How HIV research has accelerated the development of drugs and treatments for COVID-19 infection

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Drug Discovery

Repurposing

Before AIDS: IDU, 5-FU, ara-C, Ara-A

HIV/AIDS: AZT: Jerome Horowitz; early 60s; Trudy Elion and Phil Furman, early 80s

SARS-CoV-2: Remdesivir, Molnipurivir

Note: Successful repurposed drugs have been nucleoside polymerase inhibitors.

The expensive effort and investment in screening and testing libraries of other repurposed antiviral drug candidates for covid (hydroxychloroquine, favipravir, ivermectin, lopinavir/ritonavir, fluticasone, and fluvoxamine, etc) were not effective in clinical trials. All these failures were predictable based on data on in vitro activity and toxicity together with known IC_{50} and human PK.

Drug Discovery

Focused or derivative design

- Other nucleos(t)ides for HIV, HBC, HCV, others e.g. remdesivir
- HIV protease inhibitors: Saquinavir (Noel Roberts, Roche, Science 1990, DOI: 10.1126/science.218335
- Integrase inhibitors: Raltegravir (Hazuda, Merck, Science, 2000, DOI: 10.1126/science.287.5453.646
- SARS-Cov-2 M^{pro} inhibitors: Cys protease inhibitors boceprevir and telaprevir for HCV

Drug Discovery

Modifications to improve PK

- Prodrugs to improve bioavailability, e.g valACV and famciclovir, TDF
  ⟶ remdesivir prodrugs

- Pharmacologic boosters, e.g., rtv and cobisistat
  ⟶ nirmatrelvir/ritonavir

Clinical Trials

Herpesviruses

- Adverse Effect of Cytosine Arabinoside on Disseminated Zoster in a Controlled Trial: Stevens, Merigan et al (1973)
  (DOI: 10.1056/NEJM197310252891701)

- Failure of High Dose 5-Iodo-2′-Deoxyuridine for the Therapy of Herpes Simplex Virus Encephalitis — Evidence of Unacceptable Toxicity: Oxman/Boston Interhospital Study Group (1975)
  (DOI: 10.1056/NEJM197503202921201)

- Adenine Arabinoside Therapy of Biopsy-Proved Herpes Simplex Encephalitis— National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study: Whitley et al, (1977)
  (DOI: 10.1056/NEJM197708112970601)

- Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. Sköldenberg et al, Lancet 1984;2:707–11. and
- Vidarabine versus acyclovir therapy in herpes simplex encephalitis. Whitley et al, N Engl J Med 1986;314:144–9.

Clinical Trials

HIV

- AZT: The Efficacy of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex, Fischl et al (1987). (DOI: 10.1056/NEJM198707233170401)

- Combination nucleosides: A Trial Comparing Nucleoside Monotherapy with Combination Therapy in HIV-Infected Adults with CD4 Cell Counts from 200 to 500 per Cubic Millimeter, Hammer et al (1996). (DOI: 10.1056/NEJM199610103351501)

- Combination ART for complete suppression: Treatment with Indinavir, Zidovudine, and Lamivudine in Adults with Human Immunodeficiency Virus Infection and Prior Antiretroviral Therapy, Gulick et al (1997). (DOI: 10.1056/NEJM199709113371102)

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THE EFFICACY OF AZIDOTHYMIDINE (AZT) IN THE TREATMENT OF PATIENTS WITH AIDS AND AIDS-RELATED COMPLEX

A Double-Blind, Placebo-Controlled Trial

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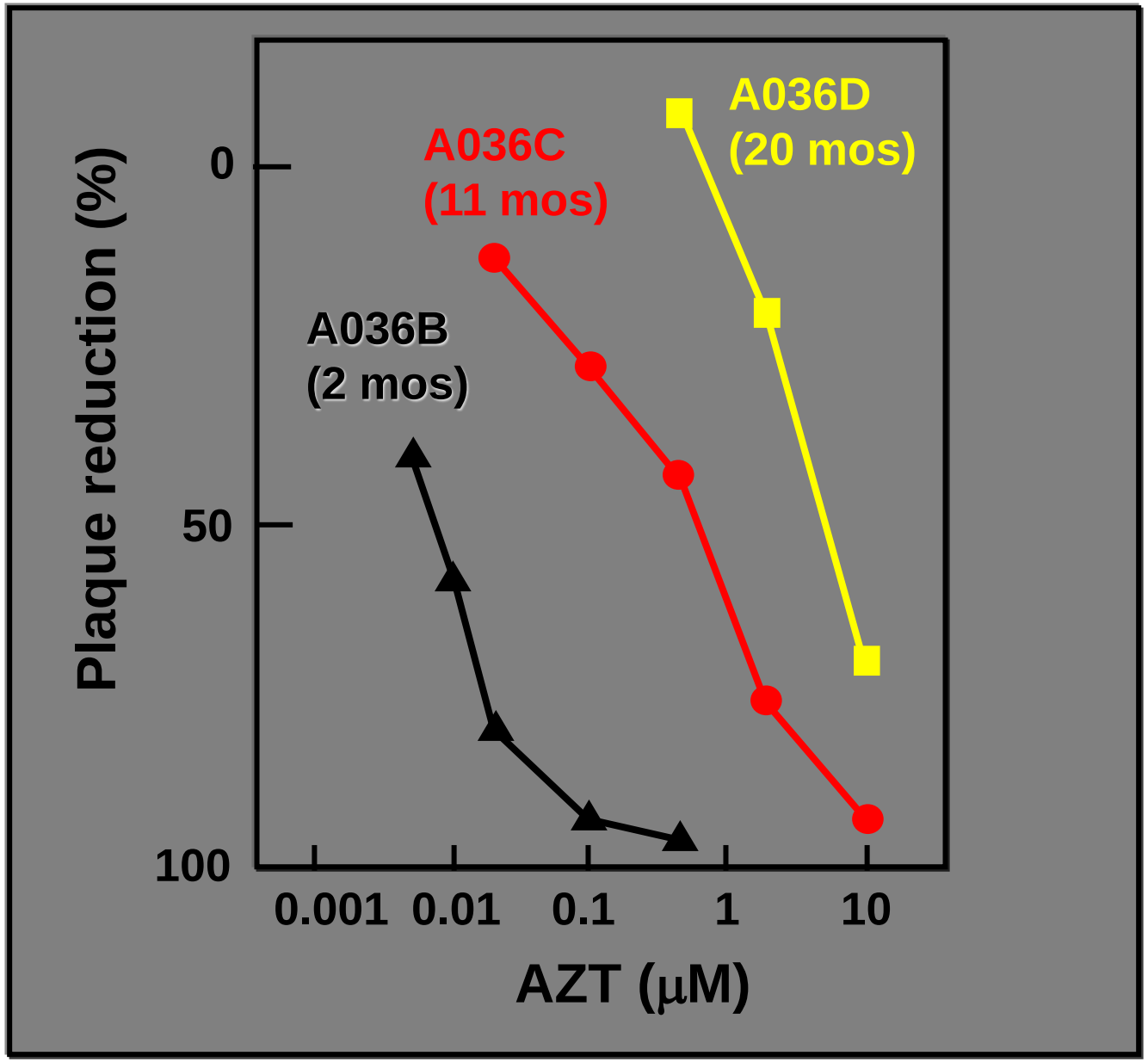
Mortality by end of study

AZT participants: 1 of 145
Placebo participants: 19 of 137

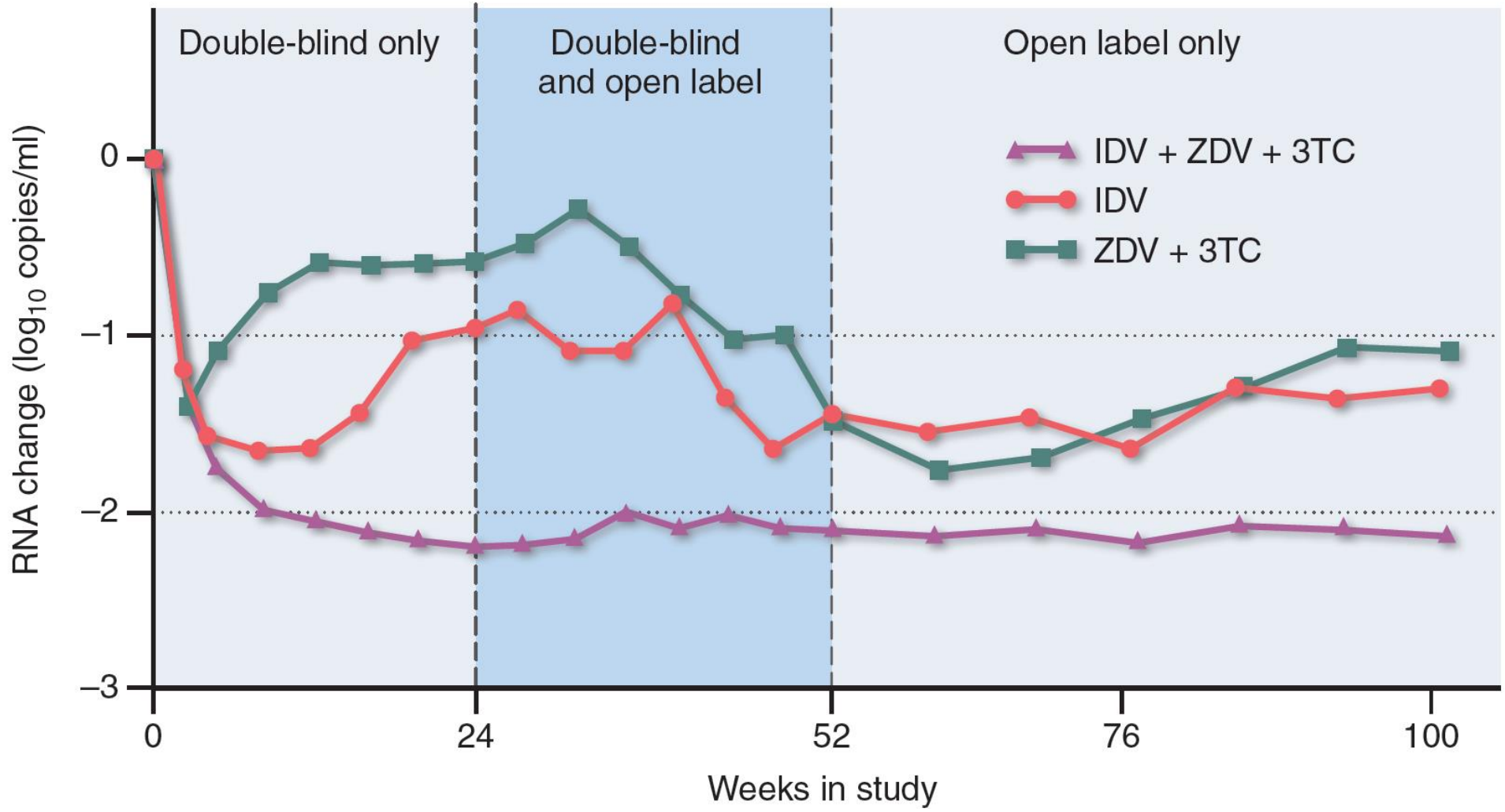
Table 1. Projected Probability of 24-Week Survival.

	PROBABILITY	P VALUE
By treatment		
AZT	0.98	<0.001
Placebo	0.78	
By diagnosis		
AIDS		
AZT	0.96	<0.001
Placebo	0.76	
AIDS-related complex		
AZT	1.00	<0.016
Placebo	0.81	
By CD4 cell count		
≤100		
AZT	0.96	<0.001
Placebo	0.70	
101–499		
AZT	1.00	0.028
Placebo	0.91	

AZT Susceptibility of Sequential Isolates of HIV-1 From a Patient Administered AZT

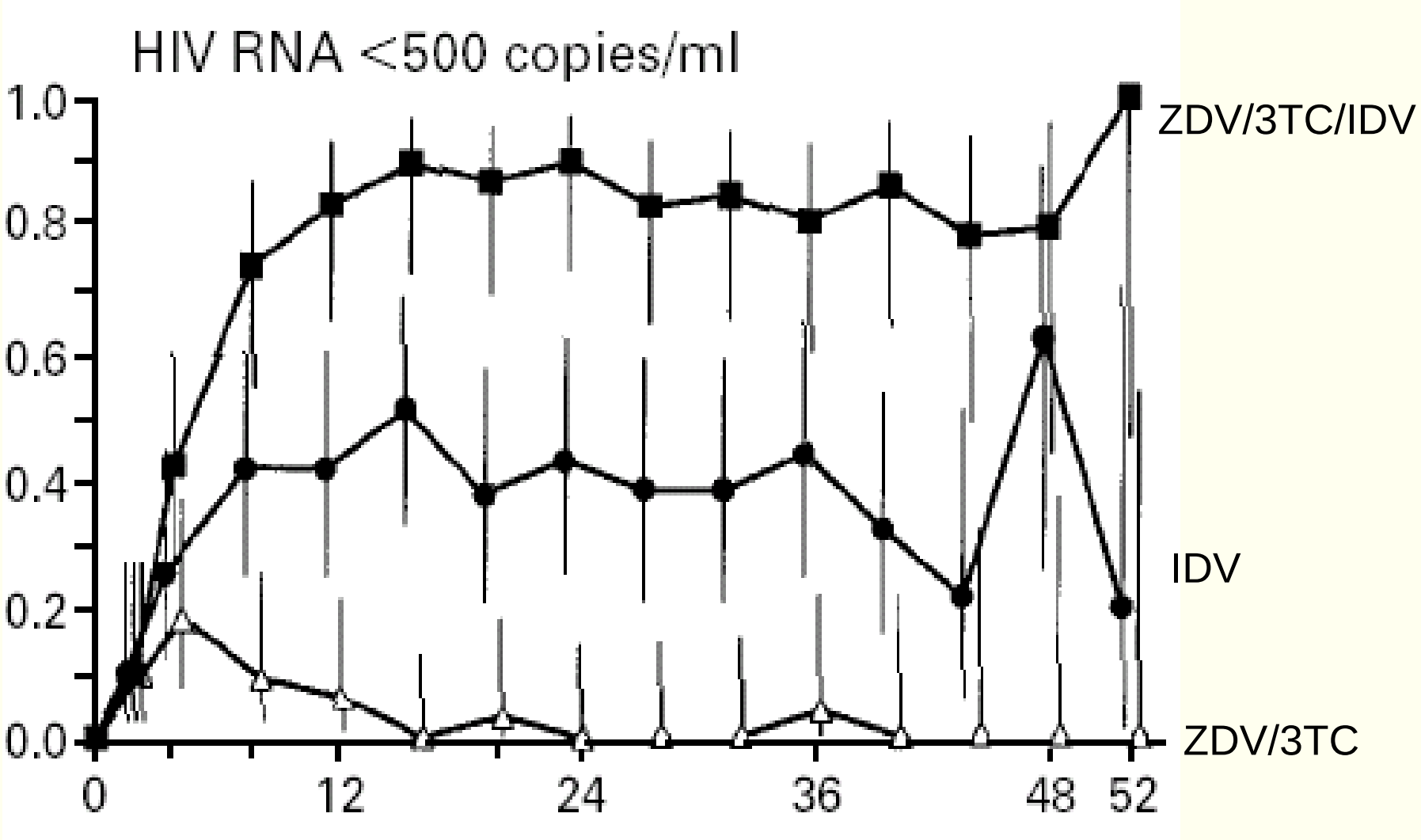


Larder, Darby and Richman, Science 1989; 243:1731.

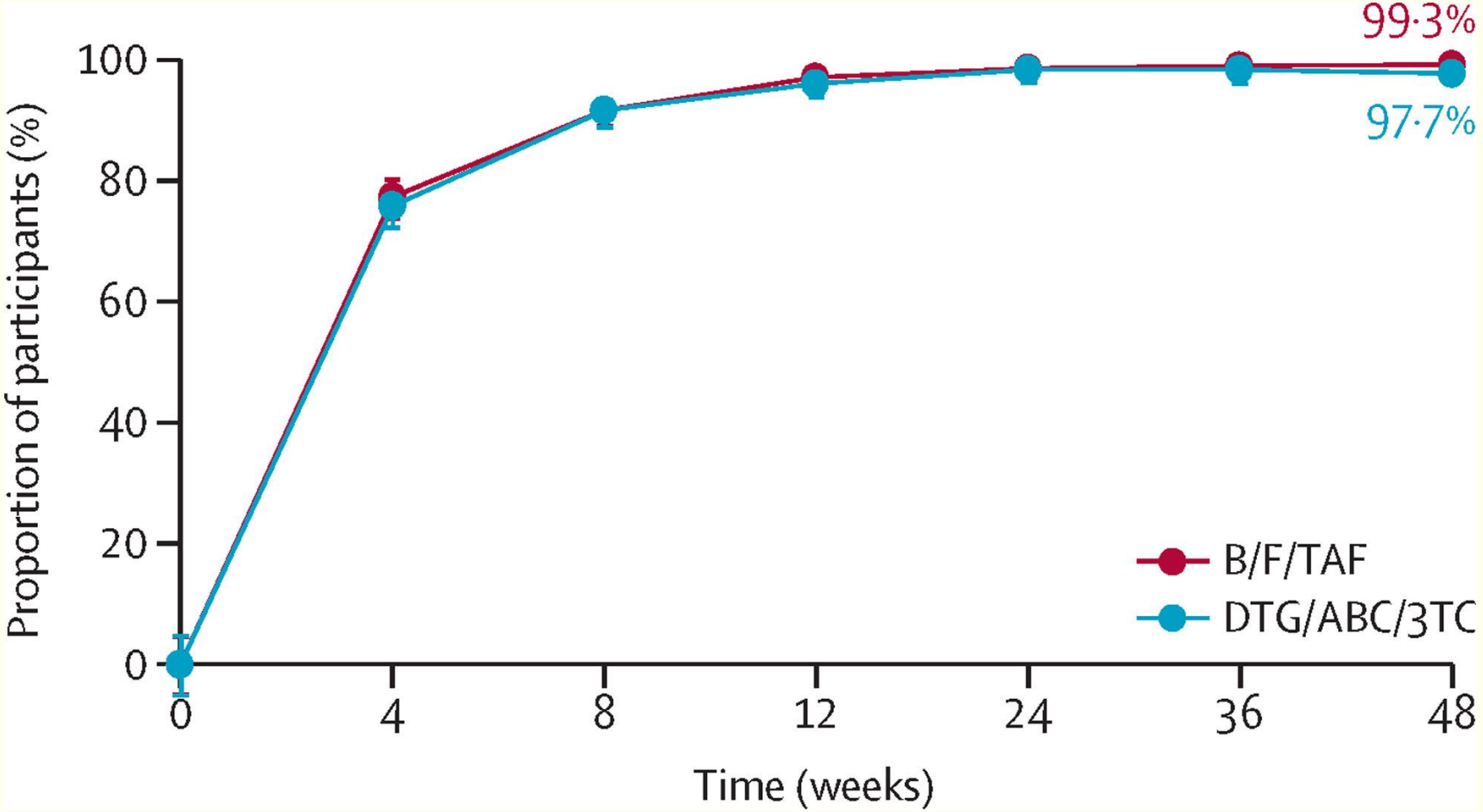


Gulick RM et al. N Engl J Med 1997;337:734-739

Merck 035 Study: Primary Virologic Endpoint



Gulick et al. NEJM 1997



The Lancet 2017 390, 2063-2072DOI: (10.1016/S0140-6736(17)32299-7)

Regulatory endpoints

- Viral load and CD4: The Relation of Virologic and Immunologic Markers to Clinical Outcomes after Nucleoside Therapy in HIV-Infected Adults with 200 to 500 CD4 Cells per Cubic Millimeter, Katzenstein et al (1996)

  (DOI: 10.1056/NEJM199610103351502)

In vivo dynamics of resistance and response.

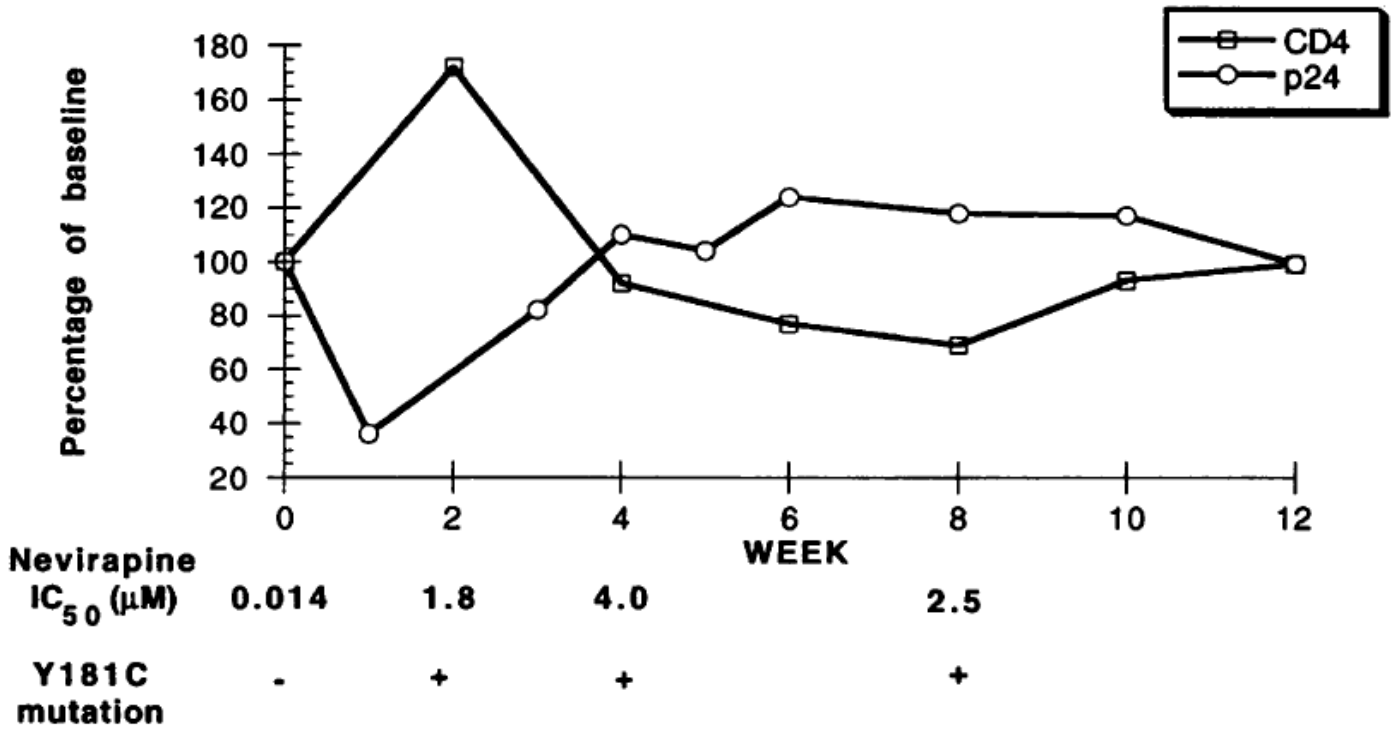


FIG. 1. Effect of nevirapine therapy on surrogate markers and drug resistance. Patient 154 was administered 12.5 mg of nevirapine daily. The responses at the indicated weeks with regard to CD4 lymphocyte count, HIV p24 antigen level in serum, nevirapine susceptibility, and the Y181C resistance mutation of the patient's virus isolate are depicted.

Richman et al, JOURNAL OF VIROLOGY, Mar. 1994, p. 1660–1666

Community Participation and Advocacy

- Access to drugs more quickly
- Surrogate endpoints rather than body counts
- Participation in clinical trial design and scientific advisory groups

Doesn’t seem to have translated from HIV to CoV, but same advocates are involved for monkeypox

New advances in drug discovery

- Alphafold: has solved the structures of over 200 million proteins
- Cryo EM
- AI/machine learning
- New developments in medicinal chemistry, e.g. click chemistry