavir	1	1.96	5.88
Emtricitabine/Tenofovir/Efavirenz	1	1.96	7.84
Lamivudine/Abacavir/Efavirenz	14	27.45	35.29
Lamivudine/Abacavir/Lopinavir-Ritonavir	6	11.76	47.06
Lamivudine/Stavudine/Efavirenz	8	15.69	62.75
Lamivudine/Stavudine/Nevirapine	3	5.88	68.63
Lamivudine/Tenofovir/Efavirenz	4	7.84	76.47
Lamivudine/Tenofovir/Lopinavir-Ritona..	5	9.80	86.27
Lamivudine/Zidovudine/Efavirenz	3	5.88	92.16
Lamivudine/Zidovudine/Nevirapine	3	5.88	98.04
Stavudine/Tenofovir/Efavirenz	1	1.96	100.00
Total	51	100.00	

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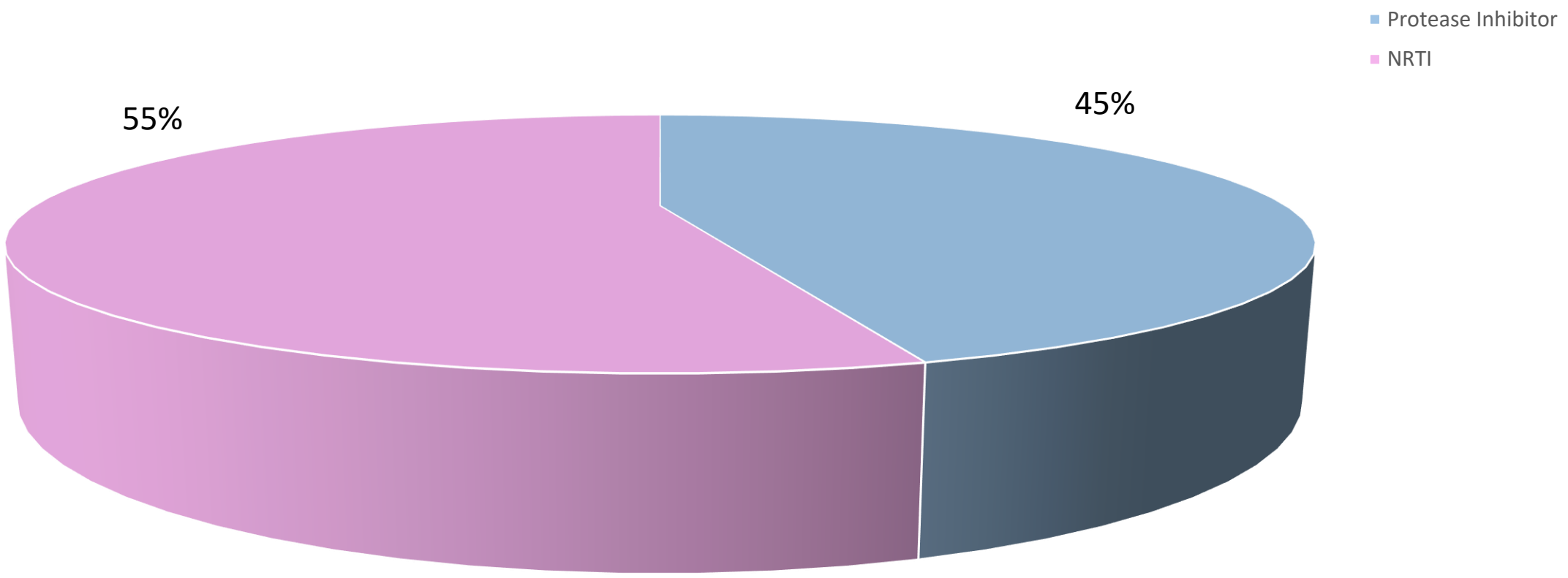
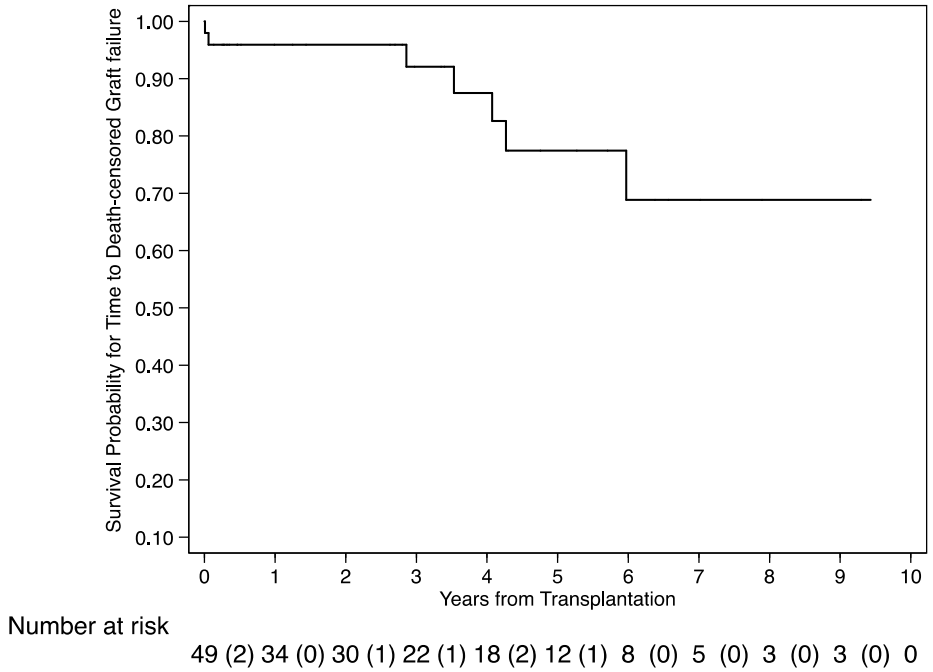
11 patients switched to PI's in 1st three months after transplant

Patients on PI based regimens within 3 months after transplant



Rejection rates: HIV Positive-to-Positive transplantation

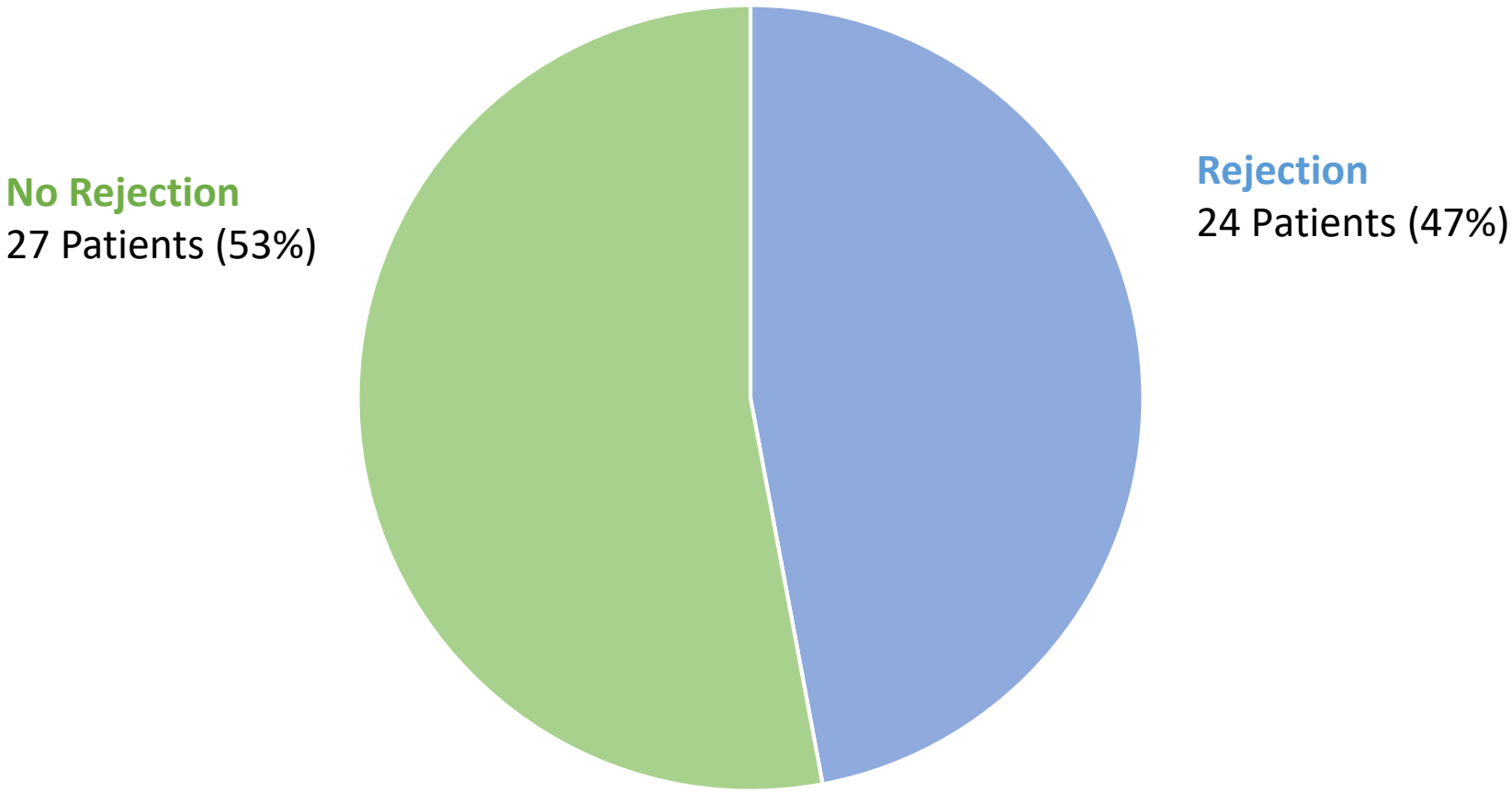
- Aggressive induction therapy still resulted in high rejection rates
- 19 patients (38.8%) experienced one or more biopsy-confirmed rejection episodes post-transplant.



Probability of 1st rejection episode:

- 26,1% at 1 year (CI 15.7-41.6%)
- 40.3% at 3 years (CI 30-57.1%)
- 44.9% at 5 years (CI 30.2-62.7%)

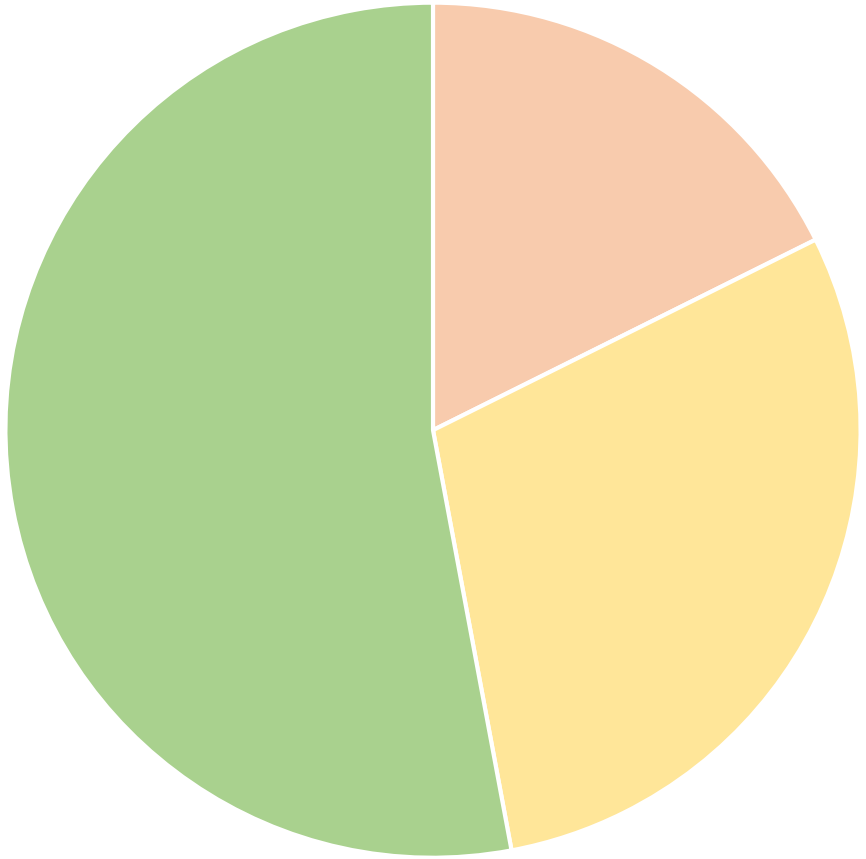
Patients who experienced one or more episode of rejection



51 HIV positive patients transplanted with HIV positive donors

Patients who experienced one or more episode of rejection

No Rejection
27 Patients (53%)

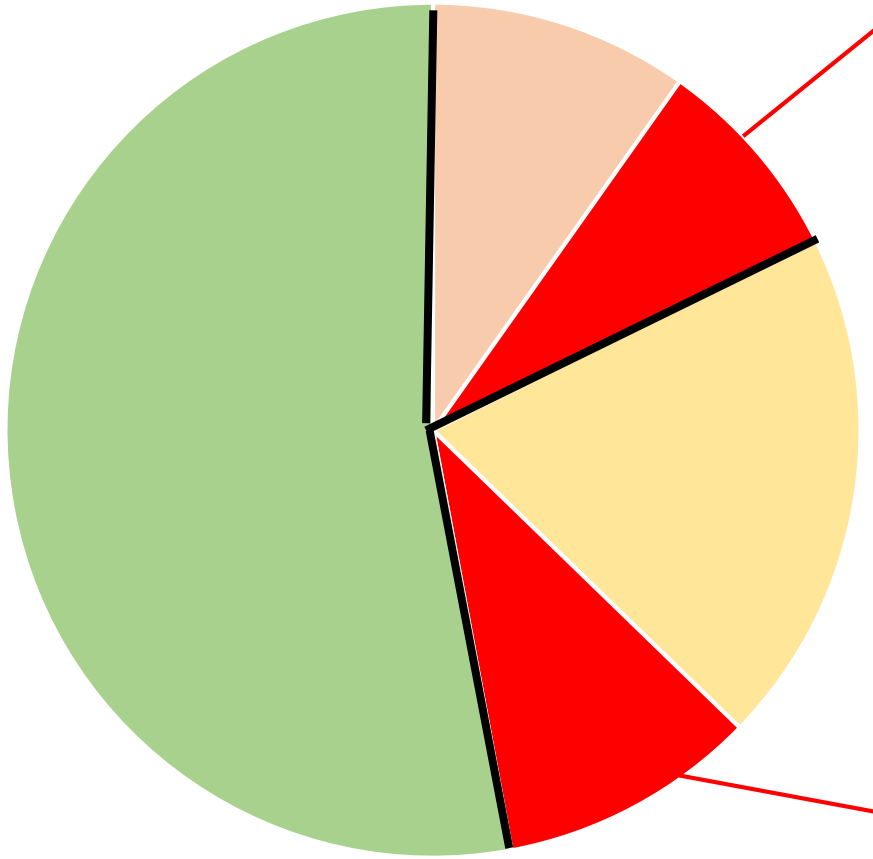


Non PI based
9 Patients
(37% of the rejection group)

PI based
15 Patients
(63% of the rejection group)

51 HIV positive patients transplanted with HIV positive donors

Patients who experienced one or more episode of rejection



Graft Loss 44%

Non PI based
9 Patients
(37% of the rejection group)

No Rejection
27 Patients (53%)

PI based
15 Patients
(63% of the rejection group)

Graft Loss 55%

51 HIV positive patients transplanted with HIV positive donors

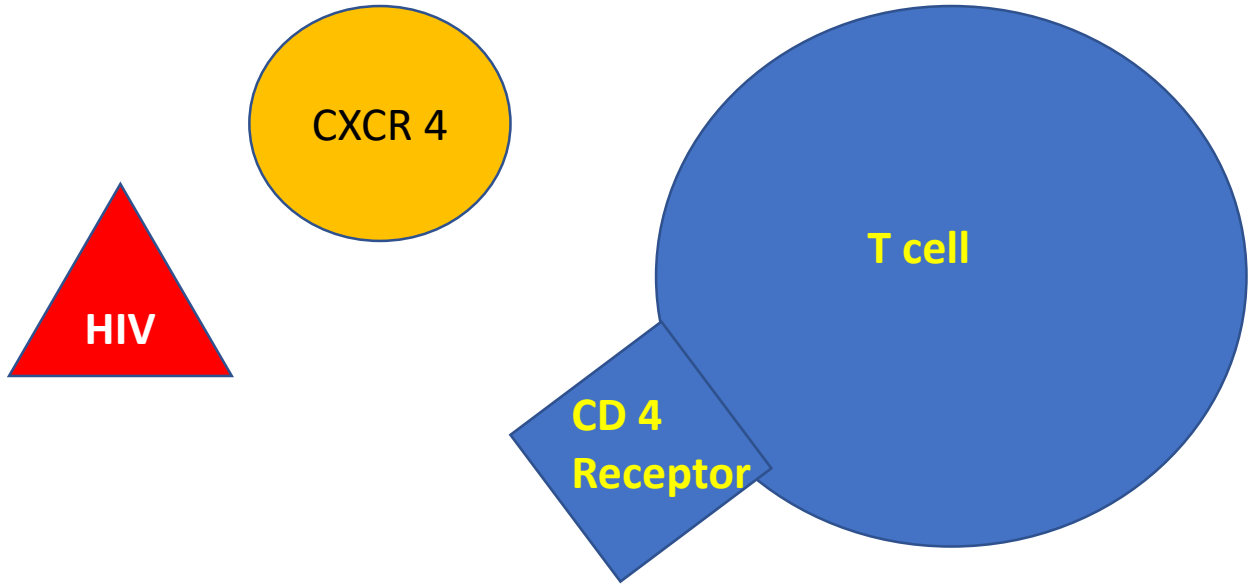
Non interacting ART

- Integrase strand transfer inhibitor-based antiretroviral regimens
- Raltegravir

South Africa:

1. Used in gene mutations with viral resistance and breakthroughs
2. Expensive
3. High threshold to make drug available to children

C-C chemokine receptor 5 (*CCR5*) polymorphisms, 32-base pair deletion (Δ32)



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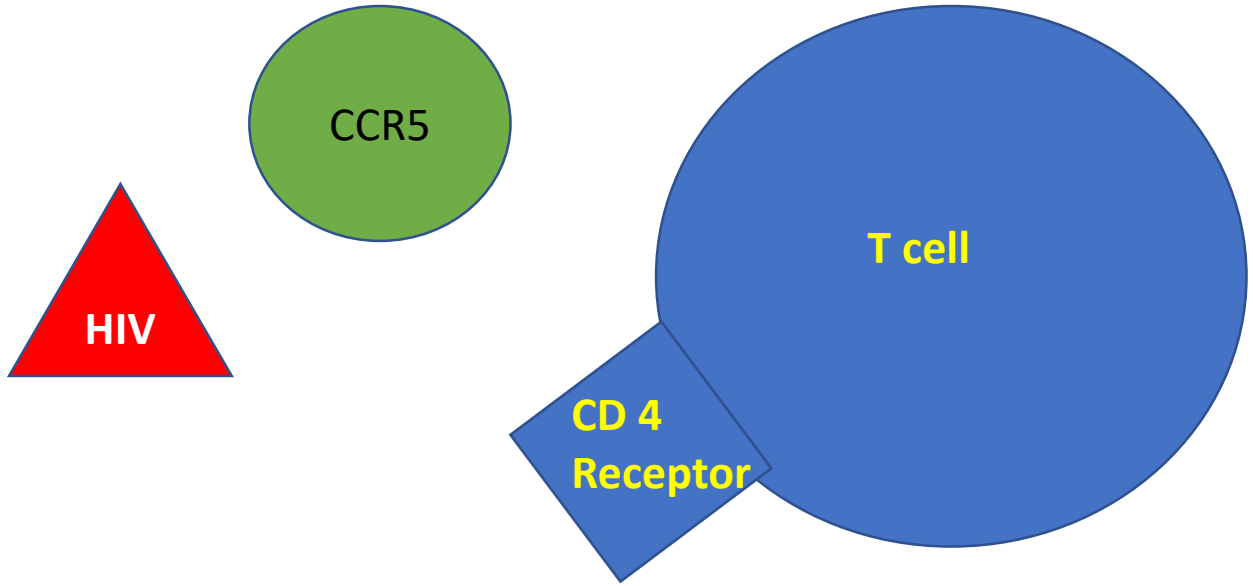


C-C chemokine receptor 5 (*CCR5*) polymorphisms, 32-base pair deletion (Δ32)

R5 tropic

- HIV that prefers R5 receptors

X4 tropic

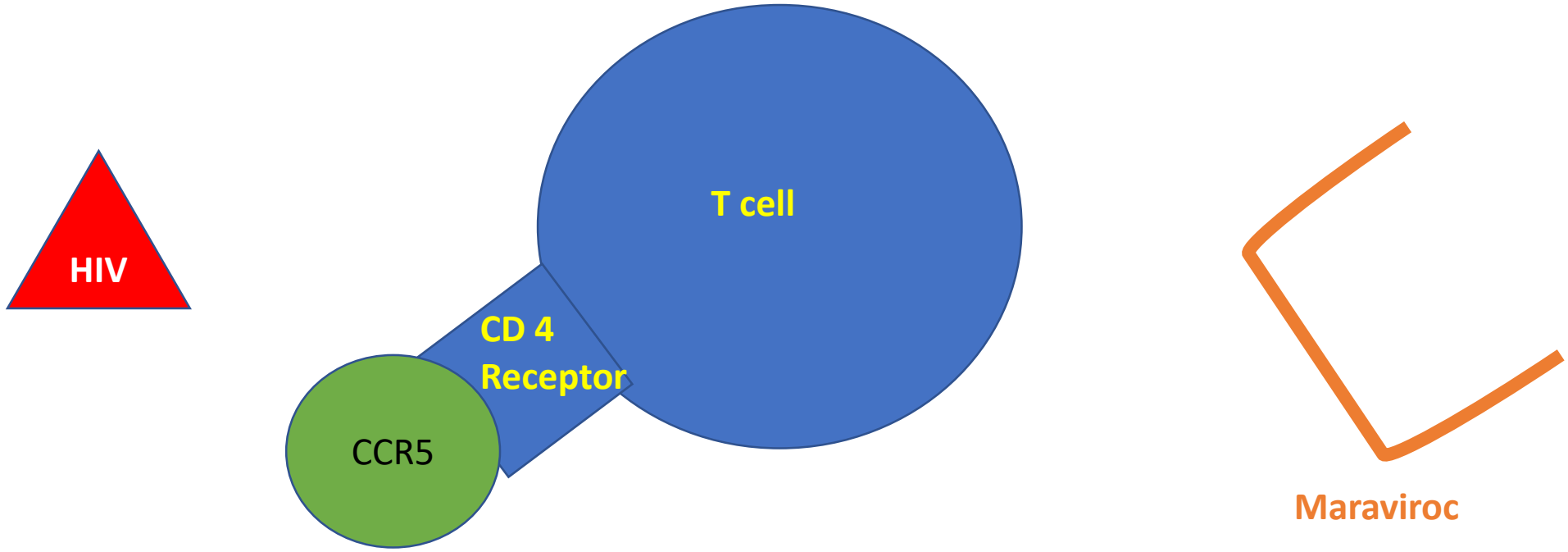
- HIV that prefers X4 receptors

Dual or mixed tropic

More commonly found in the early stages of infection
and treatment naive patients

More commonly found in the early stages of infection
The presence of CXCR4-tropic virus is a predictor of lower CD4 count, a higher viral load, and a more rapid progression to AIDS

C-C chemokine receptor 5 (*CCR5*) polymorphisms, 32-base pair deletion (Δ32)



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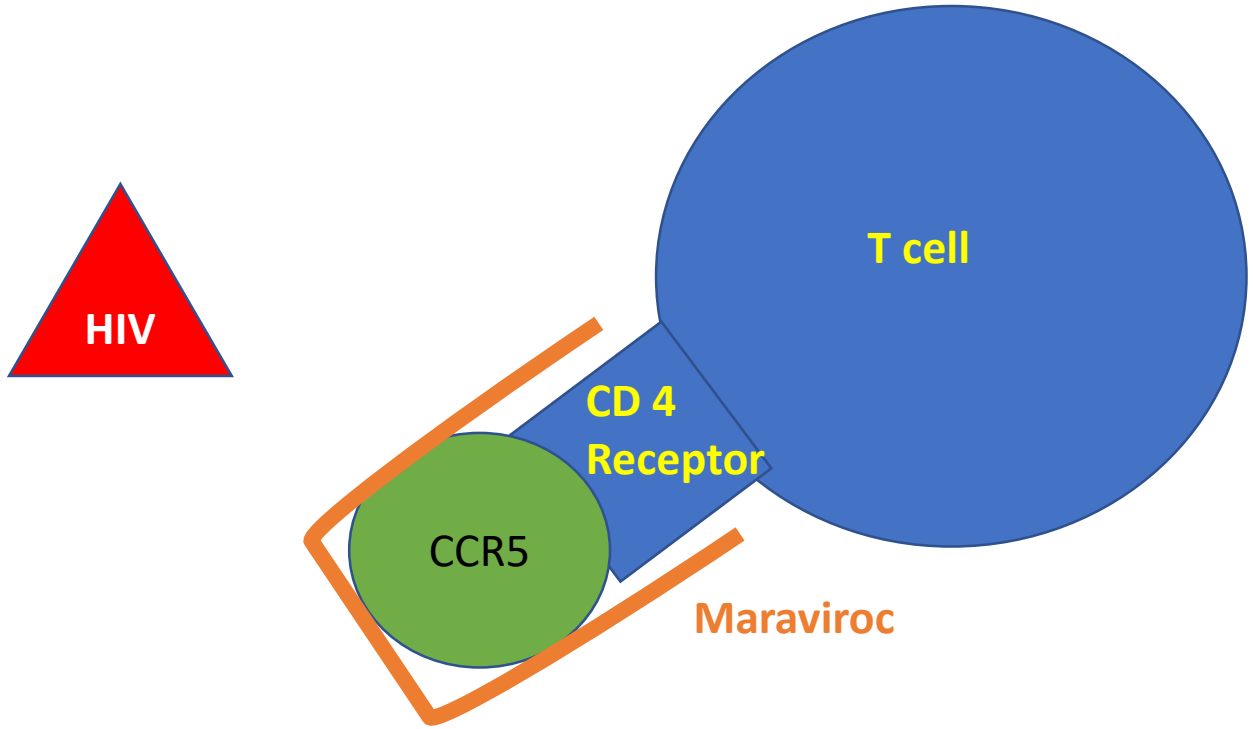


33-day course of maraviroc in Bone marrow transplant patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Blockade of Lymphocyte Chemotaxis in Visceral Graft-versus-Host Disease

Ran Reshef, M.D., Selina M. Luger, M.D., Elizabeth O. Hexner, M.D., Alison W. Loren, M.D., Noelle V. Frey, M.D., Sunita D. Nasta, M.D., Steven C. Goldstein, M.D., Edward A. Stadtmauer, M.D., Jacqueline Smith, C.R.N.P., Sarah Bailey, B.A., Rosemarie Mick, M.S., Daniel F. Heitjan, Ph.D., Stephen G. Emerson, M.D., Ph.D., James A. Hoxie, M.D., Robert H. Vonderheide, M.D., D.Phil., and David L. Porter, M.D.

ABSTRACT

Lower incidence of GVHD in high-risk patients

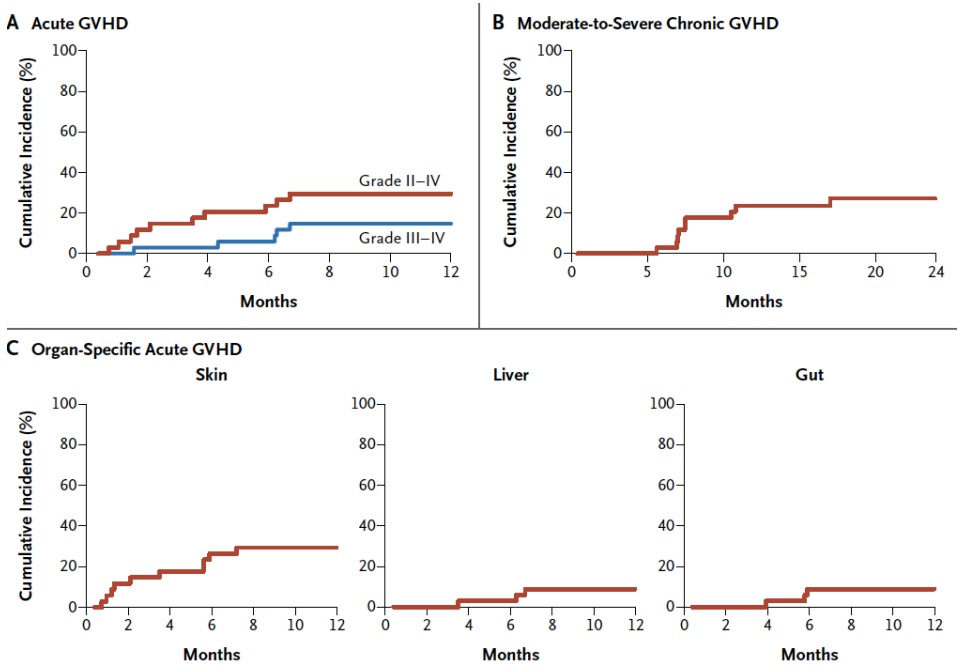


Figure 2. Clinical Trial Outcomes of Acute GVHD, Moderate-to-Severe Chronic GVHD, and Organ-Specific Acute GVHD.
Shown are cumulative incidence plots of grade II to IV and grade III or IV acute GVHD (Panel A), moderate-to-severe chronic GVHD (Panel B), and organ-specific acute GVHD (in the skin, liver, and gut) (Panel C) in 35 patients undergoing reduced-intensity conditioned hematopoietic stem-cell transplantation with maraviroc added to standard GVHD prophylaxis.

Biology of Blood and Marrow Transplantation

The Official Journal of the American Society for Transplantation and Cellular Therapy

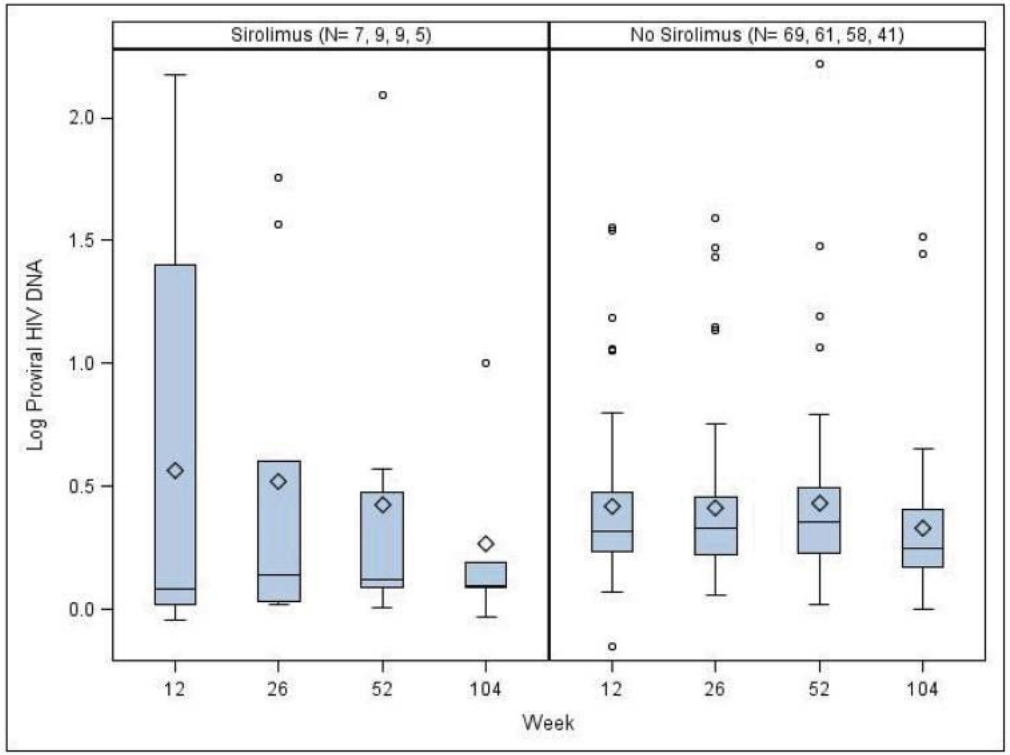
Extended CCR5 Blockade for Graft-versus-Host Disease Prophylaxis Improves Outcomes of Reduced-Intensity Unrelated Donor Hematopoietic Cell Transplantation: A Phase II Clinical Trial

Ran Reshef[1,2,*], Alex Ganetsky[1], Edward P. Acosta[3], Robin Blauser[1], Lisa Crisalli[1], Jessica McGraw[1], Noelle V. Frey[1], Elizabeth O. Hexner[1], James A. Hoxie[1], Alison W. Loren[1], Selina M. Luger[1], James Mangan[1], Edward A. Stadtmauer[1], Rosemarie Mick[4], Robert H. Vonderheide[1], David L. Porter[1]

- The 1-year rate of moderate to severe chronic GVHD:
  8 ± 5%
- Disease relapse:
  30 ± 8%.
- Overall survival at 1 year:
  70 ± 8%.
- Extended course resulted in a significantly higher GVHD-free, relapse-free survival

There was less GVHD if maraviroc troughs were greater than a median 65 ng/mL, but there was a lot of variability in trough levels (range 12-316)

MTOR inhibitors



The association between sirolimus exposure and lower frequency of cells containing HIV DNA levels posttransplant suggest that the immune-modifying drugs may affect the level of HIV persistence during effect therapy

Stock et al AJT 2014

- PI based regimens save money but are difficult to manage

- Newer (but more expensive ART) avoid drug interactions and might have better long term rejection rates
- Integrase inhibitor-based regimens are preferred due to the absence of interactions with calcineurin and mTOR inhibitors