The Implication of Viral Load Measurement in Assessing the Epidemiologic Control of HIV/AIDS

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CEID
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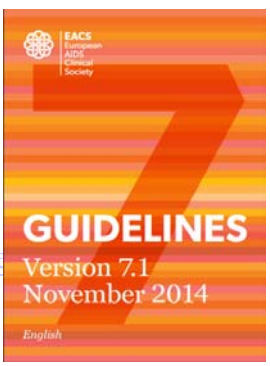
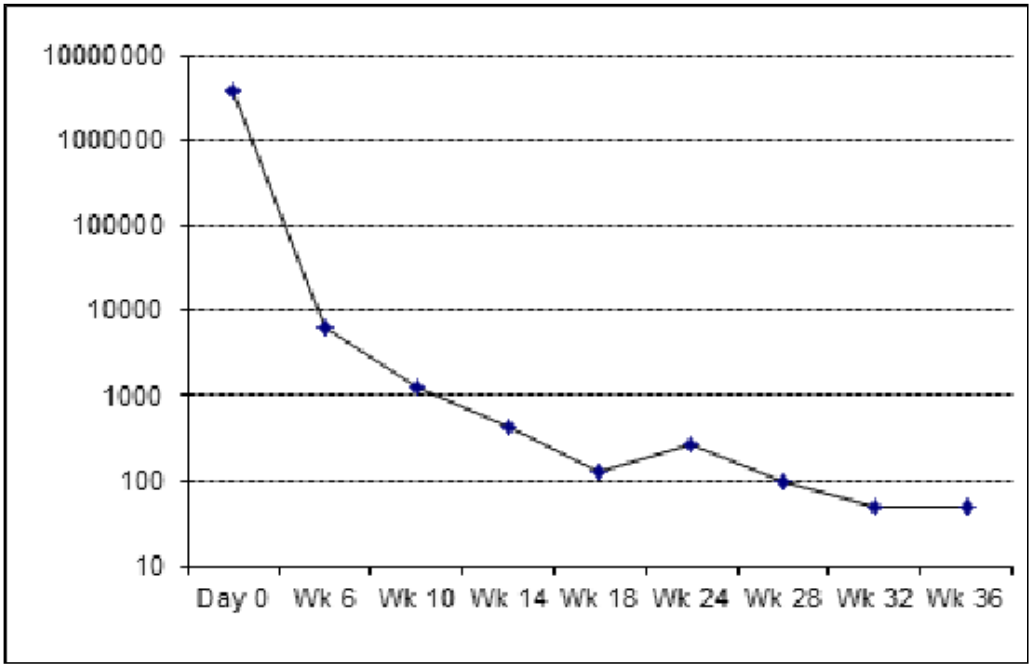
Summarizing
current approach to HIV treatment

- Combination treatment – 2NRTI plus one NRTI/boosted PI / INSTI
- Early treatment – moving away from CD4 guided therapy
- Public health role of effective and early HIV treatment considered
- Shrinking role of CD4 monitoring acknowledged



Natural history of HIV infection with treatment – decrease in viral load at individual level



http://hivbook.com/tag/viral-load/ accessed on 13 October 2014

Viral load measures at population level

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™

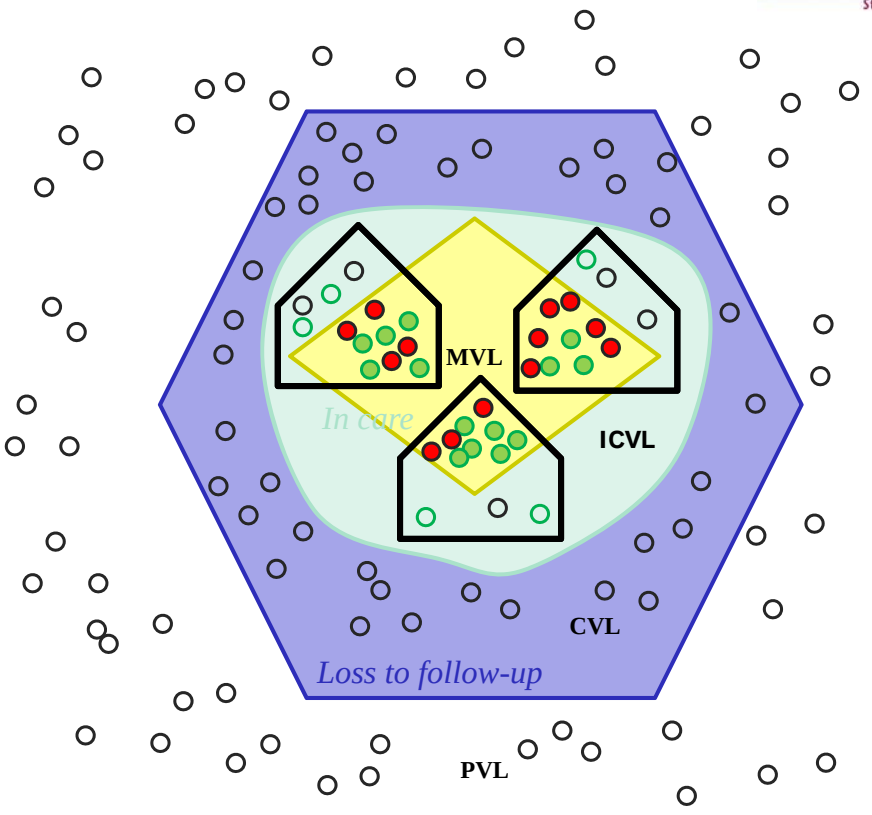
Viral Load Measures

	Component Measures				
Population Viral Load	In care with undetectable VL	In care with detectable VL	In care, no VL*	Diagnosed but not in care	Undiagnosed
Community Viral Load	In care with undetectable VL	In care with detectable VL	In care, no VL	Diagnosed but not in care	
In-Care Viral Load	In care with undetectable VL	In care with detectable VL	In care, no VL		
Monitored Viral Load	In care with undetectable VL	In care with detectable VL			

*No VL = missing/unknown, for a variety of reasons (e.g., incomplete reporting).

http://www.cdc.gov/hiv/topics/surveillance/resources/factsheets/inc/content/viral_load_table.htm

Viral load measures at population level



Undiagnosed individuals

HIV specialist clinic

Patients with viral load records
- Viral load >500/mL
- Viral load ≤500/mL

Patients without viral load records
- Viral load >500/mL (estimated)
- Viral load ≤500/mL (estimated)

Viral load measures
- Monitored viral load (MVL)
- In-care viral load (ICVL)
- Community viral load (CVL)
- Population viral load (PVL)

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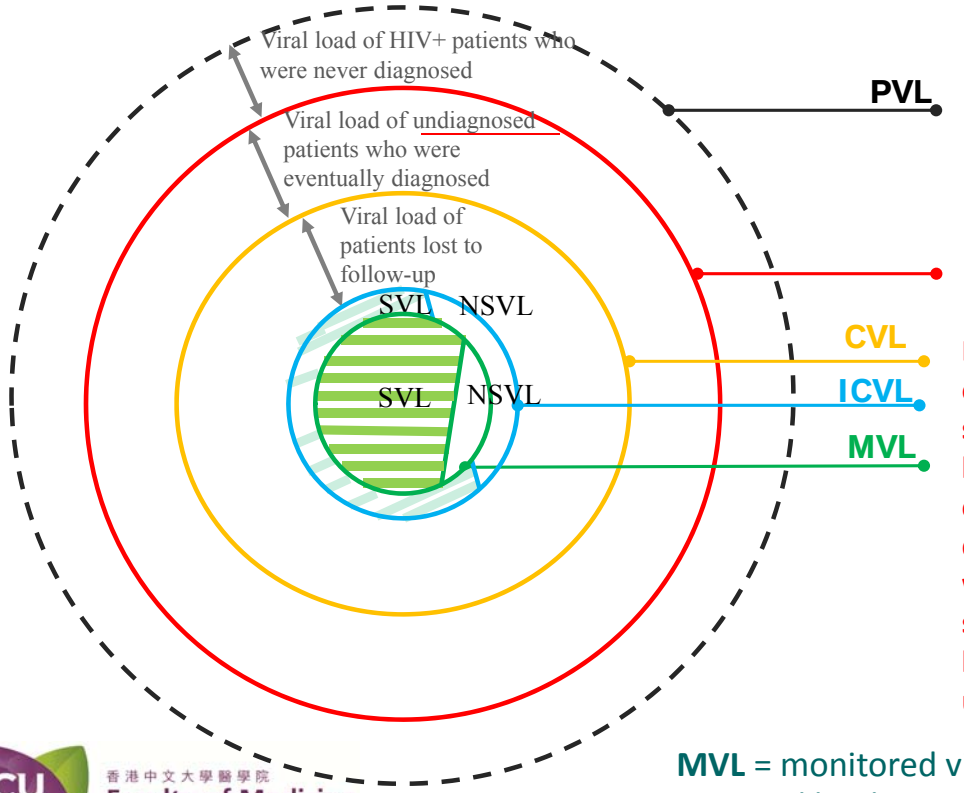
MVL = monitored viral load; **ICVL** = in care viral load; **CVL** = community viral load; **PVL** = population viral load

Population viral load cannot be 'calculated'.....



fCVL

By back-calculation, we estimated each person's seroconversion time, followed by the construction of viral load curves from seroconversion to diagnosis. Annual full CVL (fCVL), was then estimated by the summation of viral loads of both diagnosed and undiagnosed HIV+ individuals.

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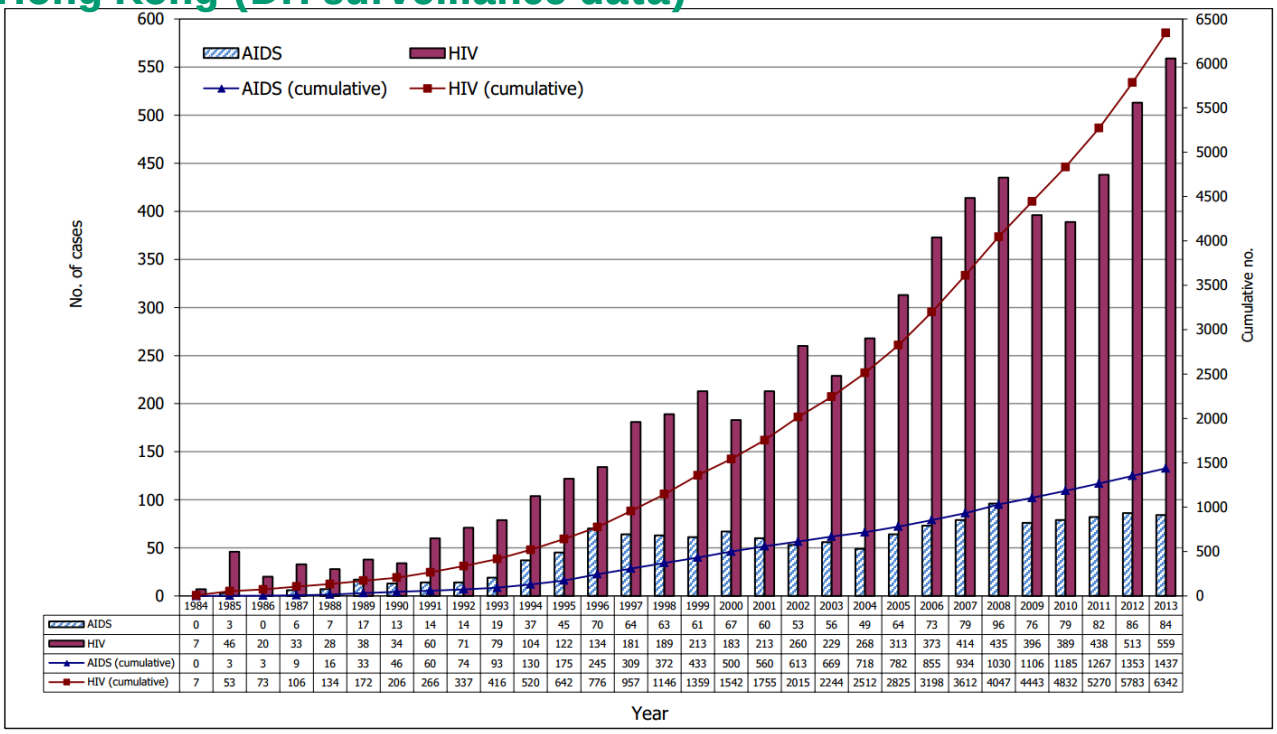
MVL = monitored viral load; **ICVL** = in care viral load; **CVL** = community viral load; **fCVL** = "full" community viral load

Conventional epidemic curves –

Hong Kong (DH surveillance data)



	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
AIDS	0	3	0	6	7	17	13	14	14	19	37	45	70	64	63	61	67	60	53	56	49	64	73	79	96	76	79	82	86	84
HIV	7	46	20	33	28	38	34	60	71	79	104	122	134	181	189	213	183	213	260	229	268	313	373	414	435	396	389	438	513	559
AIDS (cumulative)	0	3	3	9	16	33	46	60	74	93	130	175	245	309	372	433	500	560	613	669	718	782	855	934	1030	1106	1185	1267	1353	1437
HIV (cumulative)	7	53	73	106	134	172	206	266	337	416	520	642	776	957	1146	1359	1542	1755	2015	2244	2512	2825	3198	3612	4047	4443	4832	5270	5783	6342

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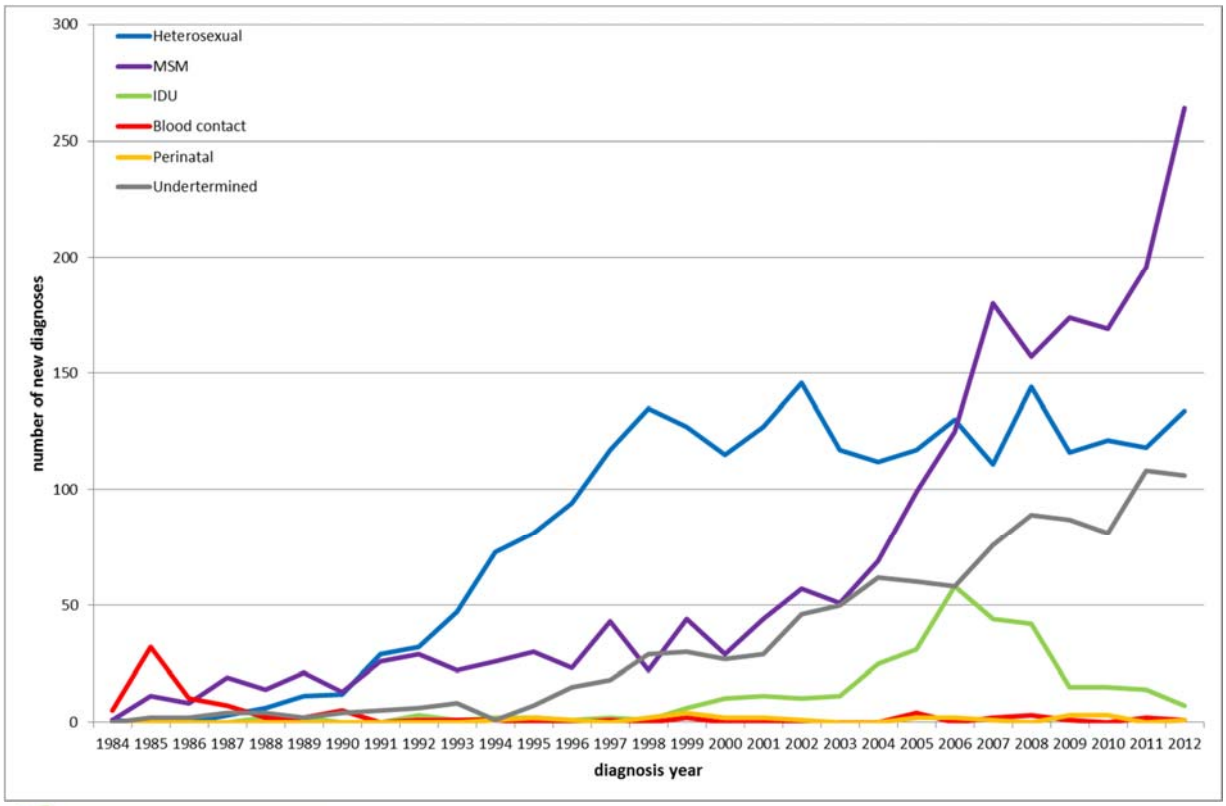
Source: Virtual AIDS Office of Hong Kong, Department of Health, HKSAR
http://www.info.gov.hk/aids/english/surveillance/sur_report/hiv13.pdf

Conventional epidemic curves by subpopulation



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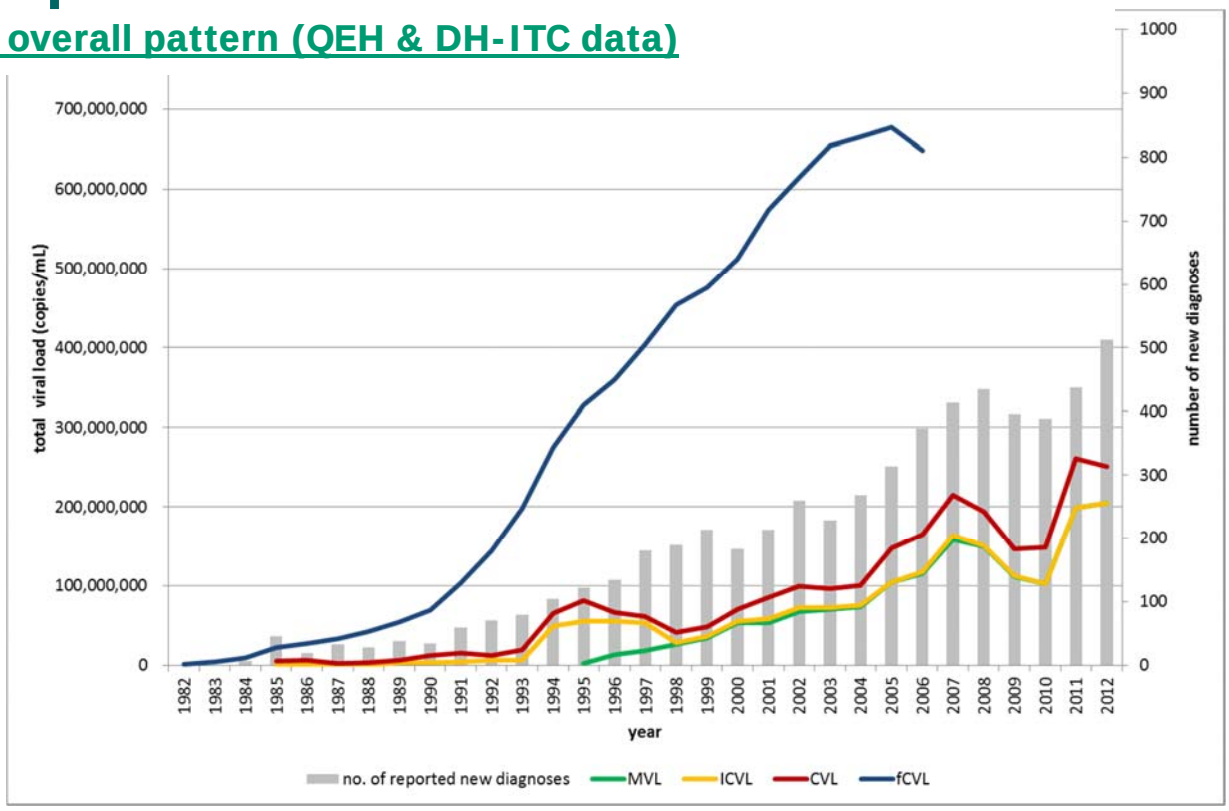
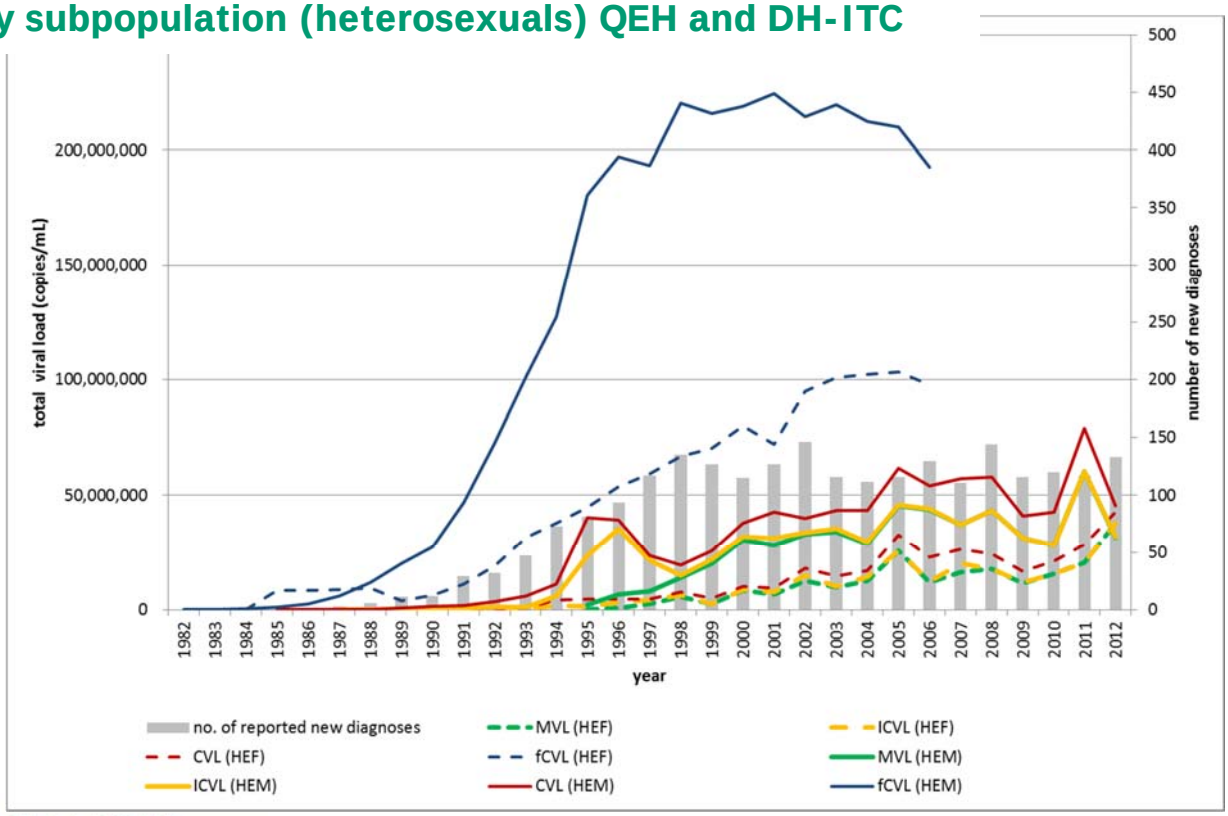
Population level viral load curves

– overall pattern (QEH & DH-ITC data)



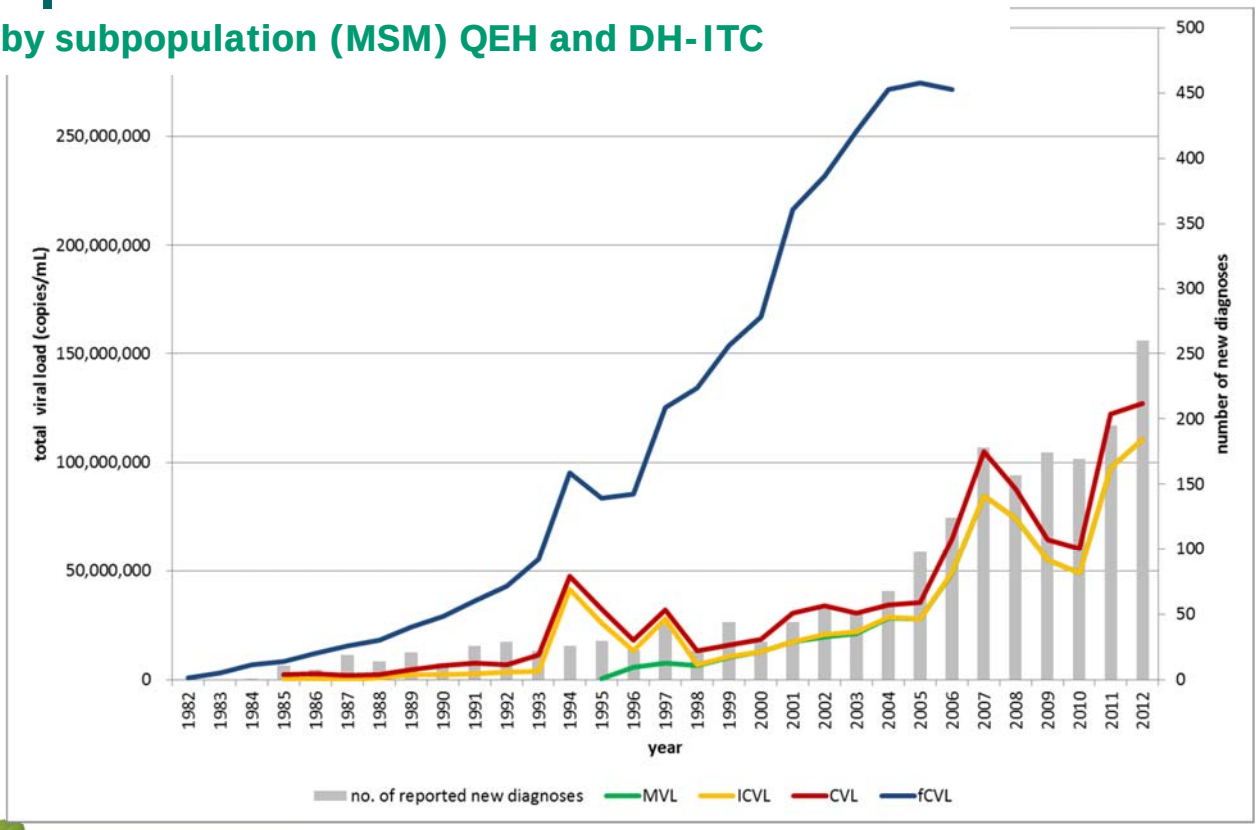
Population level viral load curves

– by subpopulation (heterosexuals) QEH and DH-ITC



Population level viral load curves

– by subpopulation (MSM) QEH and DH-ITC



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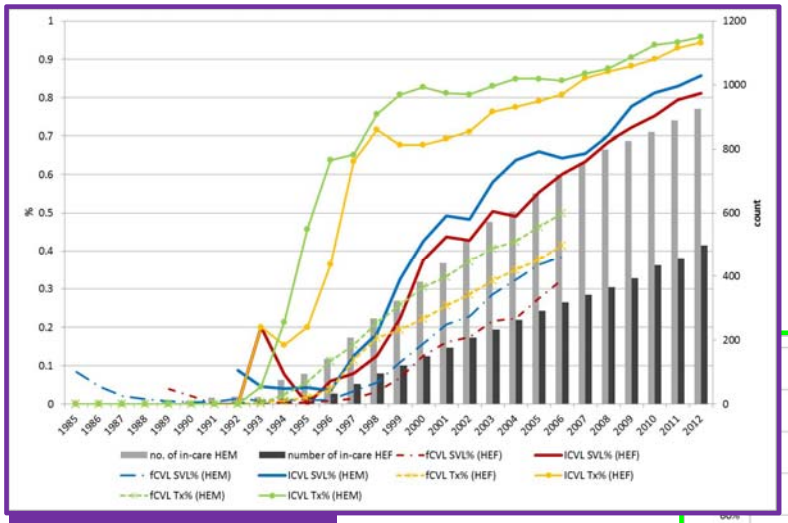
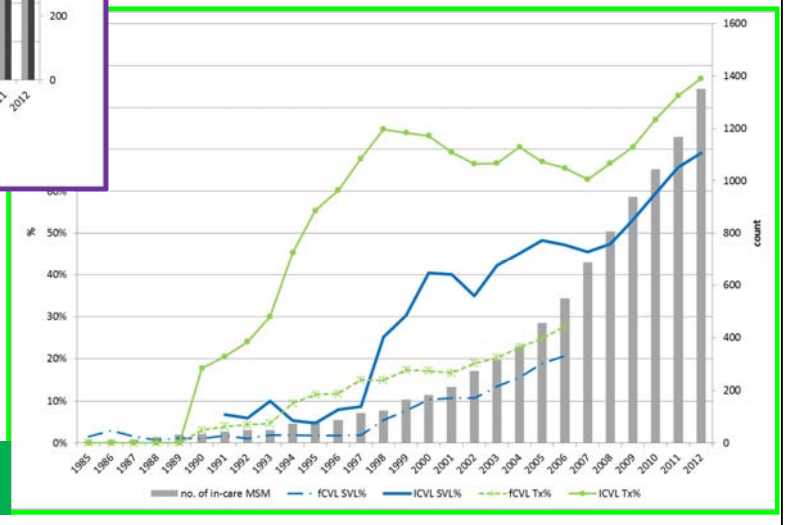
Viral load suppression in the population



heterosexuals

- Treatment %↑, SVL%↑
- time lag between increase of treatment coverage and proportion of patients with SVL
- Treatment % in MSM < heterosexuals

Data from QEH and DH-ITC



MSM

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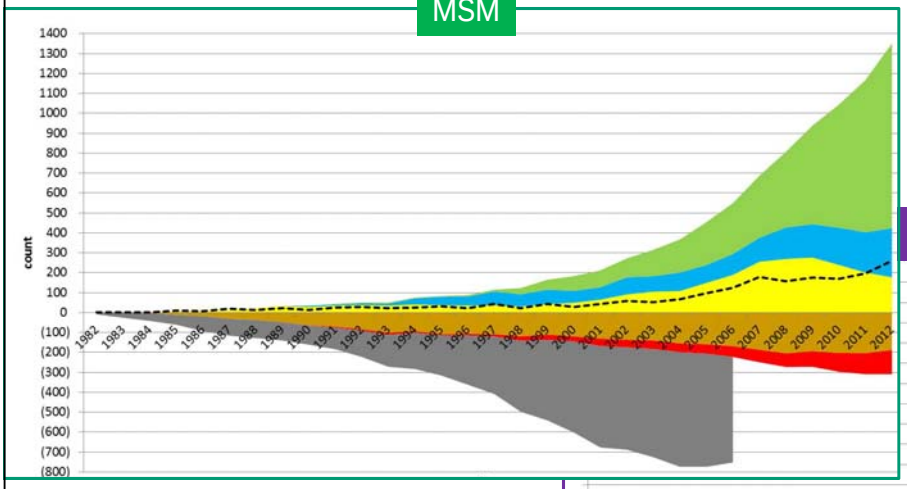
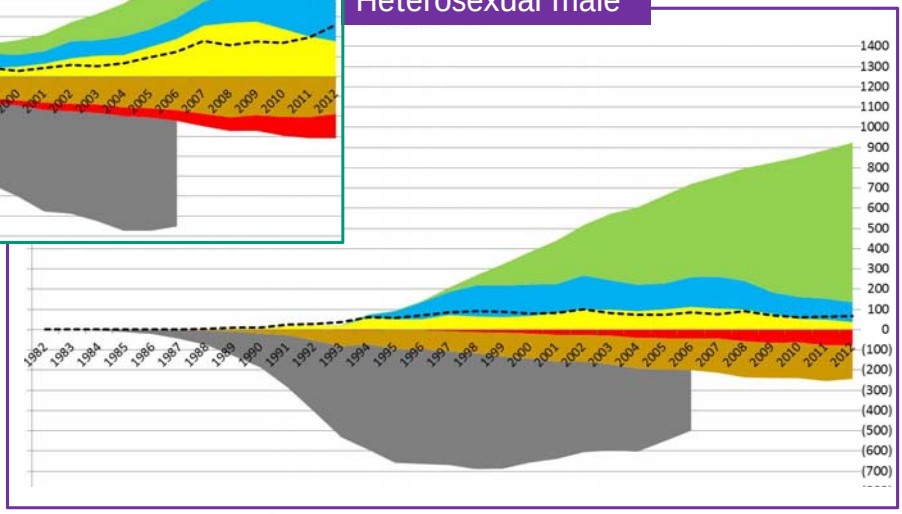
MSM



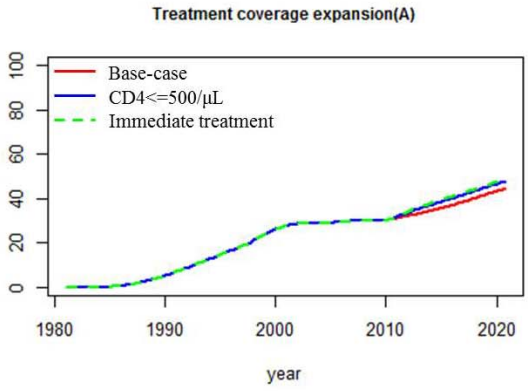
Heterosexual male

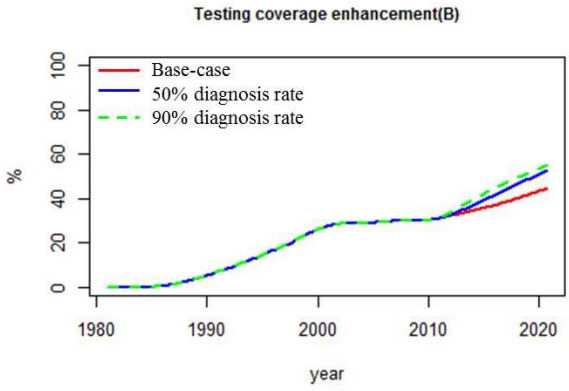


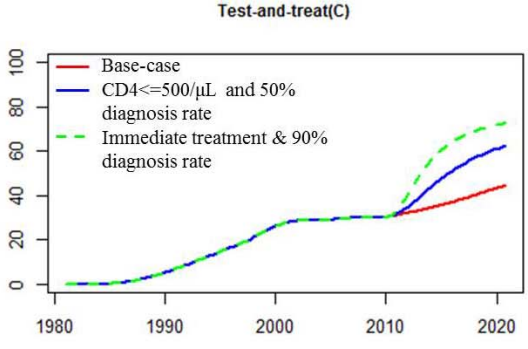
Data from QEH and DH-ITC

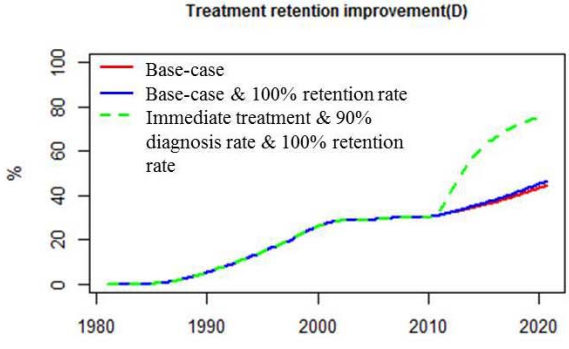
diagnosed
on treatment with NSVL
on treatment with SVL
diagnosed but lost to follow-up
initiated treatment but lost to follow-up
undiagnosed
newly diagnosed (surveillance)

Modelling viral load suppression under different scenarios









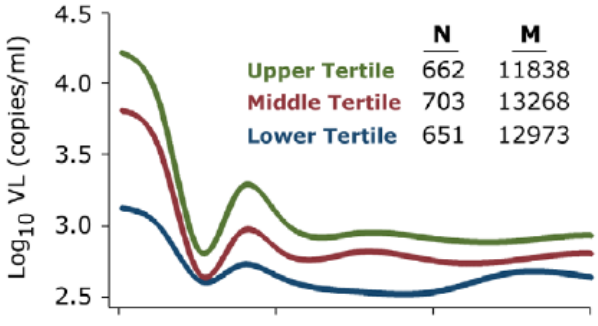
Data from QEH and DH-ITC for parameters setting

HIV epidemiology from a viral load perspective

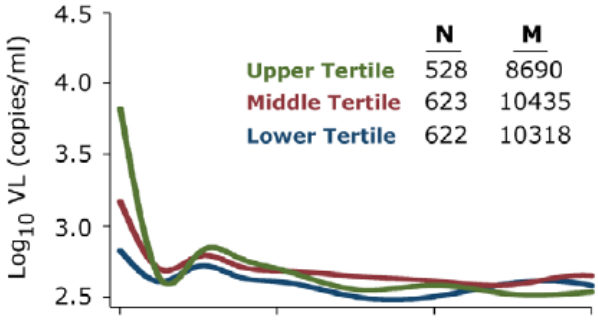
- Treatment %↑, SVL%↑, potential of HIV transmission ↓
- Population viral load (fCVL) curve predated incidence curves and unadjusted viral load measures by years
- Further reduction of HIV transmission potential in the population is small if treatment coverage is already optimal
- Reduction of the undiagnosed population is the single most important strategy to achieve effective epidemiologic control
- Non-locally acquired infection, assuming same treatment coverage and timeliness, is unlikely to contribute to the epidemic unless local transmission networks are present
- Epidemiological understanding from viral burden in population *per se* cannot predict outbreaks.

VL trajectories during HAART

US Military HIV Natural History Study



All subject



Those achieving VL suppression

PLOS ONE

Marconi VC, Grandits G, Okulicz JF, Wortmann G, et al. (2011) Cumulative Viral Load and Virologic Decay Patterns after Antiretroviral Therapy in HIV-Infected Subjects Influence CD4 Recovery and AIDS. PLoS ONE 6(5): e17956. doi:10.1371/journal.pone.0017956
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0017956

2011 PLoS one
OPEN ACCESS Freely available online

Cumulative Viral Load and Virologic Decay Patterns after Antiretroviral Therapy in HIV-Infected Subjects Influence CD4 Recovery and AIDS

Vincent C. Marconi[1,2*], Greg Grandits[2,3], Jason F. Okulicz[2,4], Glenn Wortmann[5], Nancy Crum-Cianflone[2,7], Michael Polis[2,8], Michael Landrum[2,4], Matthew J. Do[9], Brian Agan[2], Hemant Kulkarni[10,11*], the Infectious Disease Clinical Research Working Group[¶]

J Infect Dis. 2009;200:79-87

Cumulative HIV Viremia during Highly Active Antiretroviral Therapy Is a Strong Predictor of AIDS-Related Lymphoma

Alexander Zoufaly,[1] Hans-Jürgen Stellbrink,[2] Matthias an der Heiden,[3] Christian Kollan,[3] Christian Hoffmann,[2] Jan van Lunzen,[1] Osamah Hamouda,[3] and the ClinSurv Study Group
of Medicine, University Medical Center Hamburg-Eppendorf and [2]IPM Study Center, Hamburg, many

JAIDS 2014;67:204–211 EPIDEMIOLOGY AND PREVENTION

Cumulative HIV Viremia and Non–AIDS-Defining Malignancies Among a Sample of HIV-Infected Male Veterans

Marc ... PhD,‡ Xianglin L. Du, ...

CLINICAL SCIENCE

Clin Infect Dis 2011;53(9):927–935

Viremia Copy-Years Predicts Mortality Among Treatment-Naive HIV-Infected Patients Initiating Antiretroviral Therapy

...onia Napravnik,[2,3,a] Stephen R. Cole,[3] Joseph J. Eron,[2,3] Bryan Lau,[4] Heidi M. Crane,[5] ...H. Willig,[1] Richard D. Moore,[6] Steven G. Deeks,[7] Michael S. Saag,[1] and ... on behalf of the ...h Network of Integrated Clinical Systems (CNICS) Cohort Study

JAIDS 2014;66:55-64

Determinants of Viremia Copy-Years in People With HIV/AIDS After Initiation of Antiretroviral Therapy

Stephen T. Wright, MAppStat,* Jennifer Hoy, MBBS,†‡ Brian Mulhall, MBBS,*§ Catherine C. O'Connor, DrPH, MM,*‖¶ Kathy Petoumenos, PhD,* Timothy Read, PhD,# Don Smith, MD,**†† Ian Woolley, MD,†‡‡ and Mark A. Boyd, MD* on behalf of the Australian HIV Observational Database

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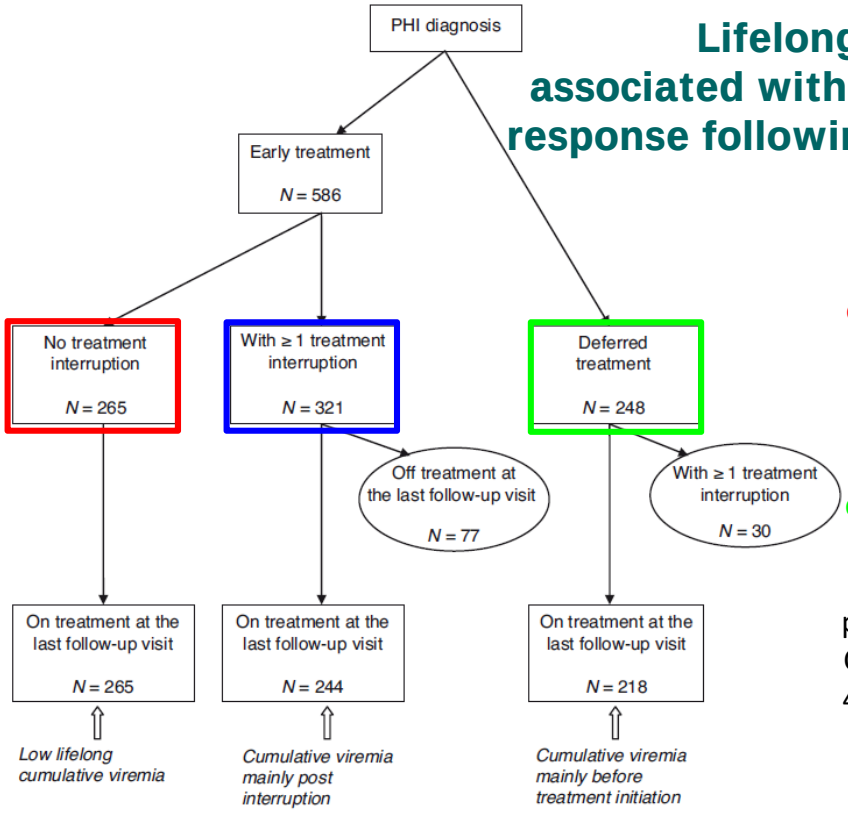

Lifelong cumulative viraemia is associated with a better immunological response following treatment of primary infections

CD4 was highest following **early continuous treatment** of patients who had the lowest cumulative viraemia. Latest CD4 cell count was not associated with cumulative HIV viraemia in **early intermittent** vs **deferred treatment** group. In contrast, patients with high cumulative HIV viraemia (>66th percentile vs. <33rd percentile) were less likely to achieve a CD4/CD8 ratio of more than 1 (26.8 vs. 43.3%, P=0.003), even after controlling for the baseline CD4/CD8 ratio, treatment duration, sex and age..

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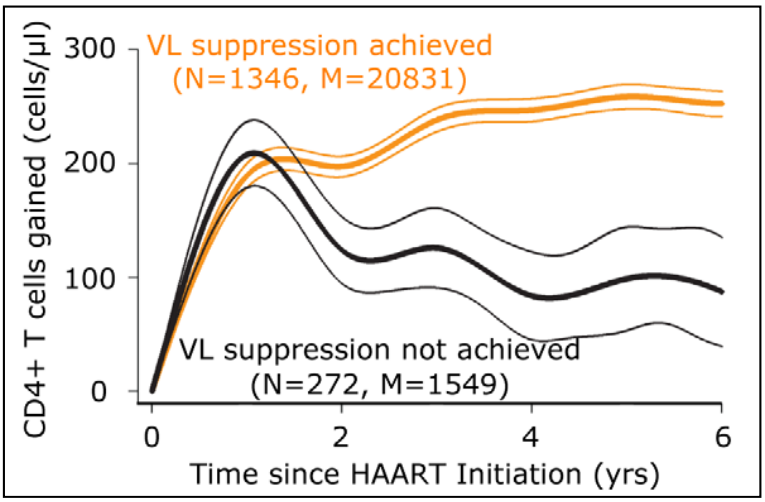
Seng R, Goujard C, Krastinova E, et al. Influence of lifelong cumulative HIV viremia on long-term recovery of CD4+ cell count and CD4+/CD8+ ratio among patients on combination antiretroviral therapy. *AIDS* 2015;29:595-607.

CD4/CD8 ratio
as a 'new' biomarker of HIV infection

Associations of a low ratio

- T cell activation, senescence, and dysfunction and with chronic inflammation
- A higher risk of disease progression, similar to IDU, HCV infection, elderly people
- non-AIDS illnesses usually including cardiovascular, renal, and liver diseases, non-AIDS cancers
- Other infections, for example CMV
- Surrogate of chronic inflammation.

Diversifying roles of 2 longstanding HIV markers



Marconi VC, Grandits G, Okulicz JF, Wortmann G, et al. (2011) Cumulative Viral Load and Virologic Decay Patterns after Antiretroviral Therapy in HIV-Infected Subjects Influence CD4 Recovery and AIDS. PLoS ONE 6(5): e17956. doi:10.1371/journal.pone.0017956 http://www.plosone.org/article/info:doi/10.1371/journal.pone.0017956

CD4
Absolute count for informing urgency of HAART, monitoring response, as outcome measure

CD4/CD8
Another outcome measure, morbidity index

VL
Marker of response to treatment

Population VL
Population risk of transmission

Cumulative VL
Lifetime risk of disease progression

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Mandy Li (data management)

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Dr MP Lee (population viral load studies;)
Dr Owen Tsang (population viral load studies)

Ongoing clinical studies

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