The nucleoside analogues zidovudine, tenofovir alafenamide, and cladribine induce EBV lytic gene expression without subsequent viral replication

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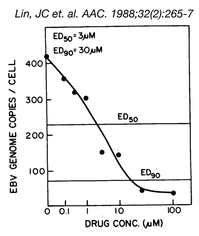
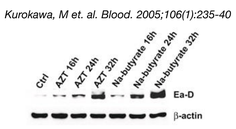
BACKGROUND AND LITERATURE

- Antiretroviral regimens containing nucleoside analogs have been reported to induce prolonged remission in MS.
- An early study (1988) showed that the antiretroviral nucleoside analog zidovudine (AZT) directly inhibits lytic DNA replication of EBV, a herpesvirus implicated by epidemiological studies as a cause of MS.



- Paradoxically, subsequent studies established AZT as a potent lytic-induction agent in primary EBV+ B-cell lymphomas.

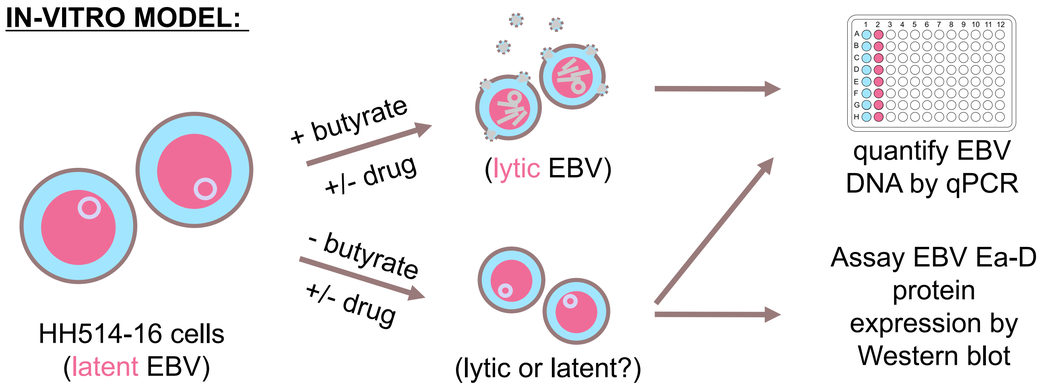


- Do other nucleoside analogs affect EBV in the lytic and/or latent phase?

METHODS

OBJECTIVE: To determine whether nucleoside analogs other than AZT have anti-EBV effects, we tested 8 nucleoside analogs licensed for the treatment of HIV (NRTIs), 3 anti-herpesviral drugs (AHVs), and cladribine, a drug licensed for the treatment of MS.

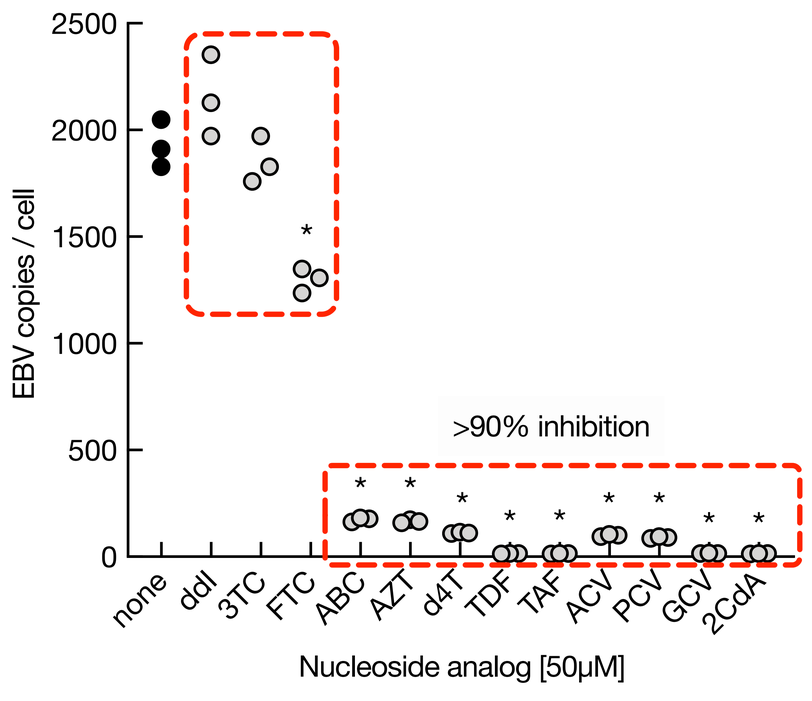
IN-VITRO MODEL:



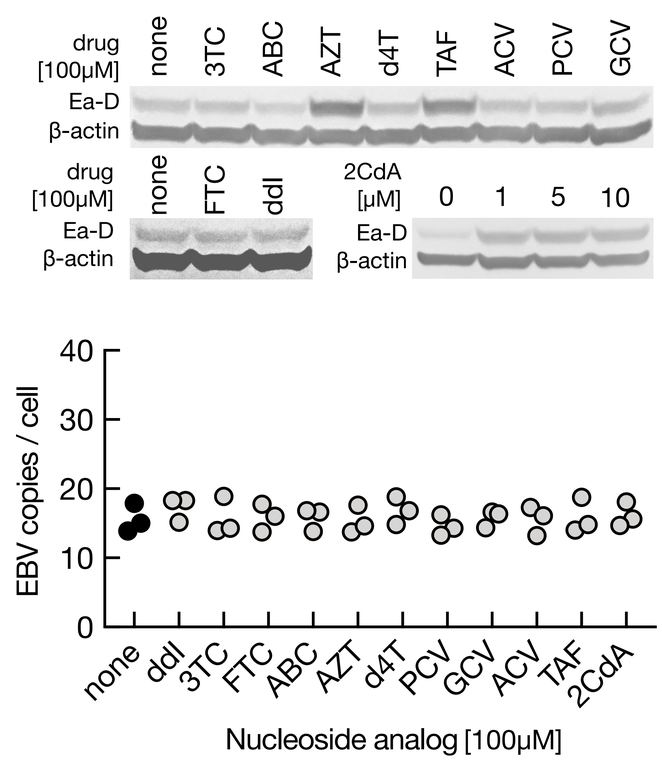
DRUGS

Abbv	Full name	Analog	Use
ddI	didanosine	dI	NRTI
3TC	lamivudine	dC	NRTI
FTC	emtricitabine	dC	NRTI
ABC	abacavir	dG	NRTI
AZT	zidovudine	dT	NRTI
d4T	stavudine	dT	NRTI
TDF	tenofovir disoproxil fumarate	dA	NRTI
TAF	tenofovir alafenamide	dA	NRTI
ACV	acyclovir	dG	AHV
PCV	penciclovir	dG	AHV
GCV	ganciclovir	dG	AHV
2CdA	cladribine	dA	MS

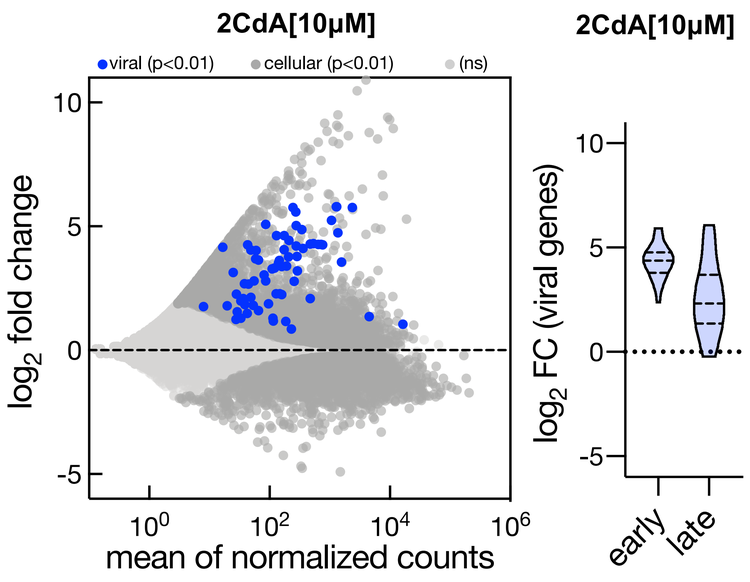
EFFECTS ON EBV LYTIC DNA REPLICATION

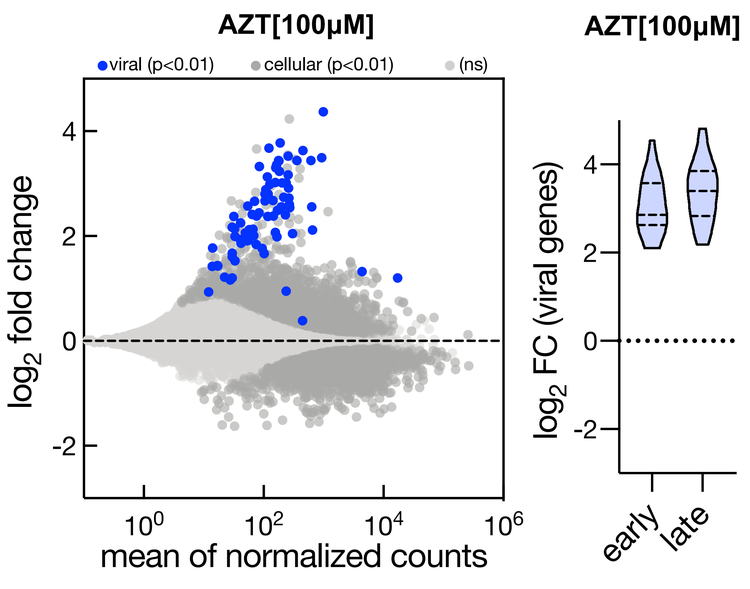


EFFECTS ON EBV LATENCY

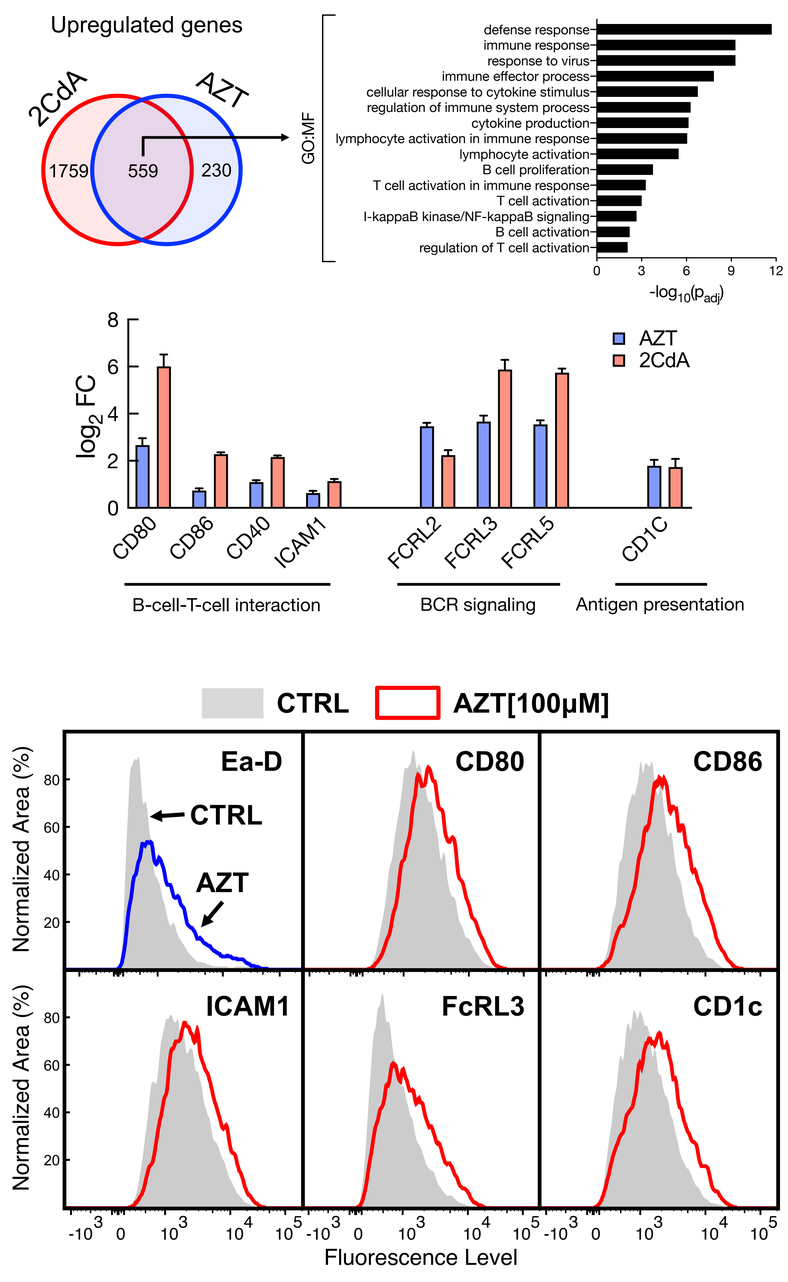


EFFECTS ON VIRAL GENE EXPRESSION





EFFECTS ON CELLULAR GENE EXPRESSION



KEY FINDINGS

- The nucleoside analogs ABC, d4T, TDF, TAF and 2CdA (in addition to AZT) directly inhibit lytic EBV DNA replication.
- AZT, TAF, and 2CdA can also induce EBV lytic gene expression from latency, without subsequent viral DNA replication. Increased viral antigen production may be an avenue to increase immune recognition of EBV+ cells.
- Additionally, AZT and 2CdA both increase expression of cellular immunoregulatory genes including CD40, CD80, CD86, ICAM1, FcRLs, and CD1.
- The effects of nucleoside analogs on EBV may be related to their reported effects in MS case reports.

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