HAART 3.0
Verso una terapia senza tossicità: un traguardo realmente possibile?

Antonio Di Biagio
IRCCS AOU San Martino-IST, Genova

Perugia, 30 marzo 2017

Conflitto d'interessi

- **Finanziamento per ricerca: Gilead, ViiV, Abbvie**
- **Advisory Board: Gilead, ViiV, Janssen, MSD, Abbvie**
- **Partecipazioni a convegni ECM: Gilead, BMS, Abbvie, MSD**

***Nessuno tipo di condizionamento nel preparare questa presentazione**

La terapia antiretrovirale oggi

- Senza una cura definitiva la HAART va proseguita tutta la vita
- La combinazione di 3 farmaci è oggi lo standard of care
- Sono disponibili diversi STR con tre farmaci attivi
- Il successo a lungo termine richiede di minimizzare/eliminare gli eventi avversi a medio e lungo termine
- Abbiamo farmaci e strategie innovative a disposizione
- Nuovi farmaci sono in varie fasi di sviluppo

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The Survival Benefits of AIDS Treatment in the United States

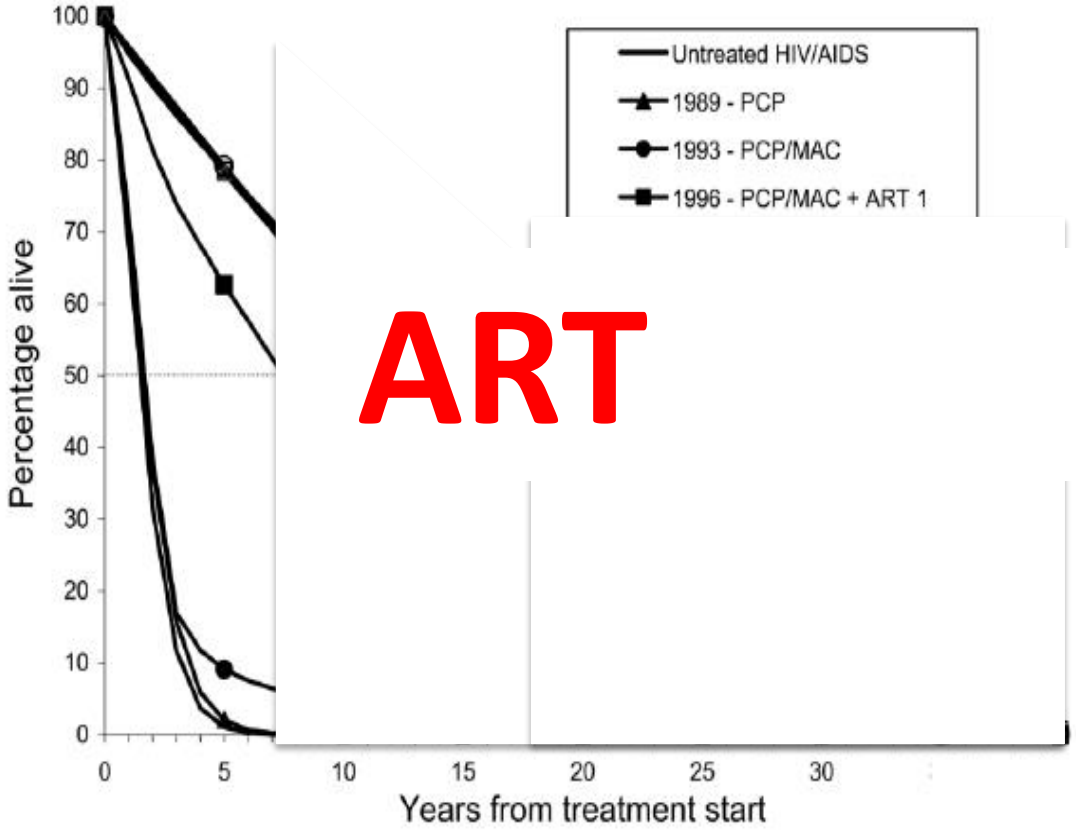
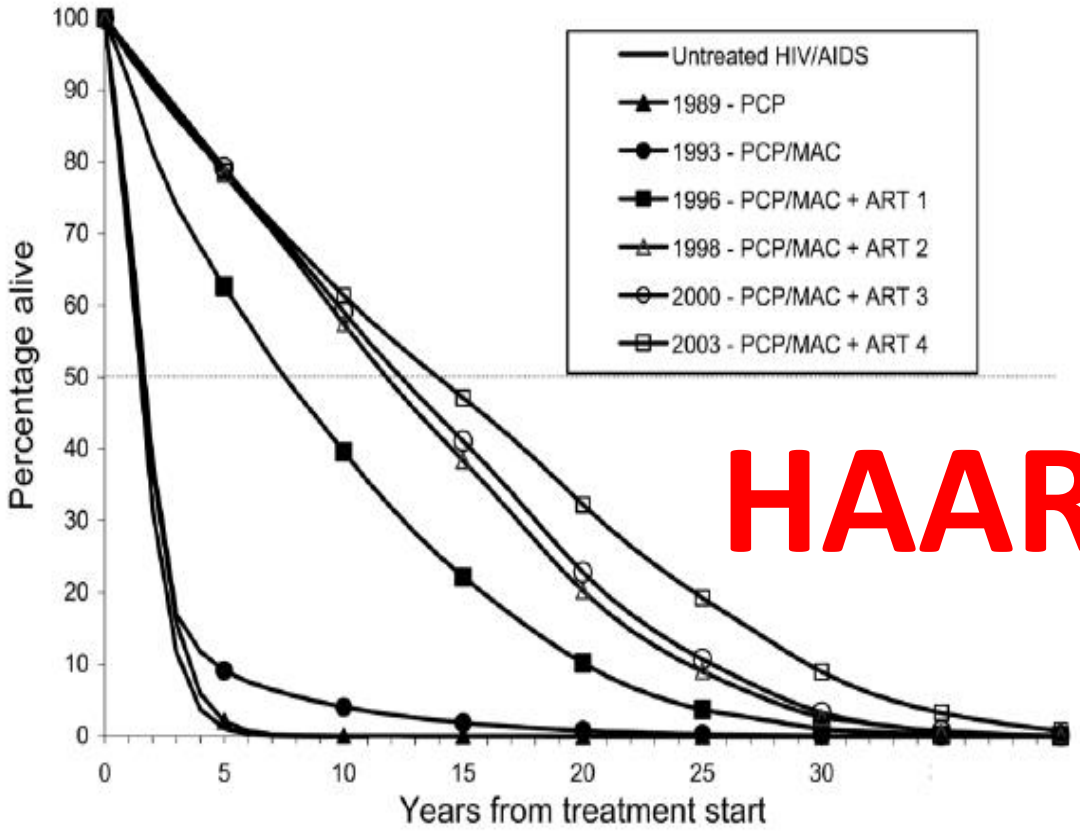


Figure 2. Survival curve produced by model simulations of the cohort that received diagnoses in the first year of each treatment era, with a mean age at treatment start of 39 years (SD, 9 years). ART, antiretroviral therapy; MAC, *Mycobacterium avium* complex; PCP, *Pneumocystis jiroveci* pneumonia.

The Survival Benefits of AIDS Treatment in the United States



HAART 1.0

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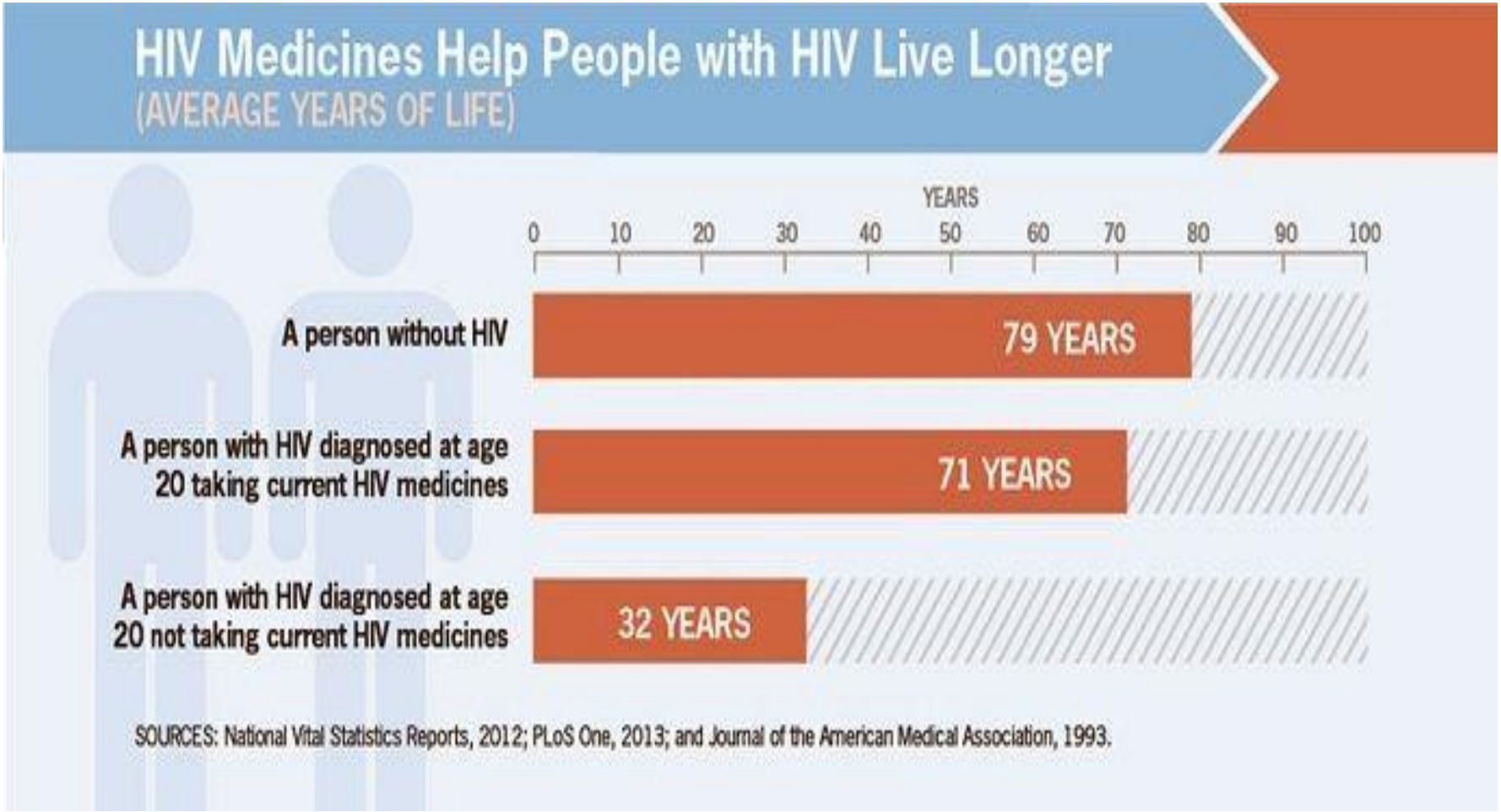
HAART 2.0


HIV Medicines Help People with HIV Live Longer
(AVERAGE YEARS OF LIFE)
YEARS
0
10
20
30
40
50
60
70
80
90
100
A person without HIV
79 YEARS
A person with HIV diagnosed at age 20 taking current HIV medicines
71 YEARS
A person with HIV diagnosed at age 20 not taking current HIV medicines
32 YEARS
SOURCES: National Vital Statistics Reports, 2012; PLoS One, 2013; and Journal of the American Medical Association, 1993.

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- Farmaci e strategie innovative
- Nuovi farmaci sono in varie fasi di sviluppo

SIMIT
Società Italiana di Malattie Infettive e Tropicali

In collaborazione con:

Ministero della Salute

Sezioni L e M del Comitato Tecnico Sanitario

Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1

22 Novembre 2016

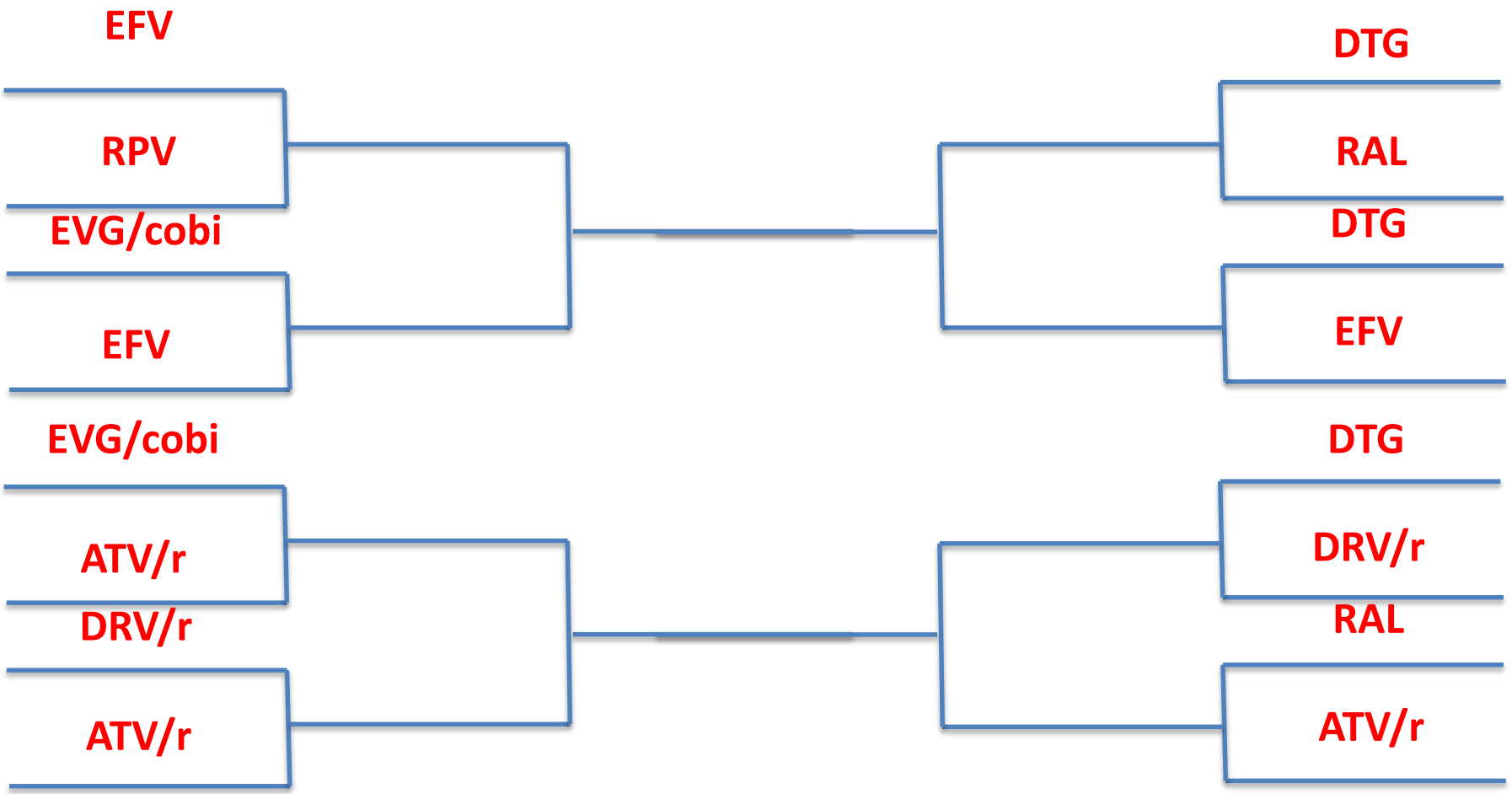
Tabella 2a - Regimi raccomandati per l'inizio della cART.

REGIME	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
Regimi raccomandati		
TDF/FTC+RAL	[AI]	[8-11,25]
TAF/FTC+RAL	[AII]	[3-5, 8-11,25]
TDF/FTC/EVG/COBI	[AI]	[17,18,26-28]
TAF/FTC/EVG/COBI	[AI]	[3, 6]
TDF/FTC+DTG	[AI]	[8,9,13]
TAF/FTC+DTG	[AII]	[3-5, 8,9,13]
ABC/3TC+DTG	[AI]	[8,9,12,13]
ABC/3TC/DTG	[AI]	[8,9,12,13,30]
TDF/FTC/RPV (in caso di valori di HIV-RNA < 100.000 cp/mL e conta di T CD4+ > 200 cellule/µL)	[AI]	[16,31-33]
TAF/FTC/RPV	[AII]	[3-5, 16,31-33]

28

Choosing An Initial Regimen

Gandhi 2016, mod.



J Antimicrob Chemother 2014; **69**: 2202–2209
doi:10.1093/jac/dku112 Advance Access publication 15 April 2014

Journal of Antimicrobial Chemotherapy

Temporal trends in the discontinuation of first-line antiretroviral therapy

Alejandro Gonzalez-Serna[1]*, Keith Chan[1], Benita Yip[1], William Chau[1], Rachel McGovern[1], Hasina Samji[1], Viviane Dias Lima[1,2], Robert S. Hogg[1,3] and Richard Harrigan[1,2]

[1]BC Centre for Excellence on HIV/AIDS, Vancouver V6Z1Y6, BC, Canada; [2]Division of AIDS, Department of Medicine, University of British Columbia, Vancouver V6T1Z4, BC, Canada; [3]Faculty of Health Sciences, Simon Fraser University, Burnaby V5A1S6 BC, Canada

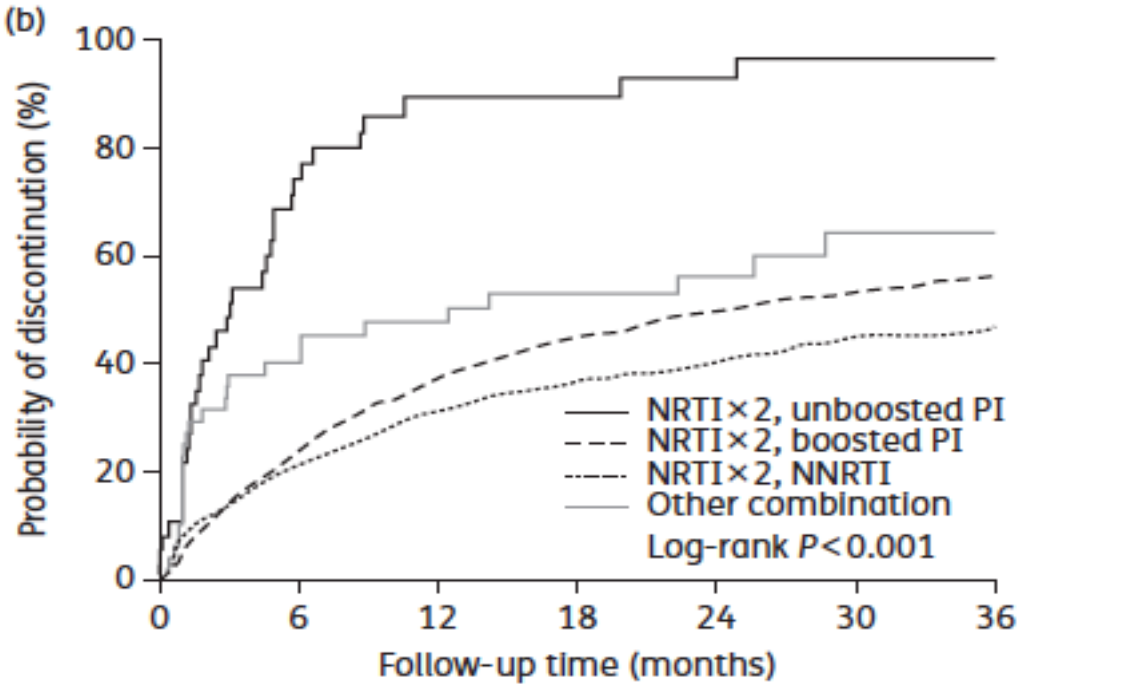
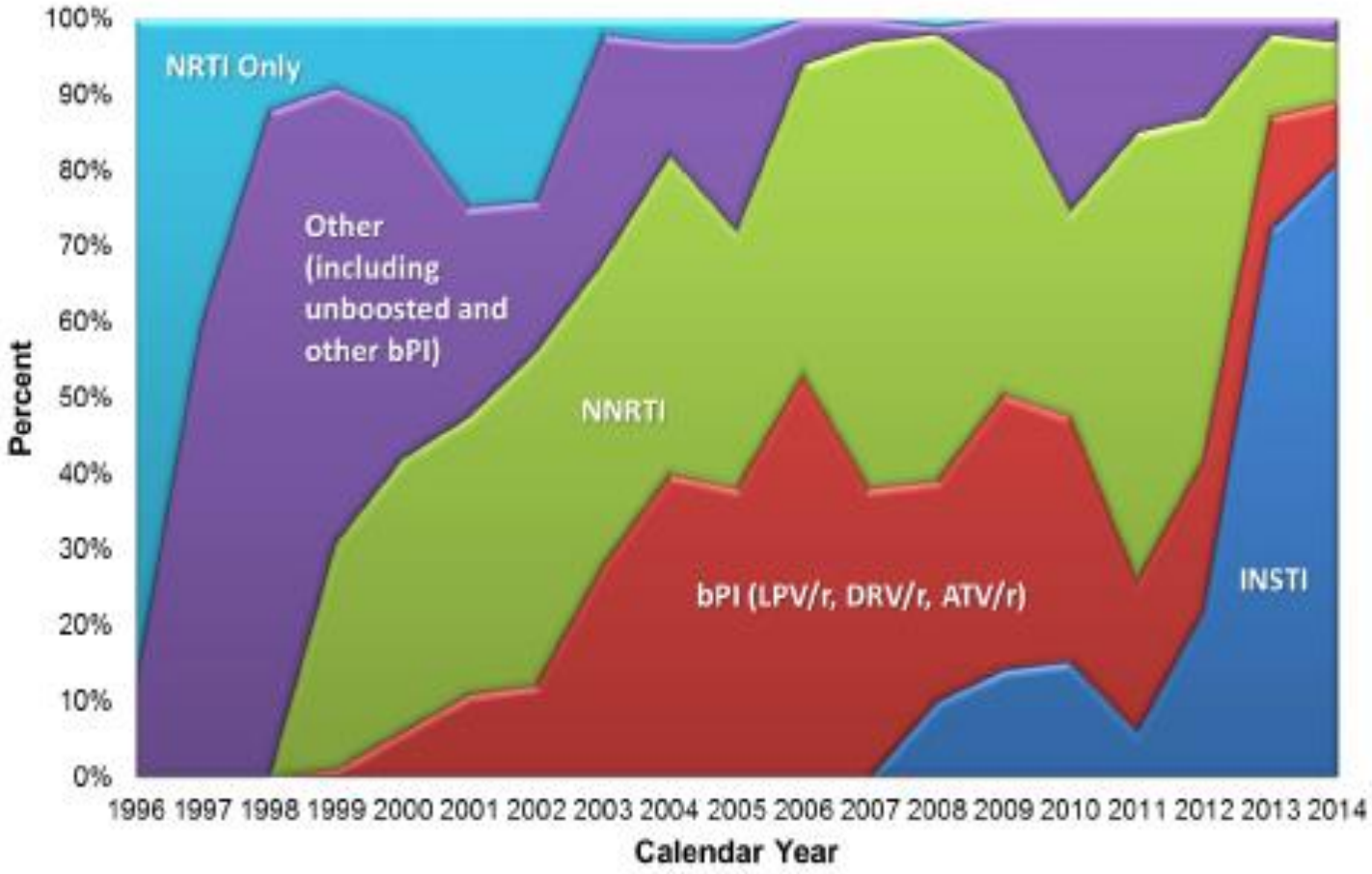


Figure 2: Changes in initial ART regimen by year



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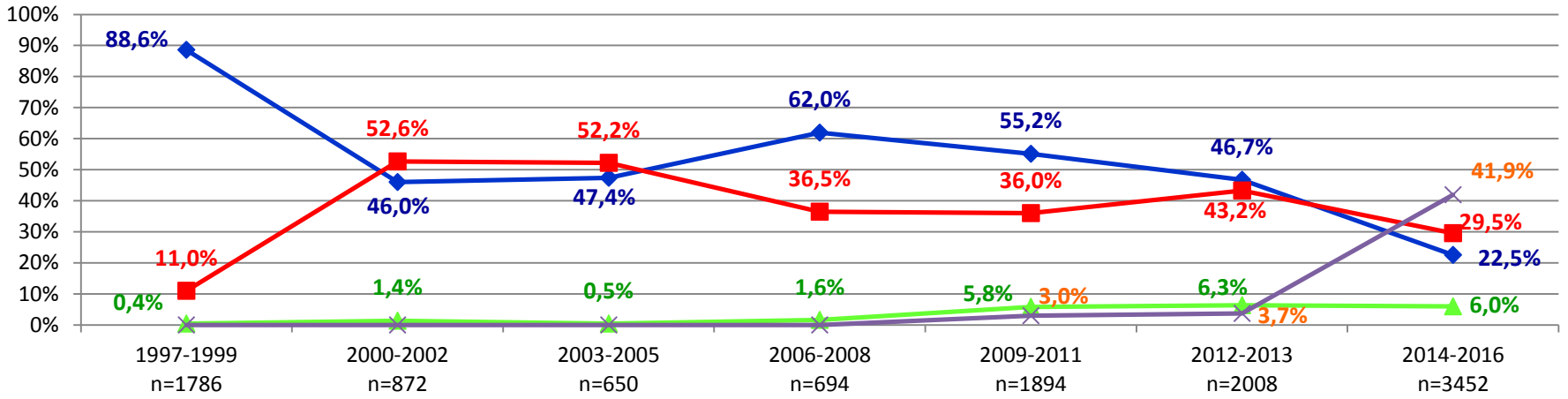
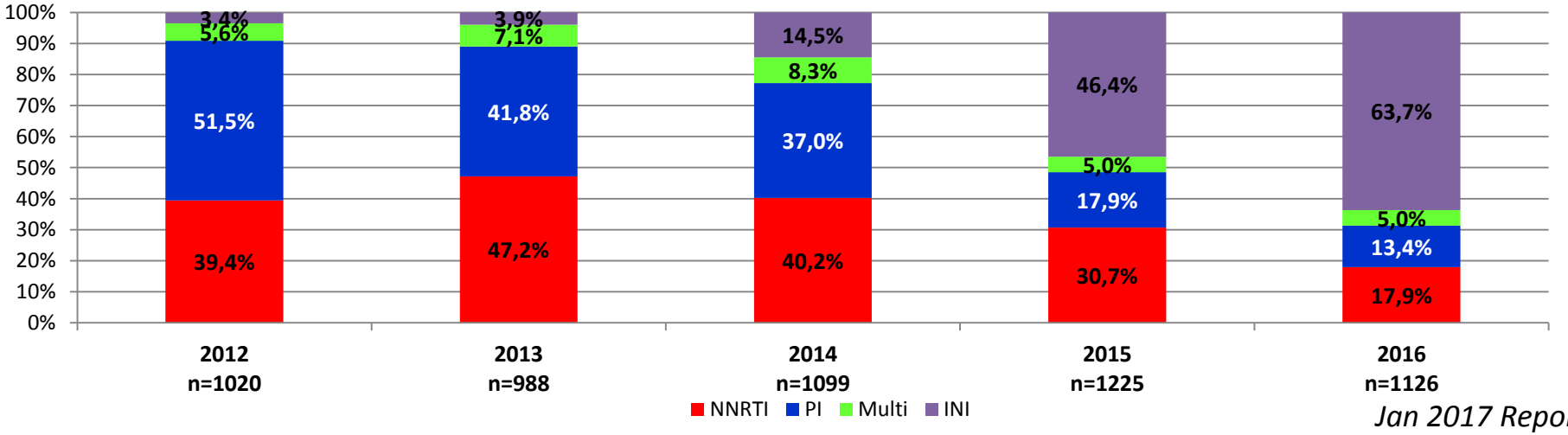
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Proportion of usage of different ART classes as third drug in first line regimen according to calendar period of starting (NRTIs not considered)



Proportion of usage of different ART classes as third drug in first line regimen according to calendar year of starting (only last 5 years)



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Potenziali vantaggi e svantaggi di un regime Single Tablet (STR)

VANTAGGI

- Semplice
- Facile da assumere
- In genere poco costosi
- Riducono aderenza selettiva

SVANTAGGI

- Impossibile adeguare dosaggio dei singoli componenti (es. problemi renali, tollerabilità)
- Non disponibile per tutte le cART

PLOS ONE

Published: February 2, 2017

RESEARCH ARTICLE

Effectiveness and tolerance of single tablet versus once daily multiple tablet regimens as first-line antiretroviral therapy - Results from a large french multicenter cohort study

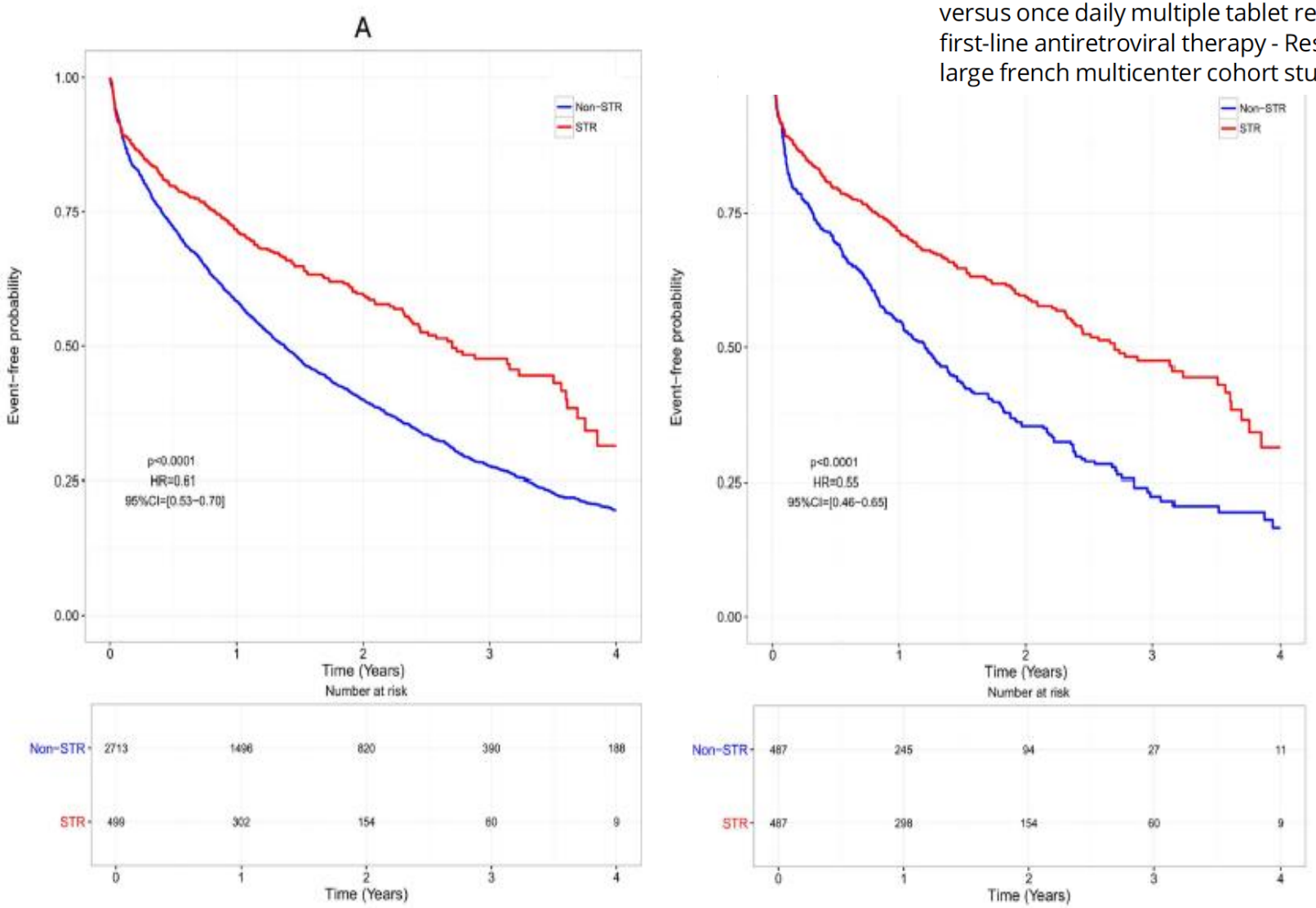

Fig 1. Overall effectiveness over time. Only patients remaining on the same therapy at the end of follow-up are considered as treatment success. Failure is defined as treatment discontinuation, occurrence of adverse event, or any cause of treatment modification.

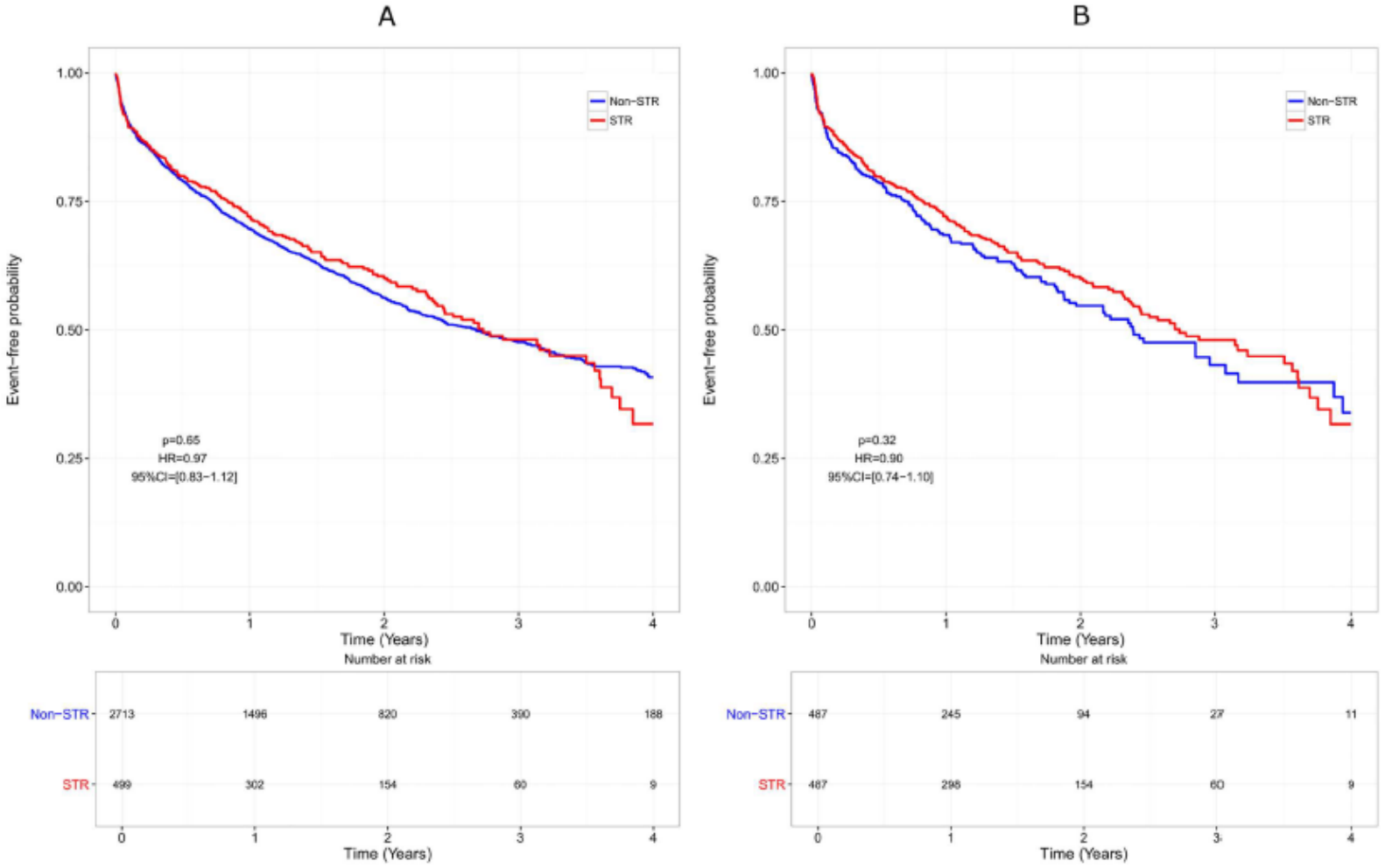

Fig 2. Overall effectiveness over time (simplification censored). Only patients remaining on the same therapy at the end of follow-up are considered as treatment success. Failure is defined as treatment discontinuation, occurrence of adverse event, or any cause of ment modification except treatment simplification (censored).

Published: February 2, 2017

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- Farmaci e Strategie innovative a disposzione
- Nuovi farmaci in arrivo

Feeling Tired

Nausea & Vomiting

Diarrhea

Headache

Short-Term Side Effects of HIV Medications

Fever

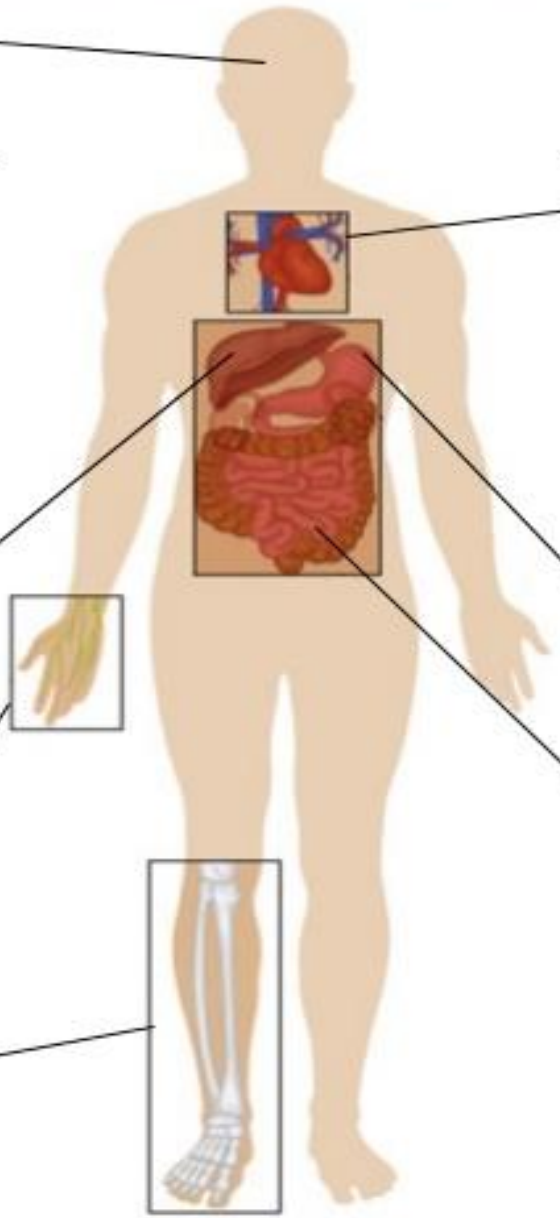
Muscle Pain

Occasional Dizziness

Insomnia

AIDSinfo
For more information, visit: aidsinfo.nih.gov

Common Side Effects of HIV Meds



FACE

Lipoatrophy
Loss of fat in cheeks, temples or extremities

BODY

Lipodystrophy
Increase in abdominal size, breast size, and/or dorsocervical fat pad (buffalo hump)

LIVER

Hepatotoxicity
Liver damage

NERVES

Neuropathy
Nerve damage causing strange sensations and pain, starting in the hands/feet

BONES

Osteoporosis, Osteopenia
Bone loss

SKIN

Rashes

HEART

Hyperlipidemia, High Cholesterol and High Glucose
Increase in the amount of fat, cholesterol, or sugar in the blood that can lead to heart disease

KIDNEYS

Nephrotoxicity, Kidney Stones
Kidney damage

GUT

Nausea, Diarrhea and Vomiting

BLOOD

Anemia
Low number of blood cells; causes fatigue

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2015
EMA/688896/2015

Updated advice on body fat changes and lactic acidosis with HIV medicines

EMA recommends removal of class warnings for several medicines

EMA's review covered centrally authorised HIV medicines. The following centrally authorised medicines no longer require a warning concerning fat redistribution: Aptivus, Atripla, Combivir, Crixivan, Edurant, Emtriva, Epivir, Eviplera, Evotaz, Intelence, Invirase, Kaletra, Kivexa, Lamivudine ViiV, Norvir, Prezista, Reyataz, Rezolsta, Stribild, Sustiva, Telzir, Triumeq, Trizivir, Truvada, Viramune, Viread, Zerit and Ziagen.

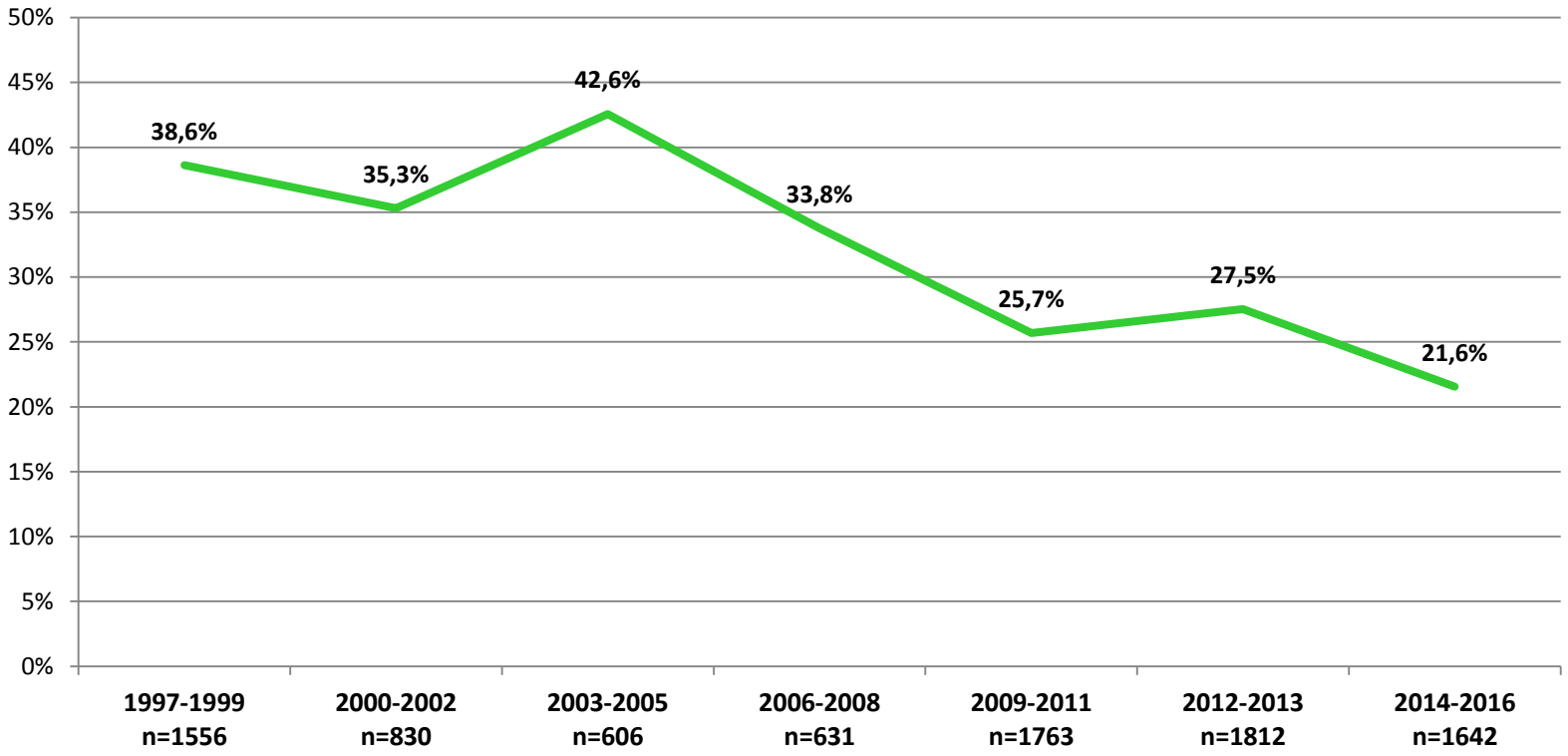
For lactic acidosis, the following medicines no longer require a class warning: Atripla, Emtriva, Epivir, Eviplera, Kivexa, Lamivudine ViiV, Stribild, Triumeq, Truvada, Viread and Ziagen.

Combivir, Trizivir and Zerit will now have a warning about fat loss (lipoatrophy) and will also retain the lactic acidosis warning.

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Italian Cohort I. C. O. N. A. Naive Antiretrovirals

Proportion of patients stopping at least one drug of their first ART regimen within 1 year, according to calendar period of starting



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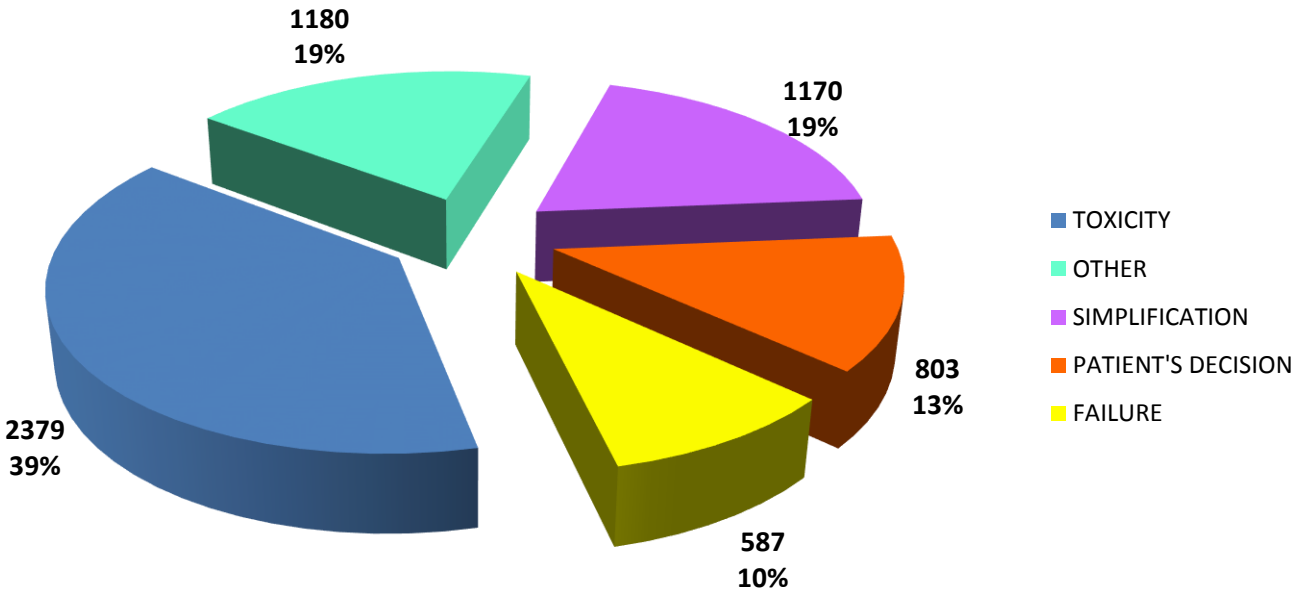
Italian Cohort I. C. O. N. A. Naive Antiretrovirals

Distribution of reasons for stopping at least one drug included in the first regimen N=6119



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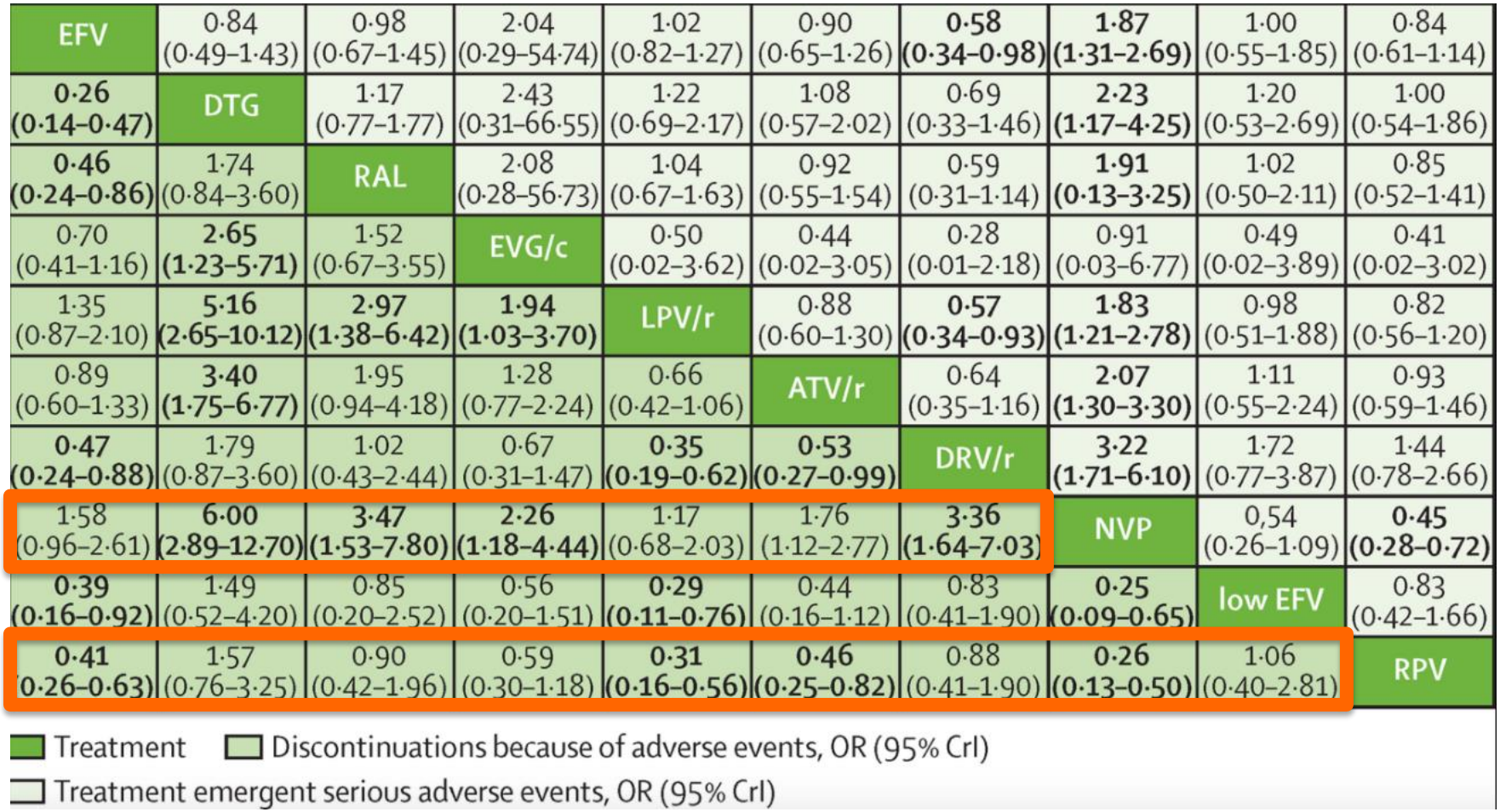
Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta analysis



EFV	0·84 (0·49–1·43)	0·98 (0·67–1·45)	2·04 (0·29–54·74)	1·02 (0·82–1·27)	0·90 (0·65–1·26)	**0·58 (0·34–0·98)**	**1·87 (1·31–2·69)**	1·00 (0·55–1·85)	0·84 (0·61–1·14)
0·26 (0·14–0·47)	DTG	1·17 (0·77–1·77)	2·43 (0·31–66·55)	1·22 (0·69–2·17)	1·08 (0·57–2·02)	0·69 (0·33–1·46)	**2·23 (1·17–4·25)**	1·20 (0·53–2·69)	1·00 (0·54–1·86)
0·46 (0·24–0·86)	1·74 (0·84–3·60)	RAL	2·08 (0·28–56·73)	1·04 (0·67–1·63)	0·92 (0·55–1·54)	0·59 (0·31–1·14)	**1·91 (0·13–3·25)**	1·02 (0·50–2·11)	0·85 (0·52–1·41)
0·70 (0·41–1·16)	**2·65 (1·23–5·71)**	1·52 (0·67–3·55)	EVG/c	0·50 (0·02–3·62)	0·44 (0·02–3·05)	0·28 (0·01–2·18)	0·91 (0·03–6·77)	0·49 (0·02–3·89)	0·41 (0·02–3·02)
1·35 (0·87–2·10)	**5·16 (2·65–10·12)**	**2·97 (1·38–6·42)**	**1·94 (1·03–3·70)**	LPV/r	0·88 (0·60–1·30)	**0·57 (0·34–0·93)**	**1·83 (1·21–2·78)**	0·98 (0·51–1·88)	0·82 (0·56–1·20)
0·89 (0·60–1·33)	**3·40 (1·75–6·77)**	1·95 (0·94–4·18)	1·28 (0·77–2·24)	0·66 (0·42–1·06)	ATV/r	0·64 (0·35–1·16)	**2·07 (1·30–3·30)**	1·11 (0·55–2·24)	0·93 (0·59–1·46)
0·47 (0·24–0·88)	1·79 (0·87–3·60)	1·02 (0·43–2·44)	0·67 (0·31–1·47)	**0·35 (0·19–0·62)**	**0·53 (0·27–0·99)**	DRV/r	**3·22 (1·71–6·10)**	1·72 (0·77–3·87)	1·44 (0·78–2·66)
1·58 (0·96–2·61)	**6·00 (2·89–12·70)**	**3·47 (1·53–7·80)**	**2·26 (1·18–4·44)**	1·17 (0·68–2·03)	1·76 (1·12–2·77)	**3·36 (1·64–7·03)**	NVP	0,54 (0·26–1·09)	**0·45 (0·28–0·72)**
0·39 (0·16–0·92)	1·49 (0·52–4·20)	0·85 (0·20–2·52)	0·56 (0·20–1·51)	**0·29 (0·11–0·76)**	0·44 (0·16–1·12)	0·83 (0·41–1·90)	**0·25 (0·09–0·65)**	low EFV	0·83 (0·42–1·66)
0·41 (0·26–0·63)	1·57 (0·76–3·25)	0·90 (0·42–1·96)	0·59 (0·30–1·18)	**0·31 (0·16–0·56)**	**0·46 (0·25–0·82)**	0·88 (0·41–1·90)	**0·26 (0·13–0·50)**	1·06 (0·40–2·81)	RPV

Treatment Discontinuations because of adverse events, OR (95% CrI)

Treatment emergent serious adverse events, OR (95% CrI)

Kanters S, Lancet HIV 2016

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- **Farmaci e strategie oggi**
- Nuovi farmaci sono in diverse fasi di sviluppo

HAART 3.0

FARMACI

TAF or TDF

- **When should you definitely use TAF over TDF?**
  - Patient with osteoporosis or osteopenia
  - Patient with renal disease (eGFR >30) or evidence for proximal tubular dysfunction (e.g. proteinuria)
  - Growing proportion of patients: “graying of the epidemic”

- **When should you definitely not use TAF?**
  - Patient on rifamycin (may decrease TAF levels)
  - Pregnant women
  - For pre-exposure prophylaxis (PrEP)

[1]Elion R et al, JAIDS, 2013. [2]Raffi F et al, Lancet, 2013. [3]Cahn P et al, Lancet, 2013

Which INSTI?

INSTI	PROS	CONS
RAL	• Longest-track record • Fewest drug interactions	• Twice daily (once daily formulation coming – ONCEMRK trial) • Not coformulated as part of single-pill regimen
EVG/c	• Available in single-pill regimen with TDF/FTC, TAF/FTC	• Most drug interactions (because of cobi) • Food requirement
DTG	• Available in single-pill regimen with ABC/3TC • High genetic barrier to resistance	• Not coformulated with tenofovir • Largest pill size of single pill regimens • Drug interaction with metformin

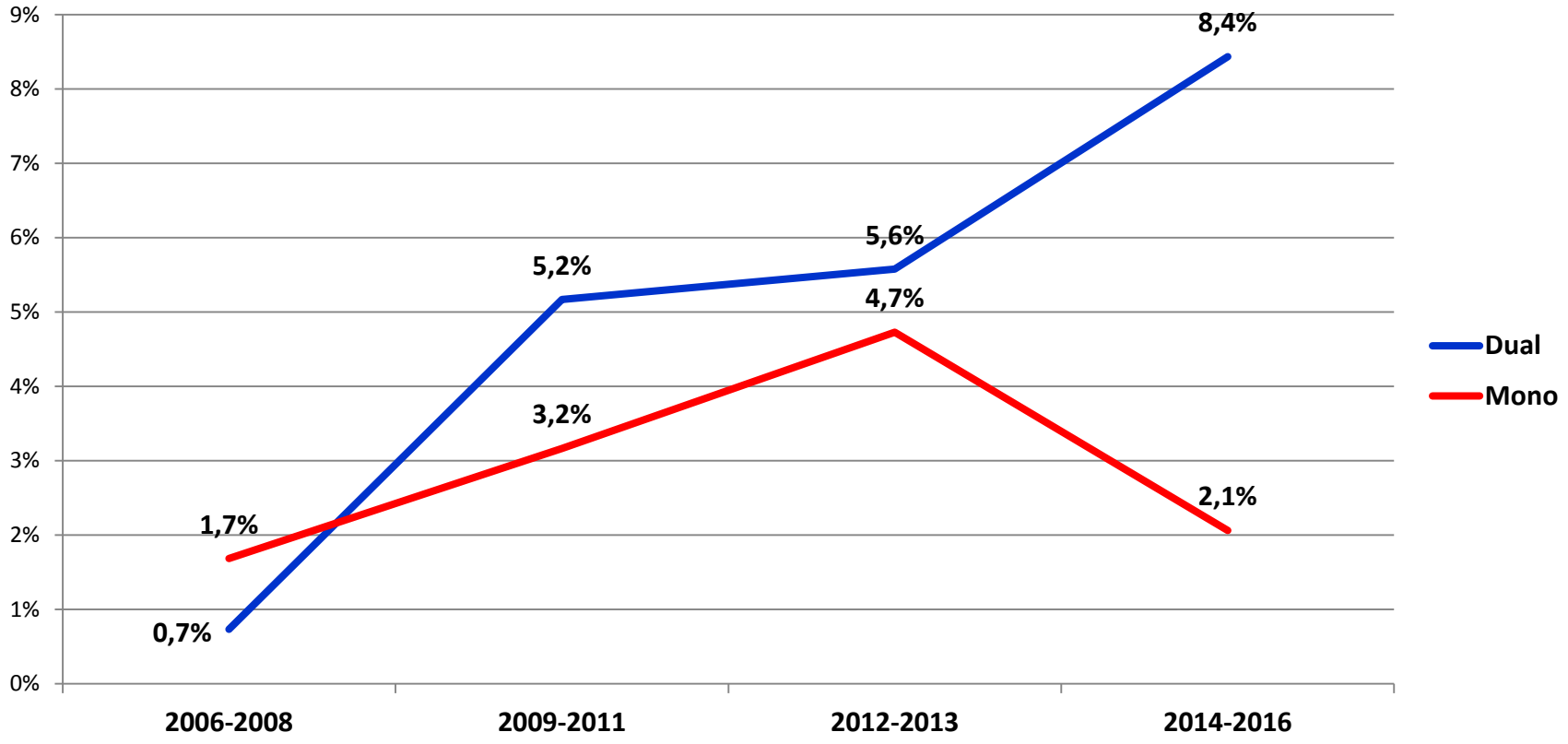
HAART 3.0

STRATEGIE

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Italian Cohort I.C.O.N.A. Naive Antiretrovirals

Proportion of mono/dual PI therapies according to calendar period of starting



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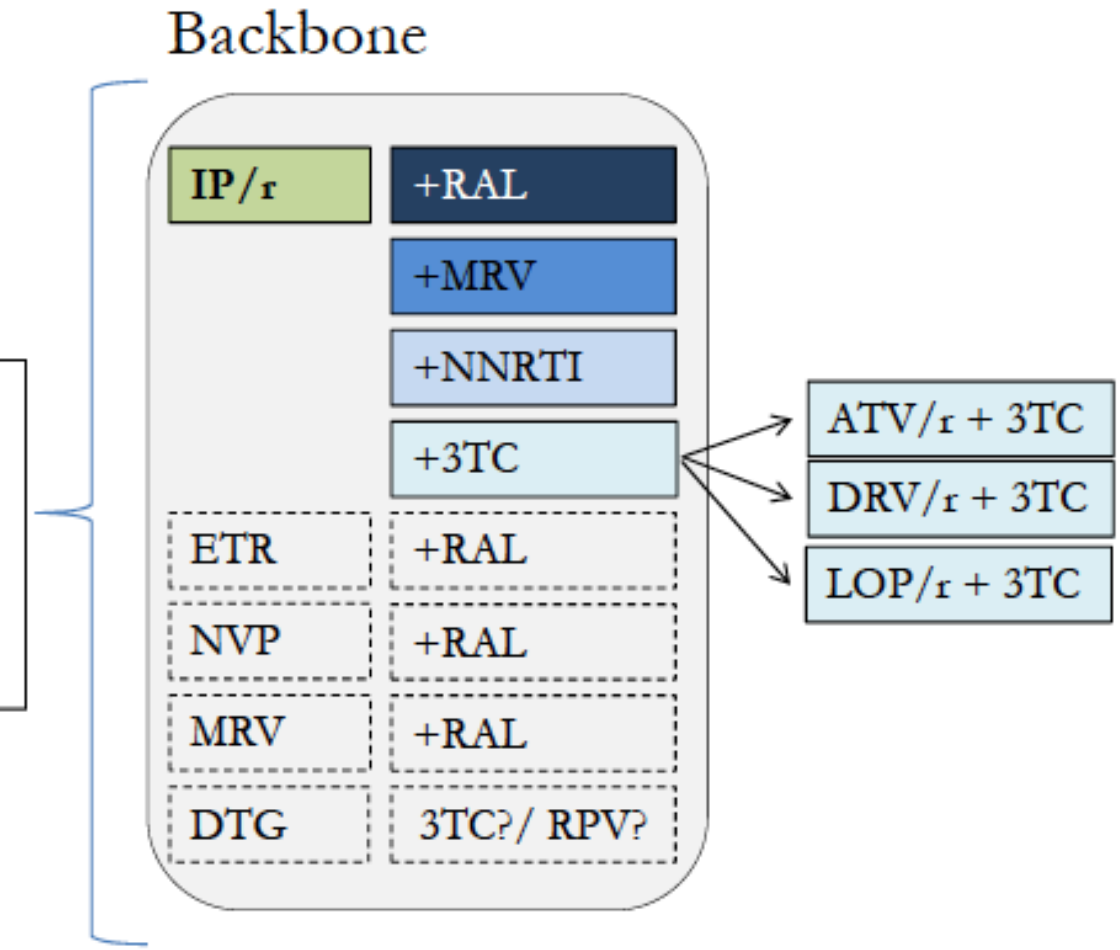
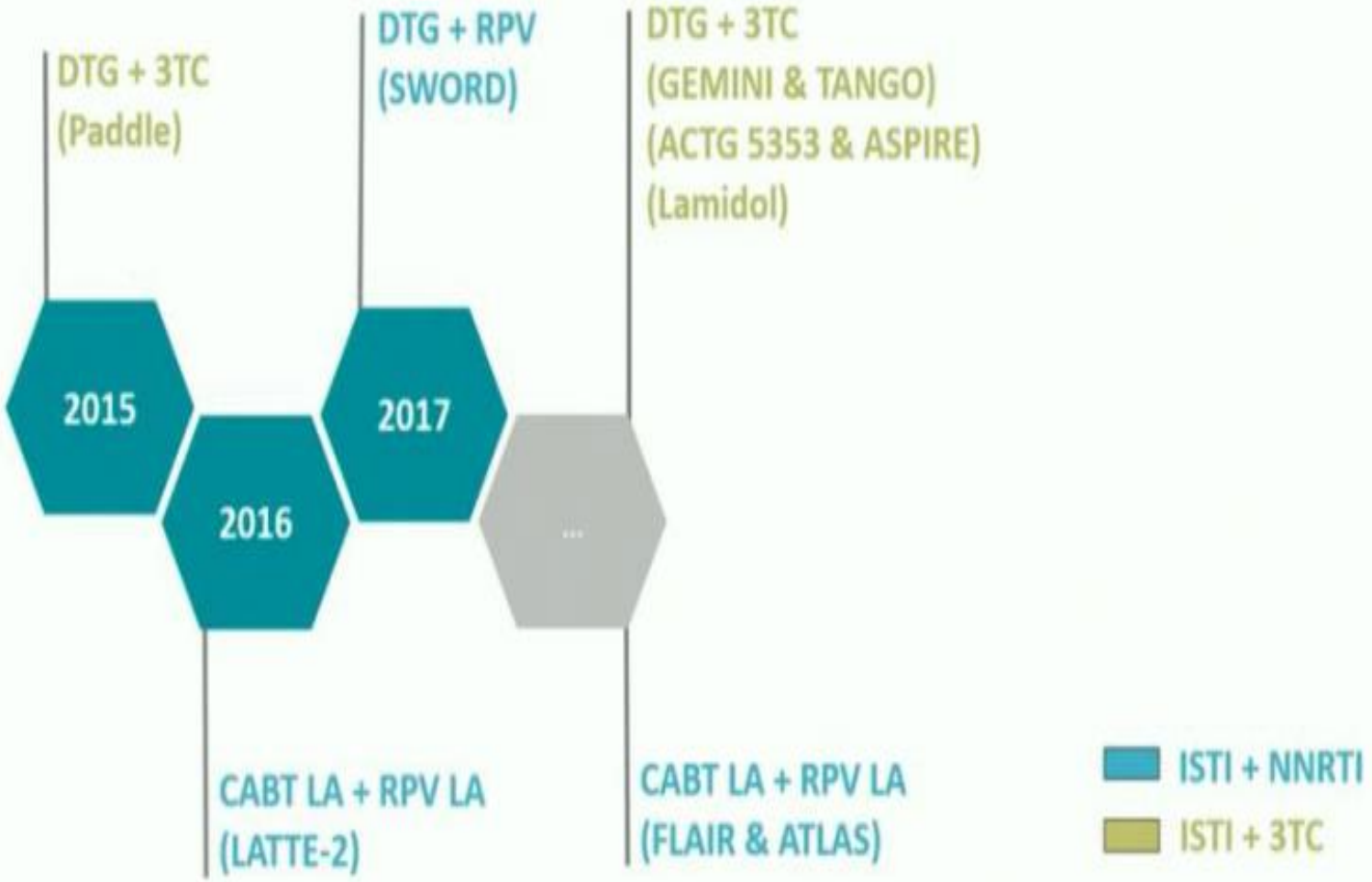
Dual strategies in treatment maintenance

2-drug regimens:

1. «toxicity-sparing»
2. enough potency by setting
3. good penetration into sanctuaries
4. high genetic barrier



Reduced drug regimens in suppressed and naive patients.
Simplicity 2.0



Courtesy Jose Arribas

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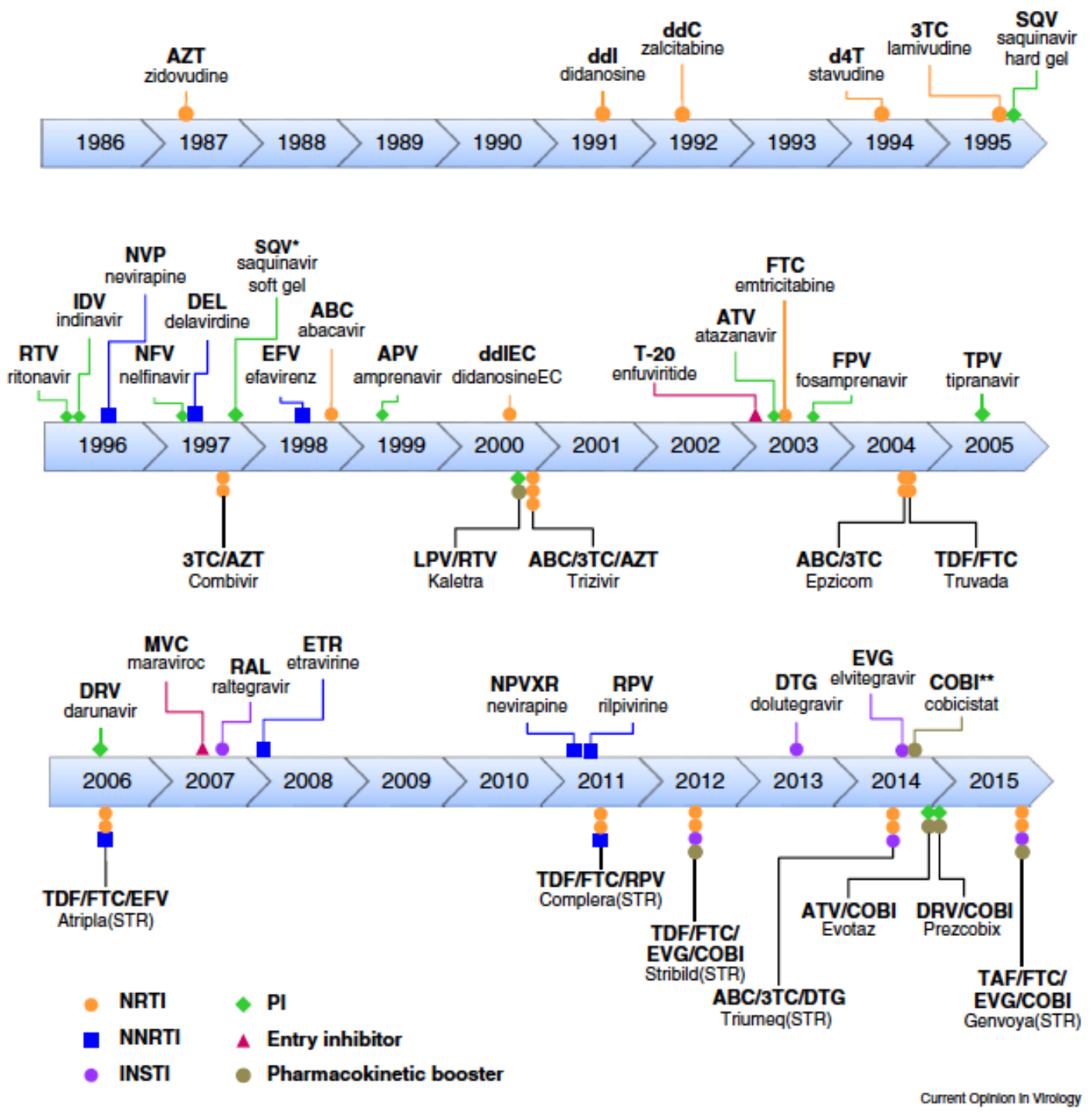
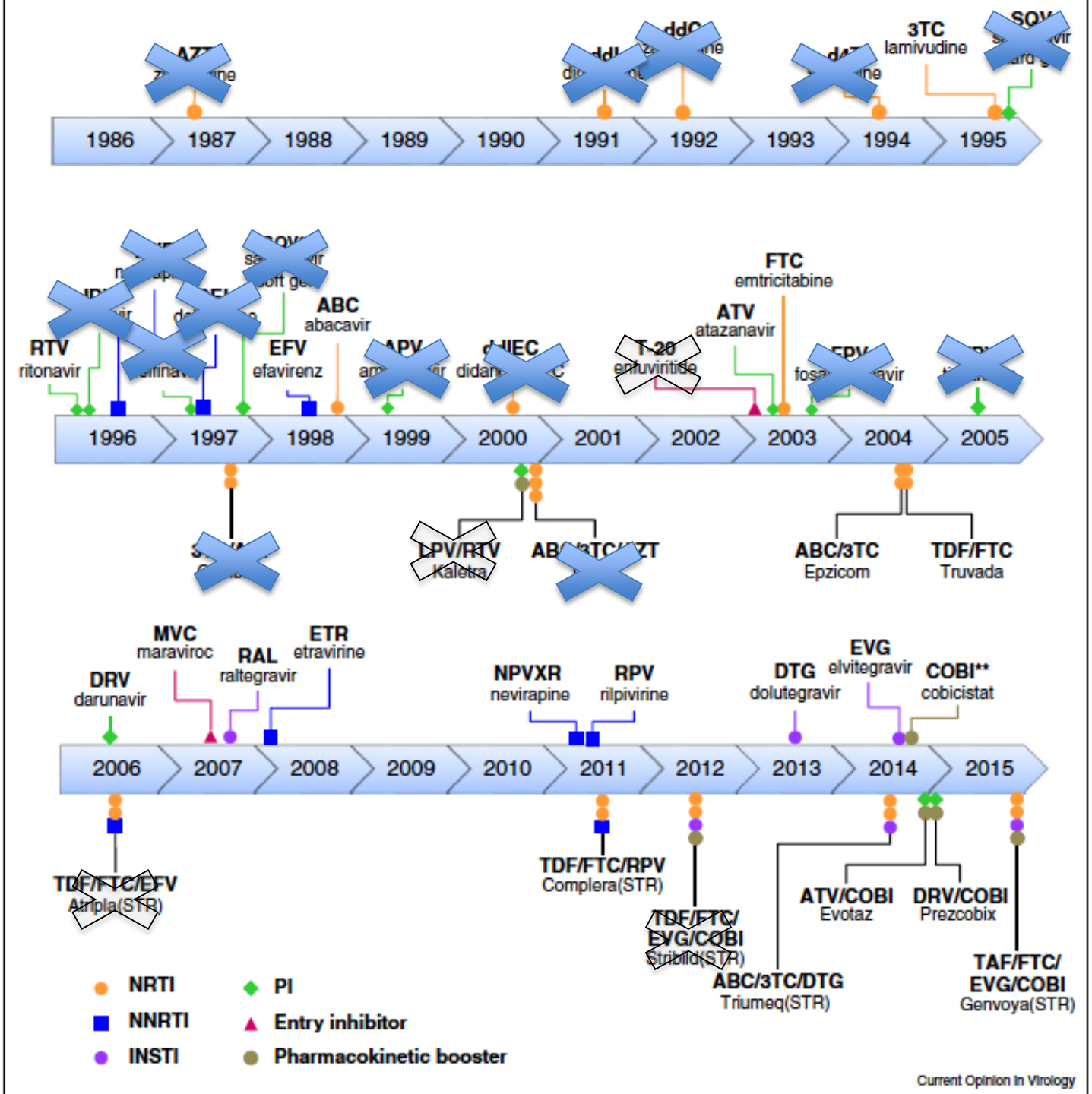
- Farmaci e strategie
- **Nuovi farmaci sono in varie fasi di sviluppo**

Perchè abbiamo bisogno di nuovi farmaci?

- **Una persona di 25 anni che si infetta oggi con HIV potrebbe affrontare 60 anni di cART, un neonato con infezione forse 80 anni**
- **La terapia dovrebbe essere sicura, tollerata e con differenti scelte:**
  - **Rene, CV, fegato e osso**
  - **Sicura in gravidanza, per neonati e bambini**
  - **Aderenza, stile di vita, therapy fatigue, tollerabilità**
  - **Invecchiamento e farmaco interazioni (es CYP 3A4 inhibition)**


AZT
zidovudine
ddI
didanosine
ddC
zalcitabine
d4T
stavudine
3TC
lamivudine
SQV
saquinavir
hard gel
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
NVP
nevirapine
SQV*
saquinavir
soft gel
IDV
indinavir
DEL
delavirdine
ABC
abacavir
FTC
emtricitabine
ATV
atazanavir
RTV
ritonavir
NFV
nelfinavir
EFV
efavirenz
APV
amprenavir
ddIEC
didanosineEC
T-20
enfuviritide
FPV
fosamprenavir
TPV
tipranavir
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
3TC/AZT
Combivir
LPV/RTV
Kaletra
ABC/3TC/AZT
Trizivir
ABC/3TC
Epzicom
TDF/FTC
Truvada
MVC
maraviroc
RAL
raltegravir
ETR
etravirine
DRV
darunavir
NPVXR
nevirapine
RPV
rilpivirine
DTG
dolutegravir
EVG
elvitegravir
COBI**
cobicistat
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
TDF/FTC/EFV
Atripla(STR)
TDF/FTC/RPV
Complera(STR)
TDF/FTC/
EVG/COBI
Stribild(STR)
ABC/3TC/DTG
Triumeq(STR)
ATV/COBI
Evotaz
DRV/COBI
Prezcobix
TAF/FTC/
EVG/COBI
Genvoya(STR)
NRTI
NNRTI
INSTI
PI
Entry inhibitor
Pharmacokinetic booster
Current Opinion in Virology

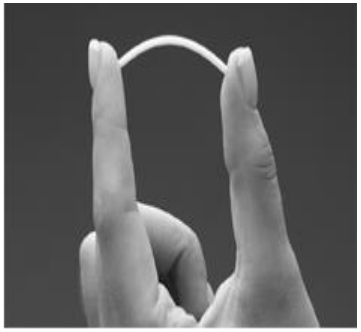

3TC
lamivudine
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
RTV
ritonavir
EFV
efavirenz
ABC
abacavir
FTC
emtricitabine
ATV
atazanavir
T-20
enfuviritide
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
LPV/RTV
Kaletra
ABC/3TC
Epzicom
TDF/FTC
Truvada
MVC
maraviroc
RAL
raltegravir
ETR
etravirine
DRV
darunavir
NPVXR
nevirapine
RPV
rilpivirine
DTG
dolutegravir
EVG
elvitegravir
COBI**
cobicistat
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
TDF/FTC/EFV
Atripla(STR)
TDF/FTC/RPV
Complera(STR)
TDF/FTC/
EVG/COBI
Stribild(STR)
ABC/3TC/DTG
Triumeq(STR)
ATV/COBI
Evotaz
DRV/COBI
Prezcobix
TAF/FTC/
EVG/COBI
Genvoya(STR)
NRTI
NNRTI
INSTI
PI
Entry inhibitor
Pharmacokinetic booster
Current Opinion in Virology

New Agents

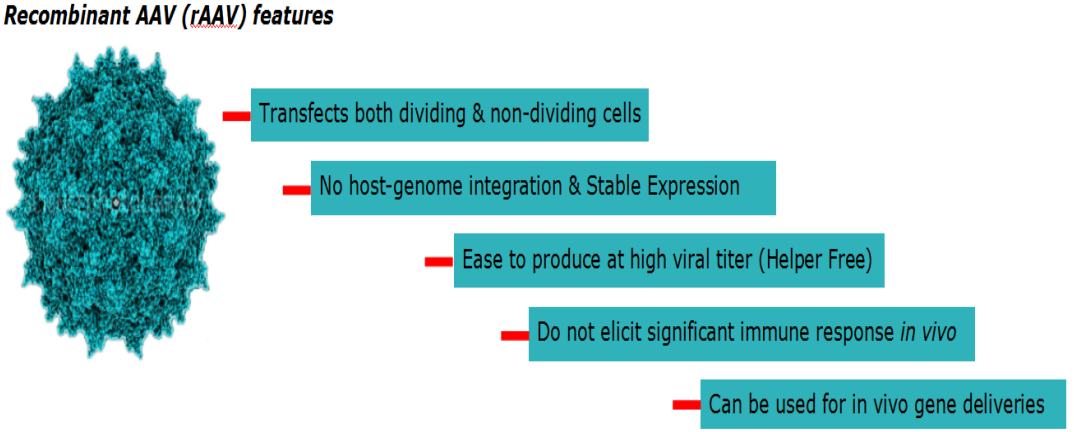
- Integrase Inhibitors
  - Bictegravir
  - Raltegravir OD
- PI
  - GS-PI1
  - F/TAF/D/cobi
- AC
  - GS-CA1
- N(t)RTI
  - EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine)(Phase I-II)
  - GS-9131[2]
  - MK-8591
- NNRTI
  - Doravirine
  - TMC278 Long acting
- Maturation Inhibitors
  - BMS 955176
- Attachment inhibitors
  - BMS 663068 -> 626529
- NANO-EFV, NANO-LPV[5]
- UB-421
- Monoclonal antibodies
  - Broadly virus neutralizing
  - Targeting entry receptors
    - Ibalizumab
    - PRO140

Antiretroviral Therapy: The Next Generation?

- Implantable (and removable) combination antiretrovirals



- Vectored delivery of combinations of antibody-based therapy or protein based therapy



How to best manage HIV patient ?

1 Treatment Failure

2 Treatment success

HIV therapy = a long life therapy

Ringraziamenti

- CISAI
- Fondazione ICONA