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Aspects of HIV-care and treatment in the era of combination antiretroviral therapy.

Doctoral dissertation

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2. Professor Lars Østergaard, Aarhus University

Defence leader:

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Contents

Publications included in this dissertation

I. Lung cancer in HIV patients and their parents: a Danish cohort study.
Engsig FN, Kronborg G, Larsen CS, Pedersen G, Pedersen C, Gerstoft J, Obel N.
BMC Cancer. 2011 Jun 25;11:272.

II. Head and neck cancer in HIV patients and their parents: a Danish cohort study.
Engsig FN, Gerstoft J, Kronborg G, Larsen CS, Pedersen G, Pedersen C, Obel N.
Clinical Epidemiology. 2011;3:217-27.

III. Long-term mortality in HIV-positive individuals virally suppressed for >3 years with incomplete CD4 recovery.
Engsig FN, Zangerle R, Katsarou O, Dabis F, Reiss P, Gill J, Porter K, Sabin C, Riordan A, Fätkenheuer G, Gutiérrez F, Raffi F, Kirk O, Mary-Krause M, Stephan C, de Olalla PG, Guest J, Samji H, Castagna A, d'Arminio Monforte A, Skaletz-Rorowski A, Ramos J, Lapadula G, Mussini C, Force L, Meyer L, Lampe F, Boufassa F, Bucher HC, De Wit S, Burkholder GA, Teira R, Justice AC, Sterling TR, M Crane H, Gerstoft J, Grarup J, May M, Chêne G, Ingle SM, Sterne J, Obel N; Antiretroviral Therapy Cohort Collaboration (ART-CC) and the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord.
Clinical Infectious Diseases. 2014 May;58(9):1312-21

IV. Clinical, virological and immunological responses in Danish HIV patients receiving Raltegravir as part of a salvage regimen.
Engsig FN, Gerstoft J, Kronborg G, Larsen CS, Pedersen G, Audelin AM, Jørgensen LB, Obel N.
Clinical Epidemiology. 2010 Aug 9;2:145-51.

V. Effectiveness of antiretroviral therapy in individuals who for economic reasons were switched from a once-daily single-tablet regimen to a triple-tablet regimen.
Engsig FN, Gerstoft J, Helleberg M, Nielsen LN, Kronborg G, Mathiesen LR, Obel N.

Journal of Acquired Immune Deficiency Syndromes. 2014 Aug 1;66(4):407-13.

VI. Risk of high-level viraemia in HIV-infected patients on successful antiretroviral treatment for more than 6 months.
Engsig FN, Omland LH, Larsen MV, Rasmussen LD, Qvist T, Gerstoft J, Obel N.
HIV Med. 2010 Aug;11(7):457-61.

Throughout the text, the publications are referred to by their roman number in brackets.

Preface

All studies included in this dissertation were executed at Copenhagen University Hospital, Rigshospitalet, and published in the period 2010-2014.

None of the studies included in the dissertation has been assessed previously as part of a dissertation or PhD.

I´m especially grateful to Niels Obel and Jan Gerstoft for their support and for introducing me to practical epidemiology, statistics and a scientific mindset. I would also like to thank Lars Omland and Ann-Britt Eg Hansen and all fellow researchers in the Danish HIV Cohort Study for support, good times and valuable discussions on and off topics. Further I would like to pay my respect and gratitude to the previous generations of researchers, upon whose shoulders we stand.

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To my dear wife and son, Magaly and Christian, thank you for your love, patience and support.

Frederik Neess Engsig, Bispebjerg, 2019

Abbreviations:

ADC	AIDS defining cancers
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral treatment
ARV	Antiretroviral
cART	Combination antiretroviral treatment
CI	Confidence interval
CNS	Central nerve system
CVD	Cardio vascular disease
FDA	Federal Drug Administration
FDC	Fixed dose combinations
DHCS	The Danish HIV Cohort Study
HIV	Human immunodeficiency **Virus**
HL	Hodgkin lymphoma
HNC	Head and neck cancer
HPV	Human papilloma virus
INSTI	Integrase strand transfer inhibitor
IR	Incidence rate
IRR	Incidence rate ratio
KS	Kaposi sarcoma
MSM	Men who have sex with men
MRR	Mortality rate ratio
NADC	Non-AIDS defining cancers
NHL	Non- Hodgkin lymphoma
NNRTI	Non-nucleotide reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OBT	Optimized backbone treatment
OI	Opportunistic infections
PCP	Pneumocystis pneumonia
PI	Protease inhibitors
PrEP	pre-exposure prophylactic treatment
PYRS	Person-years at risk
RAL	Raltegravir
RAM	Resistance associated mutation
RCT	Randomized clinical trial
RT	Reverse transcriptase
STR	Single-tablet regimen
STR-TEE	Single-tablet regimen consisting of tenofovir disoproxil fumarate, emtricitabin and efavirenz
TTR-TEL	Triple-tablet regimen consisting of tenofovir disoproxil fumarate, efavirenz and lamivudine
VL	Viral load

Introduction

What first started as an epidemic in the eighties, escalated during the nineties to a still ongoing global pandemic despite huge national and international efforts (1). The initial scope of HIV research was focused on treating acquired immune deficiency syndrome (AIDS) defining conditions, developing effective tolerable antiretroviral drugs, hindering further spread of the infection, maintaining viral suppression and improving short term survival. In general, these goals were largely accomplished in the mid-nineties with combination antiretroviral therapy (cART). Still, in 2016, after decades with multiple strategies and treatment advances, an estimated 36 million individuals were infected, 1.8 million were newly infected with HIV and an estimated one million people died (2). Evidently, the burden of the pandemic is still very eminent and has led to a global treatment target launched by the UNAIDS in 2017. Rooted in the basic fact that "It will be impossible to end the epidemic without bringing HIV treatment to all who need it", using cART as prevention and supported by statistical modelling, the ambition is to end the epidemic in 2030 by globally diagnosing 90% of all infected, initiate cART in 90% of all diagnosed with HIV and achieve viral suppression in 90% of those in treatment in order (3). A disproportional large part of this challenge lies upon sub-Saharan Africa where both diagnosing HIV and cART coverage remains a huge problem but also Eastern Europe and Central Asia are facing large challenges (4,5). Still, if these challenges are overcome, pre-exposure prophylaxis is widely introduced and the elimination threshold of one new HIV infection per 1000 individuals per years is achieved, studies indicate that the 90-90-90 goals could be feasible (6–9).

In countries where cART coverage is moderate to high, the number of newly infected has declined or plateaued along with increased survival (3,10,11). As a consequence of this, the population of HIV-infected individuals is increasing and in developed countries with high cART coverage, the expected life span of HIV-infected individuals is, in general, comparable to that of uninfected individuals and the main causes of death similar those of uninfected individuals (12–15). Thus, the HIV infected population is aging and a considerable proportion of HIV-infected individuals is now above 50 years old (16–18). Following this, the focus of HIV research has shifted from treating severely immunocompromised individuals, AIDS defining diseases, HIV-infected mothers and children towards age-related non-communicable diseases comorbidities like non-AIDS defining

cancers (NADC), diabetes and cardio vascular disease (CVD), which occur more frequently in HIV-infected individuals than in un-infected individuals (19–25). Still, a large percentage of HIV-infected individuals in developed countries continue to present with AIDS defining conditions and/or low CD4 cell count at the time of HIV diagnose complicating treatment, care and the prognosis of these individuals, why research in this area continues to be relevant (26–30).
The objective of this dissertation is to discuss and interpret the results from the publications included in this dissertation in relation to existing research. The topics discussed will be non-AIDS defining cancer (NADC), mortality with focus on persistently low CD4 cell count and antiretroviral treatment, namely integrase strand transfer inhibitors (INSTIs), pill burden and cART as prevention. All studies and discussions mentioned in this dissertation concern infection with HIV-1.

The Danish HIV Cohort Study

With the exemption of [III], all my studies included in this dissertation are based on data from the Danish HIV Cohort Study (DHCS) in the period 1995-2014. DHCS was at that time an open national cohort study. The cohort is partly prevalent including all HIV-infected individuals alive per January 1. 1995 and partly incident including all newly diagnosed and immigrated HIV-infected individuals under care in one of the specialized departments in Denmark since January 1, 1995 (31,32). The cohort is unique in being national, thereby reducing selections bias significantly and allowing statistical analyses on population level. The unique personal identification number of people living in Denmark allows researchers to correlated personal data from the many Danish national registries (33). In this dissertation, data from the following Danish national registries were used: Danish Civil Registration System [I, II], Danish Cancer Registry [I, II] and The Danish Register of Causes of Death [I, II]. [V] also included data from the Danish HIV Sequence Database and Hospital Pharmacy of the Capital Region (16). Detailed descriptions of DHCS and the Danish national registries used can be found here (34–39). Observational data from two international cohort collaborations ART-CC and COHERE, which includes HIV-infected individuals from mainly Europe and North America is used in [III](40,41).

All my studies included in the dissertation are observational cohort studies. Given the nature of observational studies, knowledge can be extracted using statistical analysis to evaluate the strength of associations between exposure and outcomes. Contrary to randomized clinical trials (RCT), confounding cannot be eliminated in observational studies. In this dissertation, this has been sought overcome by adjusting the statistical analysis on the most important characteristics when possible, as well as by stratified analyses [I, II, III, IV, V, VI,]. In [I] and [II] cohorts of uninfected individuals are included, these have been matched on age and gender. In [I] and [II] the primary outcome is time to a diagnosis of lung cancer and head and neck cancer (HNC), respectively. The cumulative incidence function was used to illustrate this, recognizing death or a diagnosis of another cancer as a competing risk (42). The outcome in [III] is time to all-cause mortality, which was estimated using the Cox proportional hazards model and Kaplan-Meiers cumulative hazard function (43,44). In [III], cause specific mortality analysis was performed using a competing risk model as describe by Fine and Gray (45). In [I] and [II], the Cox proportional model was used to

estimate relative risk and risk factors for lung cancer HNC rather than all-cause mortality, which does not take the competing risk of death or other outcomes into consideration. This may led to overestimation of the relative risk (46). Still, the overall impact of this bias should not be large, as the overall survival in the study period has improved dramatically due to cART and the median age of the study populations were below 40 years.

Aside from the inherent problems, when interpreting result from cohort studies, a weakness of DHCS is its relatively small size, which limits statistical precision when looking at rare events. This especially affects the results in [I] and [II]. Still, while the number of outcomes in [I] and [II] were scarce among the HIV-infected individuals, the incidences were relative to a population-based cohort matched on age and gender, thereby adding strength to the estimate. Also, the prevalent part of the cohort may introduce a healthy survivor bias.

HIV

A cluster of *Pneumocystis carinii* (now recognized as a distinct species *Pneumocystis jirovecii*) pneumonias (PCP), an otherwise rare disease almost only seen in individuals with severely weakened immune system, in five otherwise healthy homosexuals initially led to the suspicion of an epidemic in 1981 (47). The causative agent was identified as a retrovirus in 1983 and named HIV-1 in 1986 (48). HIV-1 infects CD4-expressing T-lymphocytes and macrophages leading to chronical infection and CD4 cell depletion which in turn lead to immunodeficiency and AIDS. Depending on the stage of immune deficiency, the most frequent AIDS defining manifestations before cART were esophageal candidiasis, PCP, cytomegalovirus retinitis, HIV wasting syndrome, Kaposi´s sarcoma, AIDS dementia, Mycobacterium avium infection and Non-Hodgkin Lymphoma (7–9). The introduction of opportunistic infection prophylactics and most importantly cART around 1995 resulted in a substantial decline in the incidence of these disease among HIV infected individuals (52–57). Besides this, treatment and care for HIV infected individuals quickly advanced with new and improved diagnostic tools, drugs and algorithms for treating these previously rare diseases (58–65). Early on it became apparent that maintaining a high CD4 cell count though continuous cART treatment reduced the incidence of AIDS defining diseases significantly (49,66,67). Over time the threshold for initiating cART has increased following studies showing that even HIV-infected with high CD4 cell counts (>500 cells/mm^3) have an increased risk of both serious AIDS-related and serious non–AIDS-related events (67–71). In the late cART era where options of more potent, tolerable and less toxic ARVs combined were available, cohorts and cohort collaborations with increasingly longer follow-up time have been able to demonstrated increasing survival, in optimal settings even comparable to that of the background population (12,13,72–74).

HIV and non-AIDS defining cancers

AIDS and non-AIDS defining cancers

Before the introduction of cART, the main risk of cancer in HIV-infected individuals was constituted by Kaposi sarcoma (KS) and non-Hodgkin Lymphoma (NHL), which are AIDS defining and occurs considerably more often in HIV-infected individuals compared to uninfected (49–51,75). Eventually, also cervix cancer was recognized as an AIDS defining disease (76). All AIDS defining cancers (ADCs) are caused by or linked to latent oncogenic vira (HHP-8, EBV and HPV) and inversely related to CD4 cell count (77–82). Consequently, the introduction of cART reduced the incidence of ADCs markedly (24,83,84). Further, adherence to screening programs of HIV infected women has reduced the incidence of invasive cervical cancer to a level comparable to that of HIV-negative women (77,85–87).

The reduced incidence of ADCs after cART was followed by a surprisingly increased incidence of certain NADCs like anal cancer, liver cancer, Hodgkin's Lymphoma, lung cancer and head and neck cancer (HNC), and NADC are now one the most common causes of death in HIV-infected individuals (19,75,77,78,88–91). Although these cancers are also common to uninfected individuals, the risk appears to be 2-19 times higher in HIV-infected individuals depending on the cancer type (19,21,92). Although several of these cancers are caused by or linked to oncogenic vira (EBV, HCV, HBV, HPV), lung cancer and in part HNC are not directly (93–95). While traditional risk factors like smoking, drug use and alcohol affect the incidence of lung cancer and HNC, a similar cancer incidence pattern is also observed in individuals with immunosuppression after organ transplantation. Therefore an association with NADCs and immunosuppression, perhaps through accelerated aging due to chronic infection and inflammation, has been hypothesized (19,96,97).

Lung cancer and head and neck cancer and smoking

The two- to three-fold increased risk of both lung cancer and HNC has been confirmed in Danish HIV-infected individuals compared to age and gender matched population controls (Figure 1 and 2) (Incidence rate ratio (IRR) 2.38 (95% CI; 1.61 - 3.53) and IRR 3.05 (95% CI 1.81–5.15), respectively) [I, II] (19,25,98–104).

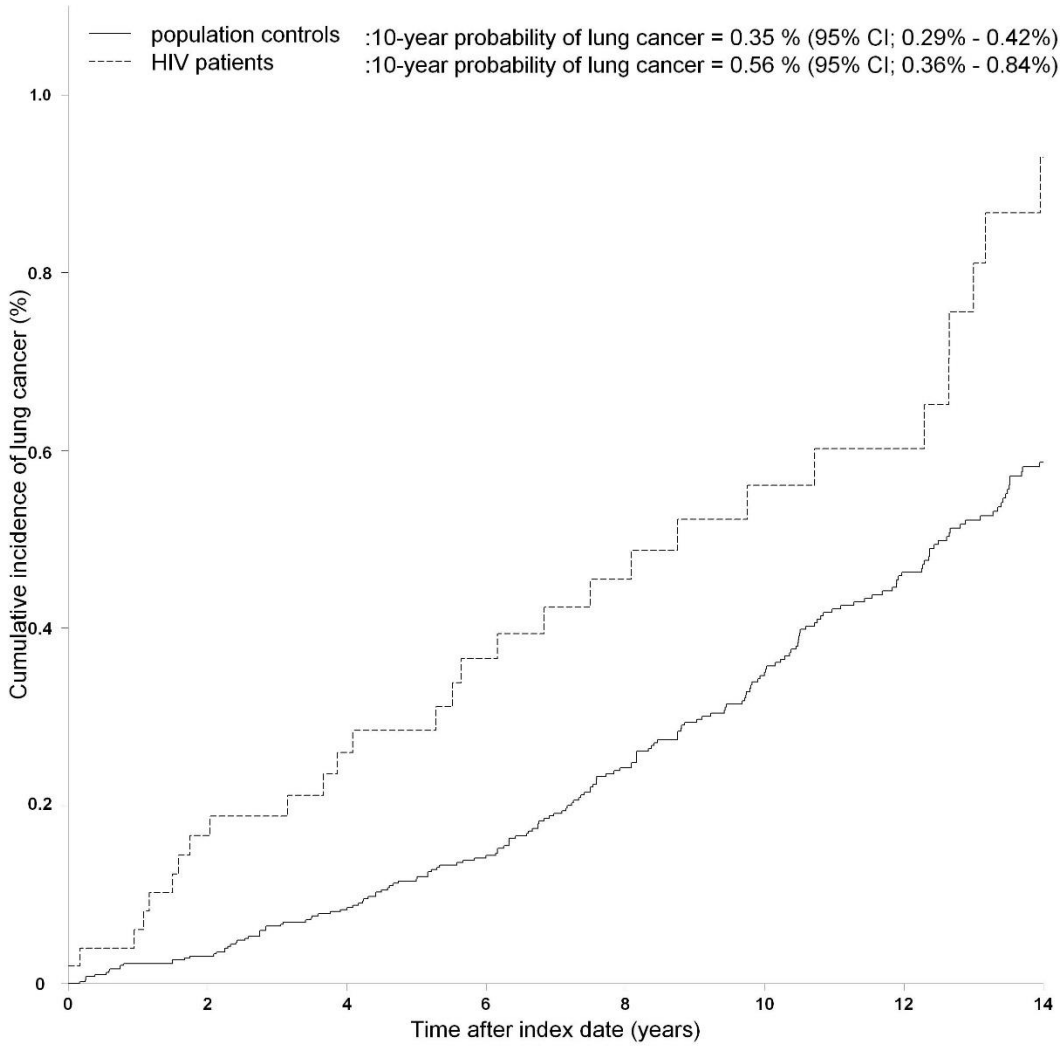

Figure 1. Cumulative incidence function for lung cancer among HIV-infected individuals and population controls matched on age and gender.

All though the main risk factor for both types of cancer is smoking, as well as alcohol consumption for HNC, data on these confounders were initially limited, especially in the control populations and most studies were therefore seriously flawed by residual confounding since differences in tobacco consumption and other behavior that could contribute to the increased risk [I, II] (19,25,98–102,102,103,105). Still, the studies showed that lung cancer and HNC rarely occurred in HIV infected non-smokers. In 2014, a study published by Helleberg *et al* on the same HIV-infected population as in [I, II] including data on smoking, demonstrated that no increased risk of a composite of all smoking related cancers (lung, head and neck, bladder and esophagus cancer) were seen among HIV-infected individuals who never smoked. The study also demonstrated an increased risk of a

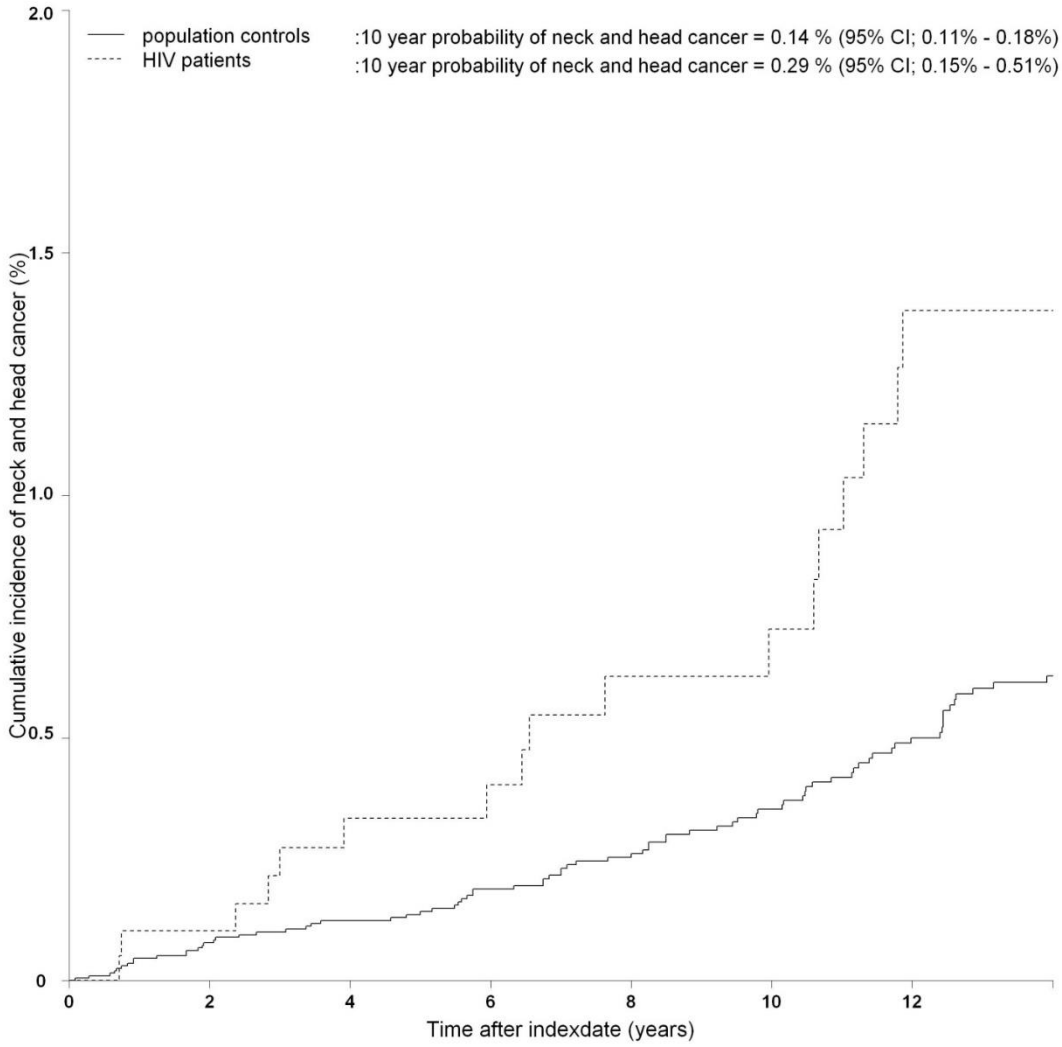

Figure 2. Cumulative incidence function for head and neck cancer among HIV-infected individuals and population controls matched on age and gender.

composite of all smoking related cancers in ever smoking HIV-infected individuals compared to ever-smoking population controls (adjusted IRR 2.95 (95% CI; 1.67–5.19))(21). As the study did not have data on the duration of smoking or daily number of cigarettes smoked, the authors note that the increased risk could be explained by a higher number of current smokers among the HIV-infected individuals in Denmark but an synergistic effect of traditional risk factors and HIV infection on the risk of lung cancer cannot be ruled out (21). Also, Lea Shepherp *et al* from the D:A:D study have demonstrated that the incidence of lung cancer remain high more than one year after smoking cessation, somewhat opposite to the effect generally observed in uninfected individuals who cease smoking (106–110). In addition, other studies have demonstrated an

increased risk of lung cancer in HIV-infected individuals independent of tobacco use related to immunodeficiency, even though the extensive use of tobacco in the HIV-infected population compared to the non-HIV infected individuals is well established both in Denmark and elsewhere (98,111–114).

The impact of immunodeficiency on lung cancer

Several studies have demonstrated an association between virus-related NADCs and immunodeficiency, namely Hodgkin lymphoma, anal cancer, cervix cancer, hepatocellular carcinoma in HBV co-infected individuals but also for lung cancer(25,114,115,130–134). For lung cancer, the association has been shown for both nadir and current CD4 cell count which increases the relative risk [I] (21,98,115). Although no studies have identified prolonged low CD4 cell count in time-updated analyses as a risk factor for lung cancer, some studies found that low cumulative CD4/CD8 ratio was a strong predictor (98,111,120). In studies adjusted for smoking, the effect of low CD4 cell count on the risk of lung cancer have persisted in most but not in all (98–100,105,111,121). Helleberg *et al* demonstrated an excess risk of smoking-related cancers among ever-smoking HIV infected individuals compared to ever-smoking population controls but close to zero smoking-related cancers among never-smoking HIV-infected individuals (111). This may be due to residual confounding (differences in tobacco consumption) but lack of oncogenic control due to immunodeficiency cannot be ruled out. This is supported by the findings of other studies showing that, 1) the risk of lung cancer among individuals on cART with a CD4 cell count >500 cells/mm^3 is comparable to that of the background population and, 2) the incidence of lung cancer has decreased following the increasing use and earlier initiation of cART, while the use of tobacco appears not to have decreased (75,112,122,123). On the other hand, declining CD4 cell count caused by undiagnosed lung cancer could explain the association between low CD4 cell count with lung cancer in HIV infected individuals (124). Additionally, bacterial pneumonia is a known risk factor for lung cancer and since HIV infected individuals have an increased risk of lung cancer inversely related to CD4 cell count, this has been proposed as another explanation for the possible relation between low CD4 cell count and the increased risk of lung cancer (120,125–127). Still, the risk of bacterial pneumonia is also higher in smokers in general and an interaction between low CD4 cell count and heavy smoking in HIV infected individuals cannot be ruled out (128). So, while

the association between low CD4 cell count and lung cancer is established to some degree, the causal mechanisms behind the association are less clear and a matter of discussion.
Also, mortality seems to be affected by HIV infection since infected individuals with lung cancer had a higher relative mortality (Mortality rate ratio (MRR) (95%CI); 2.33 (95%CI; 1.51 - 3.61)) compared to uninfected individuals with lung cancer. This has also been demonstrated by studies on larger HIV-infected populations (129–131). This suggests that immunosuppression plays a role in cancer progression and perhaps enhances the risk of complications to chemotherapy also in cancers that are not associated with viral infection.

Head and neck cancer, HPV and immunodeficiency

HPV infection is a well identified risk factor for HNC at certain sites (oropharyngeal cancer) and considered a separate disease entity with increasing incidence and a different prognosis (93,132,133). The increased incidence is possibly related to HPV infection due to changes in sexual behavior (134–136). HIV-infected individuals have a higher prevalence and persistence of HPV infection, partly related to low CD4 cell count, sexual behavior and smoking (137,138). Correspondingly several studies have demonstrated an increased risk of HPV related HNC in HIV-infected individuals, although the increased risk appears modest compared to the risk of non-HPV related HNC and not clearly associated with low CD4 cell count [II] (25,101,139,140). The overall impact of low CD4 cell count on the incidence of HNC are somewhat conflicting [II](21,139,141,142). Large cohorts studies have demonstrated an association between the incidence of HNC in HIV-infected individuals and low CD4 cell count as well as a decrease in incidence over time following increased use of cART (139,140,143). Still, these studies may have several confounders, among these most importantly lack of adjustment for smoking which seem to have a larger impact than low CD4 cell count or AIDS [II] (21,25).

The risk of lung cancer and head and neck cancer in parents

Parents to uninfected individuals also have an increased risk of lung cancer and HNC [I, II](Figure 3 and 4). This implies a family related association between HIV infection and increased risk of

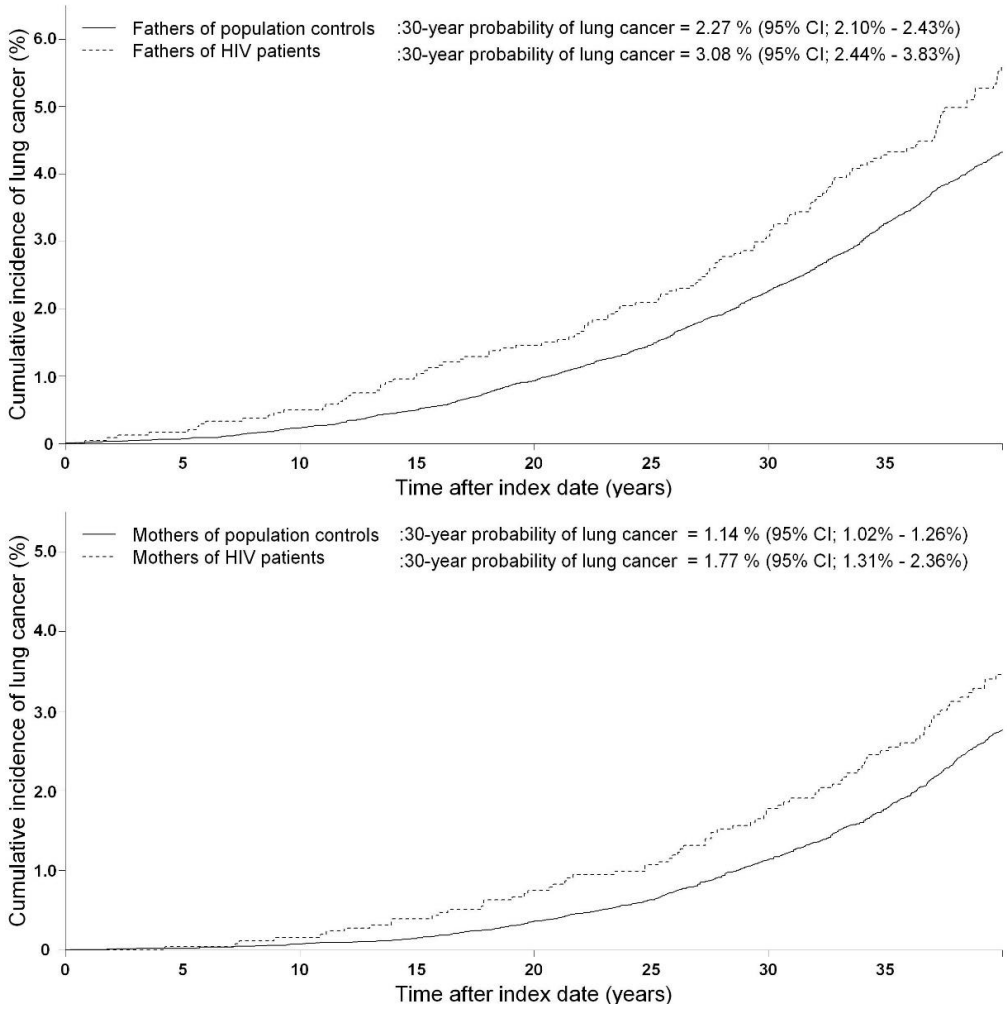

Figure 3. Cumulative incidence of lung cancer among parents of Danish HIV-infected individuals and parents of age and gender matched population controls.

smoking-associated cancer. An increased incidence of myocardial infarction is also observed in HIV-infected individuals and their parents (144). While none of these results include data on genetics, alcohol consumption and smoking, we do know that HIV-infected individuals have a higher prevalence of tobacco, alcohol and illicit drug use (21,111,112). Smoking is linked to risk-taking behavior, which is moderately to strongly related to heritability and offspring of smokers have a four times higher risk of initiating smoking (145,146). It therefore seems likely that smoking is the family related risk factor behind the increased risk of smoking related cancer in HIV-infected individuals and their parent, although other family or environmental factors are possible too.

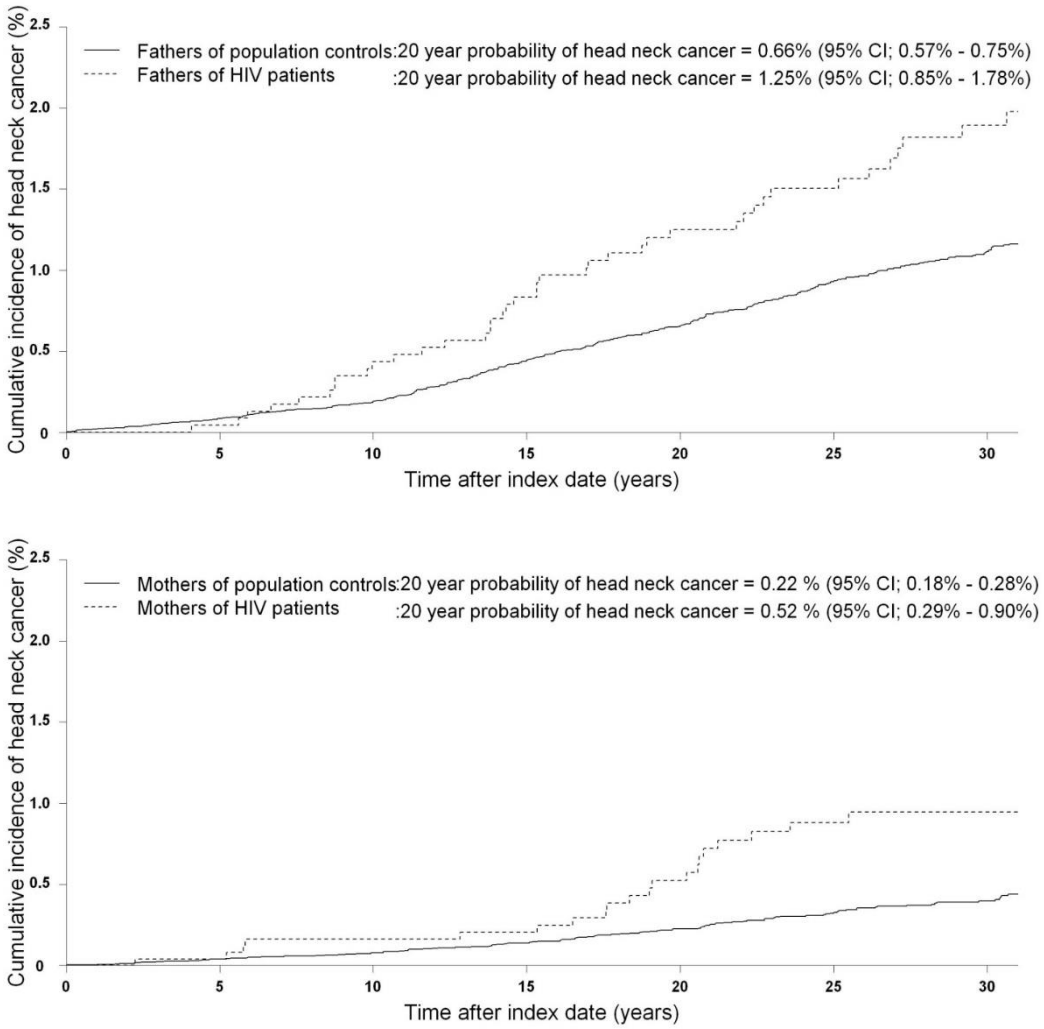

Figure 4. Cumulative incidence of head and neck cancer among parents of Danish HIV-infected individuals and parents of age and gender matched population controls.

Summary and perspective on HIV and non-AIDS defining cancers

While the association between immunodeficiency, cancer and oncogenic virus seems clear, the findings concerning namely non-virus-related NADCs indicate a more complex association with immunodeficiency (147). Several mechanism like decreased immune surveillance of de novo oncogenic transformation and malignant cells as well as chronic inflammation and immune activation has been proposed (148). The effect of low CD4 cell count on lung cancer is controversial and may be due to residual confounding or a complex interaction between smoking and immunodeficiency. Either way, as hardly any cases of smoking related NADCs occurs in HIV-infected individuals who has never smoked, the potential impact of smoking cessation is massive

and should be a top priority. Accelerated aging in HIV-infected individuals due to chronic immune activation and immune dysregulation has been proposed as a causality for the increased incidence of non-AIDS defining cancer in HIV-infected individuals (149). A recent study in Lancet HIV from the DHCS confirmed the increased risk of age related comorbidities in HIV-infected individuals but showed no sign of acceleration of the relative risk over time (23).

Immediate initiation of cART, which is now recommended globally in guidelines, will probably continue to reduce the incidence of OIs, ADCs and virus related NADCs, although the causality is not completely clear (123). Further reduction of ADCs and NADCs will be achieved by smoking cessation, treatment of HBV and HCV, HPV screening programs and HPV vaccination.

Incomplete CD4 recovery

Mortality and low CD4 cell count

Early in the epidemic, a low CD4 cell count was identified as a reliable prognostic marker for AIDS and death with a staggering mortality rates up to 72.6 (62.3–82.9) deaths per 100 PYRS in individuals with CD4 cell count < 50 cells/mm^3 (150). Accordingly, HIV-infected individuals with low CD4 cell counts also experienced the largest impact of cART but the general reduction in mortality among HIV-infected individuals was striking (12,13,73,74,150,151). Although survival in general has improved tremendously, a low CD4 cell count remains a strong predictor for increased mortality and morbidity. After cART initiation and virological control, the CD4 cell count in general increases 20 to 50 cells/mm^3 per month in the first six months and then five to ten cells/mm^3 per month between six months and 24 months depending on baseline CD4 cell count and continues to increase over years (152–155). While this holds true for most HIV-infected individuals, some HIV-infected individuals fail to increase CD4 cell count readily, termed incomplete CD4 recovery. Although persisting viral replication is a strong predictor for AIDS and death, also successfully treated HIV-infected individuals with undetectable viral load (VL) and incomplete CD4 recovery proved to have a worse prognosis. In 2000, Grabar *et al* brought attention to the subject by elegantly stratifying HIV-infected individuals into four categories according to immunologic (CD4 cell increase >= 50 cells/mm^3) and virologic response (a decreased from baseline VL of more than 1 log10 copies/mL or a plasma HIV RNA level less than 1000 copies/mL) six months after cART initiation (160). Not surprisingly, individuals who failed to both suppress VL and increase CD4 cell count sufficiently at six months had the worst prognosis, but unexpectedly they found that having incomplete CD4 recovery but sufficient VL suppression had a larger impact on survival than complete CD4 recovery but insufficient VL suppression. Individuals with incomplete CD4 recovery but sufficient VL suppression had an relative risk of clinical progression of 1.98 (95%:CI, 1.26 to 3.10) compared to those with both sufficient CD4 recovery and VL suppression (follow-up at 30 months) (160). Following this, several studies confirmed the findings of Grabar *et al* using both different increases in CD4 cell count over time and absolute CD4 cell counts at predefined time points as definition of incomplete CD4 recovery (57,60–62). Still, most of these studies did not use

baseline CD4 cell count as inclusion criteria, had short periods of viral suppression and mainly estimated short-term effects of changes in CD4 cell count on the clinical outcomes.

Long-term mortality and incomplete CD4 recovery

While short-term virological and immunological response to cART treatment was a well-established predictor for clinical progression, the prognosis for HIV-infected individuals with long-term incomplete CD4 recovery was less elucidated and clinicians disagreed whether this had an impact on survival or not, provided that the HIV-infected individuals were virally suppressed. In 2010, a study from DHCS demonstrated that nearly one out of five did not achieve a CD4 cell count above 200 cells/mm^3 after three years of sustained viral suppression and that this population had an increased MRR of 3.4 (95%CI; 1.4 - 8.0) after adjustment for age compared to those with complete CD4 recovery (166). Stratified analyses showed an excess mortality in injection drug users and individuals with prolonged immunosuppression before cART initiation. Still, the results lacked statistical power. Subsequently, two studies on incomplete CD4 recovery were published. First, a Canadian study with almost identical design (only two years of viral suppression) confirmed the finding (adjusted MRR 2.69 (95% CI: 1.26 to 5.78))(167). While the study population in this study was comparable to that in the study by DHCS in term of age, gender and IDU, they were also cART naïve HIV-infected individuals with a median CD4 cell count of 171 (IQR; 80–252) cells/mm^3 included after the year 2000 whereas almost 50% of the study population in the study by Engsig *et al* were diagnosed before 1995, had a nadir CD4 cell count of 40 cells/mm^{3}and 80% had been treated with zidovudine (166,167). So, the trend of higher mortality in HIV-infected individuals with incomplete CD4 recovery appeared to be high in both cART naïve and experienced. In 2012, a study from the Dutch ATHENA cohort using a design with two years of viral suppression (VL<500 copies/ml) showed that HIV-infected individuals with incomplete CD4 recovery had a considerably increased risk of cardiovascular events, malignancies, liver cirrhosis, AIDS or death (composite endpoint) particular due to cardiovascular events but this was also flawed by lack of statistical power(168). Also, a trend towards an increased risk of non-AIDS-defining malignancies and non-AIDS defining diseases was found in this study although not significant.

Besides lacking statistical power and/or did not including causes of death, both the Canadian and the Dutch study defined baseline as the end of the suppressed period (two years) instead of the start of the suppressed period thus allowing for decline in CD4 cell count from above 200 to below

200 cells/mm^3 in the suppressed period. This could represent a bias since decline in CD4 cell count is associated with increased risk of CVD, cancer and death (169). In order to confirm the above-mentioned results with a higher degree of statistical precision and come closer to an understanding of the mechanism behind the increased mortality in HIV-infected individuals with incomplete CD4 recovery, a study with a similar stringent design as that from DHCS was performed with data from the first collaboration between the two large cohort collaborations COHERE and ART-CC [III](166). This large cohort study, which included study participant from more than 100.000 HIV-infected individuals, confirmed an adjusted MRR of 2.60 (95% CI, 1.86–3.61) in individuals with incomplete CD4 recovery [III]. The MRRs for CD4 cell count > 200 cells/mm^3 and <= 500 cells/mm^3 did not differ significantly compared to those who achieved a CD4 cell count > 500 cells/mm^3 [III](Figure 5).

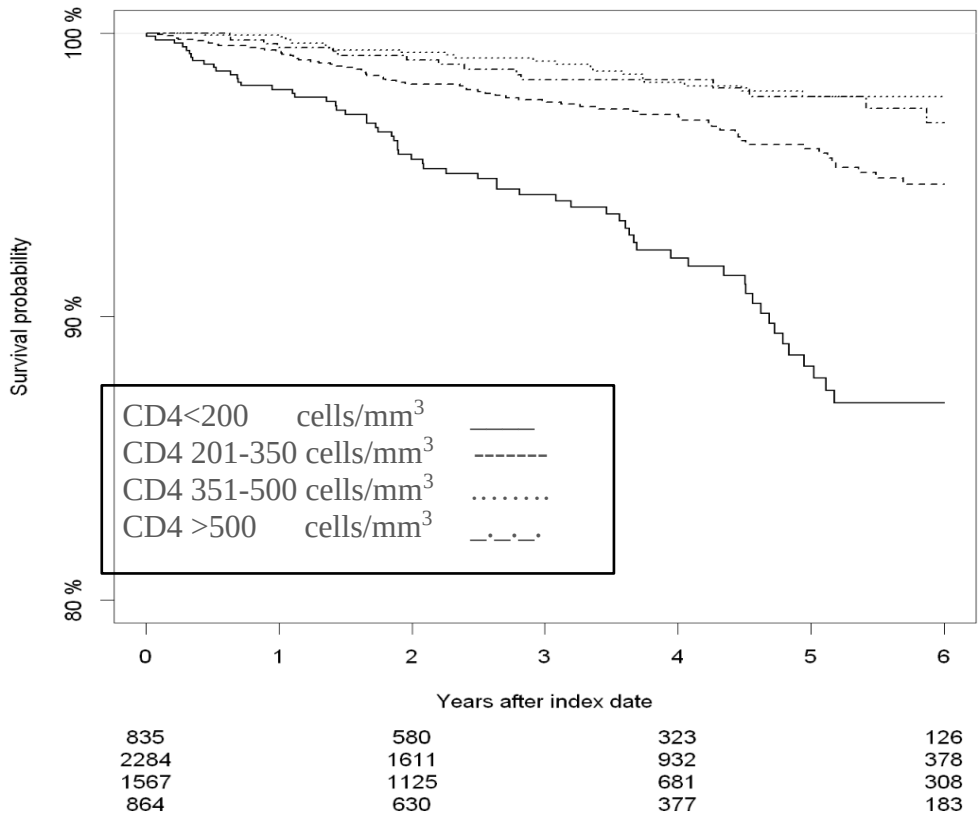

Figure 5. Cumulative probability of survival of HIV-infected individuals stratified by CD4 count at the end of the virally suppressed period: ≤200 cells/mm^3 (full line); 201–350 cells/mm^3 (broken line); 351–500 cells/mm^3 (dotted line); and >500 cells/mm^3 (broken and dotted line).

The increased mortality was consistent in all strata and sub-analyses, indicating that no single characteristic included in the model, aside from the CD4 cell count, can explain the increased mortality.

Besides an increased risk of AIDS, there were in [III] an elevated risk of both non-AIDS and AIDS related causes of death, namely from hepatitis and non-AIDS cancer (Table 1).

Causes of death	No. (%) of deaths according to CD4 count at end of suppressed period		HR (95% confidence interval)	
	≤200 cells/µL	>200 cells/µL	Unadjusted	Adjusted*
All	41 (100)	80 (100)	3.05 (2.10- 4.44)	2.52 (1.71-3.70)
AIDS defining causes	4 (9.8)	7 (8.8)	3.39 (0.99-11.57)	2.75 (0.78-9.69)
Non-AIDS defining causes	26 (63.4)	49 (61.3)	3.14 (1.95-5.06)	2.61 (1.61-4.23)
Hepatitis	5	5	5.95 (1.72-20.56)	6.76 (1.93-23.74)
Non-AIDS cancer	14	23	3.50 (1.73-6.95)	2.89 (1.44-5.28)
Other causes of death**	6	21	1.69 (0.68-4.18)	1.24 (0.50-3.12)
Unnatural causes of death	3 (7.3)	8 (10.0)	2.27 (0.60-8.57)	2.07 (0.54-7.97)
Unknown causes of death	8 (19.5)	16 (19.5)	3.00 (1.28-7.01)	2.34 (0.98-5.59)

Adjusted for gender and age (<=50 years vs. >50 years)

**Other causes of death for patients with CD4 count ≤200 cells/µL were; 2 related to infection, 2 related to cardiovascular disease, 2 related to digestive system disease. Other causes of death for patients with CD4 count >200 cells/µL were related to infection (5) lung diseases (2), cardiovascular diseases (9), digestive system diseases (2), central nervous system diseases (2) and renal diseases (1).

Table 1. Cause-specific mortality rate ratios comparing HIV-infected individuals (ART-CC only) with CD4 cell counts <200 cells/mm^3 versus ≥200 cells/mm^3 at end of suppressed period.

While the causality in persistently low CD4 cell count, AIDS defining disease and death seems obvious, the association between low CD4 cell count and non-AIDS defining diseases and death is not entirely clear. Several other studies in the late cART era have demonstrated an increased risk of non-AIDS defining diseases, namely cardiovascular disease and NADC, related to low CD4 cell count[II, III] (19,20,115,144,170). So, an increased risk of death from this cause in HIV-infected individuals with incomplete CD4 recovery is perhaps not surprising. However, an increased incidence of cancer and cardiovascular disease is also seen in non-HIV infected immunosuppressed populations, like organ transplanted recipients, suggesting that immunodeficiency or chronic inflammation is involved in the causality (19). Finally, the impact of traditional risk factors like the use of tobacco on mortality, CVD and non-AIDS cancer has been thoroughly demonstrated in HIV infected and an association between low CD4 count and the use of tobacco has been demonstrated (21,22,111,168). Thus, not being able to control for the use of tobacco in [III] is a significant weakness which could have confounded the results.

Risk factors for incomplete CD4 recovery

[III] confirmed that older age, type of HIV transmission, low CD4 count and longer time to viral control are risk factors for incomplete CD4 cell recovery (156,171,172). Besides the impact of age and thymus size, the exact mechanism behind insufficient immune recovery is not known and efforts to increase CD4 recovery have remained futile (158,173–175). No significant differences in terms of CD4 increase between the different antiretroviral drug classes has been demonstrated (171,176–178). Still, an accumulating body of evidence shows that for most HIV-infected individuals on cART, the CD4 cell count continues to increase over time regardless of baseline CD4, although full CD4 recovery may not happen for patients with very low baseline CD4 cell count (153,155,179–181).

Summary and perspective on incomplete CD4 recovery

HIV-infected individuals with incomplete CD4 recovery have an increased long-term mortality due to both AIDS and non-AIDS related causes of death. The mechanism behind this is not completely understood but could be related to a combination of traditional risk factors and immunodeficiency. Although HIV-infected individuals with long standing incomplete CD4 recovery are a minority, the problem is most likely persisting as the yearly incidence of HIV in western countries shows little decline and since 20-30% of the newly diagnosed HIV infected individual

continues to present themselves with a CD4 cell count below 200 cell/mm^3 or advanced HIV disease (26–28). Evidently, earlier diagnose of HIV and early initiation of cART is warranted to change this situation but also closer monitoring for non-AIDS related diseases and steps to promote cessation of tobacco use is warranted in this population.

Antiretroviral treatment

Combination antiretroviral treatment

The development of the first active NRTI, zidovudine, targeting the reverse transcriptase enzyme and thereby blocking incorporation of the virus in host cell DNA, was a huge breakthrough, proving that HIV infection was treatable. Other NRTIs followed but it soon became apparent that the use alone and in duo therapy with other NRTIs only had temporary effect in terms of viral suppression and survival, leading to resistance associated mutations (RAMs), which complicated future antiretroviral treatment (182–189). Side effects and especially the discovery of cART to circumvent the inherent ability of HIV virus to develop drug resistance and maintain viral suppression lead to an urgent need of new classes of ARV drugs.

The second ARV drug class was protease inhibitors (PIs), which in combination with 2 NRTIs attained sustained viral suppression and increasing CD4 cell count resulting in prolonged survival and was a huge breakthrough (190–195). Opposed to the first generation of PI´s, the second generation is better tolerated and have a higher barrier for viral resistance (namely darunavir), especially when boosted (190,192,196,196–205). Non-nucleotide reverse transcriptase inhibitors (NNRTI) were the third class of ARV drugs to be approved with nevirapine in 1996 (195). The first generation of NNRTIs, namely efavirenz, which proved superior to nevirapine, was highly effective and widely used in combination with two NRTIs (206–209). Second generations NNRTIs rilpivirine, etravirine and doravirine do not have same CNS side effects seen in efavirenz but share the same drug interactions and pharmacokinetics (long plasma half-life) as first generation NNRTIs (208,210–215). Alongside the development and introduction of PIs and NNRTIs, new NRTIs were developed without the mitochondrial side effects seen in the first generations of NRTIs (95,216,217). The newer NRTIs are in general highly effective and tolerable and have a synergistic effect in combination with other ARV drug classes resulting in a high efficacy why they remain the back bone of HIV treatment (207,218–224). Entry inhibitors was the fourth class of ARVs introduced in 2003 but are only used under special circumstances due to the route of administration of enfurvirtide (injection) and the tropism of maraviroc (225–228).

Integrase strand transfer inhibitors

Following high efficacy of newer ARVs, better adherence due to fewer side effects and low pill burden, the risk of triple-class failure has decreased since the early cART era but it is not insignificant (152,153,229–232). Especially HIV-infected individuals exposed to the early generations of ARV drugs are more likely to harbor RAMs against one or more of the three drug classes NRTIs, PIs and NNRTIs (229,230,232–234). In case of virological failure, recommendations for salvage therapy consists of a cART regime including at least two, and preferably three, fully active ARV drugs (235). Notably for HIV-infected individuals with triple-class resistance, this posed a serious problem in the the first years of the millennium and emphasized the need for new ARV drug classes or new drugs from the old classes with no or little cross resistance to the older drugs. The first integrase strand transfer inhibitor (INSTI) raltegravir (RAL) was approved by the FDA in 2007 and since then elvitegravir (2012), dolutegravir (2013) and Bictegravir (2018) has followed (236–238). The approval of RAL was based on to two clinical randomized, placebo-controlled phase III international trials (BENCHMRK I and II) conducted on HIV-1 infected patients failing therapy with triple-class RAMs comparing OBT/placebo with OBT/RAL (239–242). The regimen including RAL had superior antiretroviral activity (virological response <50 copies/ml at 24 weeks 58% and 65% for BENCHMRK 1 and 2 respectively, versus 32% and 32% in the placebo group), higher increase in CD4 cell count and no differences in observed adverse events compared to the placebo/OBT. As in most RCTs, these studies were conducted in selected populations but was soon followed by a Danish observational study (intention to treat) demonstrating that the clinical progression, immunological and virological response in individuals with triple class failure who switched to a cART regimen containing raltegravir was comparable to that of naïve HIV-infected individuals initiating a first line cART regime [IV]. A substantial CD4 increase was observed, exceeding that seen in the TRIO trial (in spite of comparable baseline CD4 cell count) perhaps due to the the discontinuation of zidovudine in a large proportion of the patients prior to salvage therapy or a healthy survivor phenomenon (243). Like in both the BENCHMRK studies and the ANRS 139 TRIO trial, most of the included HIV-infected individuals in [IV] initiating a RAL containing regime, simultaneously initiated darunavir and in some cases etravirine why the effect of RAL is hard to differentiate (240,244). While the study population was small in [IV] and follow-up limited to 72 weeks, both the BENCHMRK study and the ANRS 139 TRIO trial have since showed a favorable long-term efficacy and safety profile (240,244,245). Since [IV], other observational

studies on HIV-infected individuals on a salvage regime including RAL have been published with similar findings (246–249). Both the RCTs and the observational studies are confounded by the concomitant use of darunavir, etravirine, enfuvirtide or maraviroc and switches during follow-up, making the efficacy of RAL had to differentiate. But, INSTIs have shown high efficacy and both RAL, eltegravir and dolutegravir with an NRTI backbone in cART naïve HIV-infected individuals is shown both in RCT and observational intention-to-treat studies to be non-inferior to efavirenz plus a NRTI backbone (250–253). While, RAL were initially dosed twice daily, a single dose RAL 1200 mg in new formulation has shown to be non-inferior to 400 mg twice daily making it an even more attractive option for cART naïve patients (245). In general, INSTIs have few adverse effects. Still, eltegravir needs boosting, which may cause more side effects from drug-drug interactions and dolutegravir appear to have more CNS side effects than the other INSTIs, weight gain and a possible teratogenic effect (254–258). The latest INSTI, bictegravir, was approved in 2018 and has so far been comparable to dolutegravir in terms of efficacy and safety (259). Generally, INSTI are increasingly recommended for both first line therapy in cART naïve HIV-infected individuals and salvage regimen for cART experienced individuals (235).

Single-tablet regimens versus multi-tablet regimens

In early cART era, the pill burden was overwhelming and pills had to be dosed frequently, probably leading to poor adherence, which in turn results in virological failure, disease progress and drug-resistance, which complicated further treatment (233,260–264). Also, selective adherence is possible in separate-pill regimens. Even though the most common reason for discontinuation of cART is adverse event and the evidence for better adherence in fewer tablet in cART regimes were limited, the pharmaceutical formulation of cART drifted towards fixed dose combinations (FDCs) containing more than one drug (86,265,266). The first marketed FDC was introduced in 1997 and contained a combination of lamivudine and zidovudine (267). Several FDCs followed but contained only drugs from the same drug class why the introduction of tenofovir disoproxil fumarate, emtricitabine and efavirenz combined in a once-daily pill in 2006 was quite a breakthrough due both to the convenience but not least, to the efficacy of the drugs included (207,268). The formulation soon became one of the most widely used cART regimes in Europe and North America and was until recent years recommended for cART naïve HIV-infected individuals [V](235,269–271). In developed countries, the expiring of the patent on tenofovir disoproxil fumarate changed

this. The patent of lamivudine had already expired in 2010 and with the presumed interchangeability of emtricitabine and lamivudine, a solid cART regime consisting of branded tenofovir disoproxil fumarate, generic efavirenz and generic lamivudine was a possibility (272). With a steady growing population of HIV-infected individuals with life spans comparable to non-HIV-infected individuals as well as increasingly earlier initiation of cART, both private and public health providers had incitement to use cheaper cART regimes with high efficacy in order to increase the availability of treatment to a larger number of HIV-infected individuals and reduce cost. The prospective was nicely illustrated by Walensky et al , whom in 2012 presented a mathematical model which, with conservative estimates of efficacy, estimated that, by using generic lamivudine and generic efavirenz in combination with branded tenofovir disoproxil fumarate instead of a single-tablet regime consisting of tenofovir disoproxil fumarate, efavirenz and emtricitabine (STR-TEE), the US would save $4000 per quality-adjusted year of life (QALY) for each individual on treatment in the USA, and would save the country $920 million on its annual drugs bill (273). Since 2012, analyses with similar results from other countries has been published (274,275). As lamivudine is regarded as equivalent in terms of efficacy and tolerability compared to emtricitabine, the switch was considered safe, but the main concern was the convenience for the patient and the possible effect on adherence (276–278). Few studies have directly compared separate-pill regimen and FDCs containing the same drugs and some are potentially biased by selection (e.g. switch to FDCs due to poor adherence) but meta-analyses comparing single-tablet regimes (STR) and FDCs, that do not contain identical drugs, have shown that HIV-infected individuals treated with single-tablet regimes (STR) have higher adherence and thereby an increased likelihood of achieving viral suppression and an improved quality of life in (279,279–282).

The meantime higher prizes for ART in Denmark compared to neighboring countries (combined with economic crisis in the ´00) led to a tender in 2010 which resulted in a considerable price differences between STR-TEE and the triple-tablet regimen consisting of tenofovir disoproxil fumarate, efavirenz and lamivudine (TTR-TEL) (283). Therefore, the Capital Region of Denmark recommended that HIV-infected individuals in treatment with STR-TEE were switched from April 1, 2011 to the cheaper TTR-TEL and that also cART-naive patients eligible for STR-TEE should be started on TTR-TEL. With only the results of a mathematical model, no RCTs on the subject and a presumed advantage of STR over FDCs, this shift from STR-TEE to TTR-TEL caused some concern.

But, by comparing a historical population on STR-TEE with individuals switched from STR-TEE to TTR-TEL, DHCS demonstrated that the switch had no impact on viral suppression or CD4 cell count [V]. The level of virological suppression at week 48 after the switch was also comparable to that of HIV-infected individuals switching to STR-TEE from other regimens in older studies (284). Also, no difference was found in naive HIV-infected individuals initiating TEE-TEL compared to a historical population of cART naïve individuals initiating STR-TEE [V]. Although fewer regimens containing efavirenz were used in the later period where STR-TEE was not available, there was no difference in the fraction of switches to non–efavirenz containing regimens [V]. While lamivudine has been associated with a lower barrier to development of RAMs compared to emtricitabine in some studies, this was not observed in [V] and the two drugs are still considered interchangeable (277,278,285–289). Besides [V] only other unpublished study investigating the switch from STR-TEE to TTR-TEL exists (290). In this regional British investigation 127 (47%) HIV-infected individuals out of 268 on STR-TEE agreed to switch to either branded tenofovir disoproxil fumarate, generic lamivudine and generic efavirenz or branded combination of tenofovir disoproxil fumarate and emtricitabine in combination with generic efavirenz. The HIV-infected individuals who refused the switch, did so primarily due to the convenience of a STR and were not included in the analysis. All HIV-infected individuals who remained in the two arms maintained a VL < 40 copies/ml at week 24 and 48. No comparison of CD4 measurements was performed. Although only few studies are published on the subject it appears that separate-pill regimen in general is safe with high efficacy, significant cost saving and well tolerated by the HIV-infected individuals in treatment (291–293). Further, the impact of the use of generic ARVs and prize reduction on branded ARV have since lead to a considerable cost reduction of anti-retroviral drugs in Denmark (294).

The question of de-simplification remains most relevant as it continues to challenge the prioritization of cost versus convenience as well as patient empowerment and their possibility to influence their HIV treatment. Recently, two publications have demonstrated that one of the currently most used STRs contains dolutegravir, abacavir and tenofovir disoproxil fumarate, which may safely be switched to a triple-tablet regime containing branded dolutegravir, lamivudine and tenofovir with considerable cost saving (292,295). While the HIV-infected individuals in [V] did not have a hear-say in the switch, other studies have asked the HIV-infected individuals and the general tendency is that most HIV-infected individuals don´t oppose a switch, referring cost savings as their reasoning (292,296). That said, STRs may have clear advantages in terms of

adherence in vulnerable subgroups (e.g. homeless, IDUs) and may be more appropriate on the increasingly aging HIV-infected population who receive multiple daily tablets due to other co-morbidities or have difficulties swallowing. So, in general a switch from branded STRs is safe, as well as acceptable for most the HIV-infected individuals. Another possibility is to use generic combination tablets which is now available in the developed countries (297,298).

Combination antiretroviral treatment as prevention

Besides decreasing HIV-related morbidity and mortality, cART is now widely recognized as a means of preventing HIV transmission both in serodiscordant couples and uninfected individuals.
In 2008, the Swiss Federal Commission for HIV/AIDS stated, that "a seropositive person without additional sexually transmitted disease in antiretroviral treatment with suppressed VL cannot transmit HIV sexually" and that no barrier protection was needed in a setting with no sexually transmitted disease, cART and viral suppression for more than 12 months (299). The statement was based on studies that demonstrated that cART reduce the risk of HIV transmission considerably (300–304). Besides diminishing the concerns and fear of transmitting HIV to an uninfected partner by having unprotected sex as well as reducing the risks of facing legal charges in case of non-disclosure, it also meant that pregnancy could happen naturally without the washing of semen (305,306). The statement was highly discussed at the time and considered a gamble by some (307). Partly because viral RNA can occasionally be found in the genital tract of both men (semen) and women with plasma HIV RNA below detection level (although the ability to infect is not certain) and because most HIV-infected individuals only have their VL measured two to four times a year (308–311). Still, as viral suppression is a standard outcome for cART efficacy, numerous studies after the millennium, had shown that adult individuals on effective cART without compliance problems or harboring RAMs, attain viral suppression within a year and have a quite low risk of viral rebound (~1%), why most considered the Swiss recommendations safe (234,312–319). The low risk of viral failure has since been confirmed in other cohort studies [VI] (253,313,315). While, most studies demonstrate a further decrease in risk of viral failure associated with the length of the virally suppressed period, older age and calendar year for cART initiation, these differences are negligible [VI](313–315,319,320). Since 2008, the Swiss recommendations are largely implemented around the world and both observational and

randomized trials have confirmed that the risk of transmitting HIV in serodiscordant couples on effective cART is insignificant (8,321–324).

Recently, the pre-exposure prophylactic treatment (PrEP) with cART in HIV-uninfected individuals at risk of HIV infection is now recommended and has been introduced in an increasing number of countries as randomized studies have demonstrated a further reduction of HIV transmission (235,325–329).

Summary and perspective on antiretroviral treatment

The main goal of HIV treatment is decreased HIV-related morbidity and mortality through effective viral suppression and the absence of serious adverse events. Besides decreasing mortality and morbidity in HIV-infected individuals, cART effectively prevents transmission of HIV to uninfected sex partners and early initiation of cART in HIV-infected individuals along with wider implementation of PrEP in risk groups are important means to end the HIV epidemic. Thanks to new drug classes like INSTIs and new more tolerable and effective ARVs within the existing drug classes, finding a suitable ARV combination is rarely a problem in both treatment naïve HIV-infected individuals, and to an increasing extent in cART experienced HIV-infected individuals with RAMs. Due to an increasing population of HIV-infected individuals, early initiation of cART and implementation of pre-exposure prophylactic treatment, finding ways to decrease cost is increasingly important. An effective and safe means to achieve this, is the use of generic ARVs.

Conclusion

While the prognosis of HIV-infected individuals in general has improved considerably following the introduction of cART, HIV-infected individuals still have an increased morbidity and mortality. Of particular concern is the increased incidence of non-virus-related NADCs compared to uninfected individuals. Part of this is probably explained by traditional risk factors like smoking but also by a complex association with immunodeficiency, perhaps due to lack of immunological cancer control. Also, HIV-infected individuals diagnosed with HIV late, who do not recover completely immunologically despite effective cART and viral suppression, have an increased mortality due to both AIDS and non-AIDS related causes of death. The mechanism behind this is not understood but is possibly related to a combination of traditional risk factors and immunodeficiency.

The introduction of new drug classes of ARV medicine like integrase inhibitors and new generations of drugs in existing drug classes, both with high efficacy and a more tolerable side effect profile has improved the prognosis and treatment of HIV-infected individuals. Besides improving morbidity and mortality among HIV-infected individuals, early initiation of cART and PrEP is an effective mean to prevent HIV transmission and the use of generic HIV medicine is an effective mean in order to balance efficacy, cost and convenience.

In conclusion, morbidity and mortality associated with immunodeficiency and traditional risk factors remains a problem although the prognosis for HIV-infected individuals has improved in general. Still, finding a tolerable and effective cART regime has become less complicated due to the introduction of INSTIs and the use of generic ART can reduce the cost of medical expenses considerably and hopefully increase coverage. Chances are that early initiation of cART and PReP will decrease both morbidities related to immunodeficiency, and the incidence of HIV infections in near future.

Summary in Danish

Siden starten af firserne har HIV epidemien udviklet sig til en global pandemi på trods af nationale og internationale tiltag. I det første dekade af pandemien var indsatsen fokuseret på behandling af AIDS definerende sygdomme, hindre yderligere spredning og udvikling af effektiv behandling, der kunne give vedvarende viral suppression og forbedret overlevelse. Flere af disse mål blev nået i midt-halvfemserne med udviklingen af kombinations antiretroviral behandling (cART) men smittespredning og sen diagnose af HIV er fortsat en udfordring. Efter implementeringen af cART og som konsekvens heraf, vedvarende viral suppression og restitution af det cellulære immunforsvar, så man et generelt fald i forekomsten af opportunistiske infektioner hos HIV-smittede individer. Udover et fald i opportunistiske infektioner, så man også et fald i AIDS definerende kræftformer. I takt med den øget overlevelse og dermed stigende alder i den HIV inficerede befolkning, kunne man til gengæld observere en stigende forekomst af ikke-AIDS definerende kræftformer som lunge- og øre-næse-hals kræft, som ligger over forekomsten i baggrundsbefolkningen. Meget tyder på, at en del af forklaringen er et øget tobaksforbrug hos HIV-inficerede individer, men der ses også for lungekræft en association med lavt CD4 celletal, hvilket tyder på en synergi mellem immundefekt og klassiske risikofaktorer. Således vil lunge- og øre-næse-hals kræft kunne forbygges ved tidlig diagnose og behandling af HIV samt rygeophør. Trods betydeligt forbedret overlevelse generelt er CD4 celletallet fortsat en stærk markør for mortalitet og morbiditet. Langt de fleste oplever restitution af immunforsvaret efter start af cART men især dem, der diagnosticeres sent med HIV og er ældre når de initierer cART, er i risiko for ikke at stige adækvat i CD4 celle tal, trods vedvarende viral suppression. Denne subgruppe af HIV-inficerede har en højere dødelighed end HIV inficerede individer, som stiger i CD4 celletal. Dette er demonstreret både i flere kohortestudier, hvor man observerede en øget dødelighed både på baggrund af AIDS samt ikke-AIDS definerende dødsårsager. Denne subgruppe af HIV-smittede individer, som har vedvarende lavt CD4 celletal, bør observeres tættere og motiveres for eventuelt rygestop.

I forbindelsen med udviklingen af antiretrovirale stoffer i starten af halvfemserne, måtte man konstatere, at behandling med et eller to stoffer hurtigt resulterede i udvikling af antiretroviral resistens. Af denne grund består HIV behandling, som udgangspunkt, af en kombination af to

nukleosidanaloger og et antiretroviralt middel fra en anden stofklasse. På baggrund af tidligere udviklet resistens, transmitteret resistens eller andre problematikker som for eksempel bivirkninger, er der et behov for nye antiretrovirale stofklasser og nye stoffer indenfor kendte stofklasser uden krydsresistens med de ældre stoffer. En ny stofklasse, integrase hæmmere, blev introduceret i 2008 og viste sig at være en effektiv del af "rednings regimer" til HIV-inficerede individer med antiretroviral resistens. Dette blev vist i både randomiserede studier og kohortestudier, som demonstrerede viral suppression og CD4 stigning hos HIV inficerede individer med antiretroviral resistens, som var sammenlignelig med effekten af cART behandling hos HIV inficerede individer, der startede behandling for første gang.

Behandling med cART fører til suppression af viral replikation og HIV bliver under effektiv behandling umåleligt i blodet. Som konsekvens heraf og støttet af estimater af lav risiko for tilfældigt at kunne måle HIV i blodet hos velbehandlede patienter, anbefales brug af kondom ikke længere hos par, hvor den ene parter er smitte med HIV og velbehandlet. Således er det ikke længere nødvendigt at vaske sæd i forbindelse med befrugtning og i takt med tidlig behandling af HIV, reduceres risikoen for videre transmission af HIV. Risikoen for smitte med HIV i befolkningsgrupper med højrisiko adfærd reduceres yderligere ved forbyggende behandling med cART (PrEP) hos individer som ikke er smittede med HIV.

De første cART regimer var karakteriserede ved hyppige doseringer og høj pille byrde. Efterfølgende pille formuleringer bevægede sig mod dosering én gang dagligt af én pille bestående af flere aktive stoffer i kombination. I takt med øget overlevelse og tiltagende tidligere initiering af cART samt udløb af patenter på antiretroviral medicin, blev de-simplificering til et cART regime, bestående af flere piller med en generisk komponent doseret én gang dagligt, introduceret med udgifts reduktion til følge. I den Danske HIV Kohorte kunne man demonstrere at både behandling af tidligere ubehandlede HIV-smittede individer med et cART regime bestående af flere piller med en generisk komponent en gang dagligt samt skift fra en kombinations pille en gang dagligt hos HIV inficerede individer, der allerede var i behandling, var muligt og sikkert.

Overordnet kan man konkludere, at introduktionen af cART generelt har reduceret sygdomsbyrden hos HIV-smittede individer og øget deres overlevelse. Trods dette, har visse subgrupper fortsat øget dødelighed og på baggrund af et sammenspil mellem immundefekt og traditionelle risikofaktorer for kræft, er motivation af ryge ophør vigtigt for at øge overlevelse og reducere sygdomsbyrde yderligere. I takt med tilkomst af nye ART stofklasse med høj effektivitet

og færre bivirkninger er det sjældent et problem at finde et effektivt cART regime til både behandlingsnaive og tidligere behandlede patienter med viral resistens for ART. Behandling med cART reducer desuden smitte med HIV og udbredelsen af forebyggende cART behandling hos HIV-ikke smittede vil reducere HIV smitte yderligere. Øget overlevelse hos HIV-smittede individer og øget brug af cART også hos ikke-HIV smittede betyder øgede udgifter til medicin. Brugen af generisk HIV medicin vil kunne reducere denne udgift betydeligt uden risiko for de HIV inficerede patienter.

Summary in English

Since the eighties, the HIV epidemic has developed into a global pandemic in spite of national and international efforts. In the first decade of the pandemic, most efforts were focused on treating AIDS defining diseases, impeding further transmission of the infection and developing effective antiretroviral treatment resulting in sustained viral suppression and improved survival. Several of these goals were achieved in the mid-nineties with combination antiretroviral treatment (cART) but ongoing transmission is still a challenge. Following the implementation of cART, a general decrease in the incidence of opportunistic infections in HIV-infected individuals was observed. Beside a drop in the rate of opportunistic infections, a decrease in the incidence of AIDS defining cancers was also observed. But surprisingly, an increased incidence of non-AIDS defining cancers like lunge and head- and neck cancer was also observed compared to the background population. Several things indicate that part of the explanation behind this is that HIV-infected individuals smoke more but there is also an association with low CD4 cell counts, which indicates a synergy between immunodeficiency and classical risk factors for lunge and head- and neck cancer. Thus, early diagnosing, treatment of HIV and stop smoking interventions could reduce the incidence of lunge and head- and neck cancer in HIV-infected individuals.

In spite of an improved overall survival among HIV-infected individuals, the CD4 cell count is still a strong marker for morbidity and mortality. Most HIV-infected individuals experience a restitution of the cellular immune defense after initiation of cART but especially those diagnosed late with HIV or are elderly when they initiate cART, are at risk of failure to increase their CD4 cell count in spite of sustained viral suppression. This subgroup of HIV-infected individuals has a higher mortality compared to those who increase readily in CD4 cell count. This is demonstrated in both Denmark and in a large international cohort collaboration where an increased mortality due to both AIDS and non-AIDS defining causes of death was observed. This subgroup of HIV-infected individuals with sustained low CD4 cell count despite effective cART may benefit from closer follow-up.

After the introduction of cART, a decrease in the hospitalization of Danish HIV-infected individuals has been observed, especially for AIDS related causes. Besides the effect of cART, re-structuration of the Danish health care system had an impact on the decreased hospitalization. Despite the

decreased hospitalization, HIV-infected individuals are still admitted and seen in outpatient clinics more often than individuals not infected with HIV. Furthermore, a shift from hospitalization due to HIV related causes to non-HIV related causes was seen.

During the development of antiretroviral drugs in the start of the nineties, it was clear that treatment with just one or two drugs quickly resulted in antiretroviral drug resistance associated mutations. Therefore, cART generally consists of a combination of two nucleoside analogs and a third antiretroviral drugs from a different drugs class. Due to existing antiretroviral drug associated resistance mutations, transmitted resistance or other issues like adverse effects or allergy, there is a continued need for new antiretroviral drug classes and new drugs within existing drugs classes without cross resistance with older drugs. A new drugs class, integrase inhibitors, was introduced in 2008 and turned out to be an effective part of "salvage regimes" to HIV-infected individuals with antiretroviral resistance associated mutations. This was demonstrated in both randomized studies and one observation study from the Danish HIV Cohort Study, which demonstrated an efficacy comparable to that of cART in treatment naïve HIV-infected individuals initiating treatment.

Treatment with cART leads to suppression of viral replication and on effective treatment, HIV RNA is unmeasurable in the blood. As a consequence, and supported by an estimated low risk of viral rebound, the use of condom can be discarded in couples where only one partner is infected with HIV and on effective treatment. Therefore, it is no longer necessary to wash semen for fertilization and following increasingly earlier initiation of cART, the general risk of HIV transmission is reduced. The risk of HIV transmission in high risk population groups is further reduced with pre-exposure antiretroviral treatment of individuals who are not infected with HIV (PrEP).

The first cART regimens were characterized by frequent dosing and a high pill burden. Subsequent pill formulations moved towards once-daily dosing by one pill containing all active drugs in combination. Ensuing increased survival, increasingly earlier initiation of cART and drug patent expiration, de-simplification to cART regimens consisting of several pills with generic components dosed once daily was introduced with reduced expenses as a result. The Danish HIV Cohort Study demonstrated that treating both cART experienced and cART naïve HIV-infected individuals with a cART regime consisting of several pills with generic components dosed once daily was possible and safe.

In general, it can be concluded that the introduction of cART has reduced the disease burden in HIV-infected individuals and increased their survival. In spite of this, certain subgroups still have an increased mortality and an increased risk of certain non-AIDS defining cancers, possibly due to a synergy between immunodeficiency and traditional risk factors for cancer. An early diagnosis of HIV and initiation of cART along stop smoking interventions are important to increase survival and reduce disease burden further. Following the arrival of new drug classes with high efficacy and fewer adverse effects, finding an effective cART regime to both cART naïve and HIV-infected individuals with resistance associated mutations is less difficult. Treatment with cART reduces further transmission of HIV and PrEP treatment in uninfected population groups in high risk will reduce transmission further. Improved survival of HIV-infected individuals and increased use of cART are increasing medical expenses. The use of generic medicine is a means to reduce medical expenses considerably.

References

1. Gallo RC, Sarin PS, Gelmann EP, Robert-Guroff M, Richardson E, Kalyanaraman VS, et al. Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS). Science. 1983 May 20;220(4599):865–7.

2. Global Health Observatory (GHO) data [Internet]. who.int. 2018. Available from: http://www.who.int/gho/hiv/en/

3. UNAIDS. 90–90–90 - An ambitious treatment target to help end the AIDS epidemic [Internet]. 2017. Available from: http://www.unaids.org/en/resources/documents/2017/90-90-90

4. Podlekareva DN, Efsen AMW, Schultze A, Post FA, Skrahina AM, Panteleev A, et al. Tuberculosis-related mortality in people living with HIV in Europe and Latin America: an international cohort study. Lancet HIV. 2016 Mar;3(3):e120-131.

5. HIV/AIDS surveillance in Europe 2018 [Internet]. www.euro.who.int. Available from: http://www.euro.who.int/__data/assets/pdf_file/0004/386959/HIVAIDS-surveillance-in-Europe-2018.pdf?ua=1

6. Okano JT, Robbins D, Palk L, Gerstoft J, Obel N, Blower S. Testing the hypothesis that treatment can eliminate HIV: a nationwide, population-based study of the Danish HIV epidemic in men who have sex with men. Lancet Infect Dis. 2016 Jul;16(7):789–96.

7. Molina J-M, Charreau I, Spire B, Cotte L, Chas J, Capitant C, et al. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV. 2017 Sep;4(9):e402–10.

8. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. N Engl J Med. 2011 Aug 11;365(6):493–505.

9. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. The Lancet. 2009 Jan;373(9657):48–57.

10. Pharris A, Quinten C, Noori T, Amato-Gauci AJ, van Sighem A, the ECDC HIV/AIDS Surveillance and Dublin Declaration Monitoring Networks. Estimating HIV incidence and number of undiagnosed individuals living with HIV in the European Union/European Economic Area, 2015. Eurosurveillance [Internet]. 2016 Dec 1 [cited 2018 May 16];21(48). Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=22661

11. Antiretroviral therapy coverage (% of people living with HIV). UNAIDS estimates. [Internet]. worldbank.org. Available from: https://data.worldbank.org/indicator/SH.HIV.ARTC.ZS?name_desc=true

12. Lohse N, Obel N. Update of Survival for Persons With HIV Infection in Denmark. Ann Intern Med. 2016 Nov 15;165(10):749–50.

13. Lohse N, Hansen A-BE, Pedersen G, Kronborg G, Gerstoft J, Sørensen HT, et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. Ann Intern Med. 2007 Jan 16;146(2):87–95.

14. Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. Lancet Lond Engl. 2014 Jul 19;384(9939):241–8.

15. Ingle SM, May MT, Gill MJ, Mugavero MJ, Lewden C, Abgrall S, et al. Impact of risk factors for specific causes of death in the first and subsequent years of antiretroviral therapy among HIV-infected patients. Clin Infect Dis Off Publ Infect Dis Soc Am. 2014 Jul 15;59(2):287–97.

16. Rasmussen LD, May MT, Kronborg G, Larsen CS, Pedersen C, Gerstoft J, et al. Time trends for risk of severe age-related diseases in individuals with and without HIV infection in Denmark: a nationwide population-based cohort study. Lancet HIV. 2015 Jul;2(7):e288-298.

17. Mahy M, Autenrieth CS, Stanecki K, Wynd S. Increasing trends in HIV prevalence among people aged 50 years and older: evidence from estimates

and survey data. AIDS Lond Engl. 2014 Nov;28 Suppl 4:S453-459.

18. HIV Among People Aged 50 and Older [Internet]. www.cdc.gov. 2019. Available from: https://www.cdc.gov/hiv/group/age/olderamericans/index.html

19. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet Lond Engl. 2007 Jul 7;370(9581):59–67.

20. Friis-Møller N, Weber R, Reiss P, Thiébaut R, Kirk O, d'Arminio Monforte A, et al. Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study. AIDS Lond Engl. 2003 May 23;17(8):1179–93.

21. Helleberg M, Gerstoft J, Afzal S, Kronborg G, Larsen CS, Pedersen C, et al. Risk of cancer among HIV-infected individuals compared to the background population: impact of smoking and HIV. AIDS Lond Engl. 2014 Jun 19;28(10):1499–508.

22. Rasmussen LD, Helleberg M, May MT, Afzal S, Kronborg G, Larsen CS, et al. Myocardial infarction among Danish HIV-infected individuals: population-attributable fractions associated with smoking. Clin Infect Dis Off Publ Infect Dis Soc Am. 2015 May 1;60(9):1415–23.

23. Rasmussen LD, May MT, Kronborg G, Larsen CS, Pedersen C, Gerstoft J, et al. Time trends for risk of severe age-related diseases in individuals with and without HIV infection in Denmark: a nationwide population-based cohort study. Lancet HIV. 2015 Jul;2(7):e288-298.

24. Hessol NA, Pipkin S, Schwarcz S, Cress RD, Bacchetti P, Scheer S. The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. Am J Epidemiol. 2007 May 15;165(10):1143–53.

25. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst. 2005 Mar 16;97(6):425–32.

26. Mocroft A, Lundgren JD, Sabin ML, Monforte A d'Arminio, Brockmeyer N, Casabona J, et al. Risk factors and outcomes for late presentation for HIV-positive persons in Europe: results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE). PLoS Med. 2013;10(9):e1001510.

27. Raffetti E, Postorino MC, Castelli F, Casari S, Castelnuovo F, Maggiolo F, et al. The risk of late or advanced presentation of HIV infected patients is still high, associated factors evolve but impact on overall mortality is vanishing over calendar years: results from the Italian MASTER Cohort. BMC Public Health. 2016 25;16(1):878.

28. Brännström J, Svedhem Johansson V, Marrone G, Wendahl S, Yilmaz A, Blaxhult A, et al. Deficiencies in the health care system contribute to a high rate of late HIV diagnosis in Sweden. HIV Med. 2016;17(6):425–35.

29. O'Connell S, Enkelmann J, Sadlier C, Bergin C. Late HIV presentation - missed opportunities and factors associated with a changing pattern over time. Int J STD AIDS. 2017;28(8):814–21.

30. Darling KE, Hachfeld A, Cavassini M, Kirk O, Furrer H, Wandeler G. Late presentation to HIV care despite good access to health services: current epidemiological trends and how to do better. Swiss Med Wkly. 2016;146:w14348.

31. Obel N, Engsig FN, Rasmussen LD, Larsen MV, Omland LH, Sørensen HT. Cohort profile: the Danish HIV cohort study. Int J Epidemiol. 2009 Oct;38(5):1202–6.

32. Omland LH, Ahlström MG, Obel N. Cohort profile update: the Danish HIV Cohort Study (DHCS). Int J Epidemiol. 2014 Dec;43(6):1769-1769e.

33. Frank L. EPIDEMIOLOGY:When an Entire Country Is a Cohort. Science. 2000 Mar 31;287(5462):2398–9.

34. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449–90.

35. Helweg-Larsen K. The Danish Register of Causes of Death. Scand J Public Health. 2011 Jul;39(7 Suppl):26–9.

36. Gjerstorff ML. The Danish Cancer Registry. Scand J Public Health. 2011 Jul;39(7 Suppl):42–5.

37. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health. 2011 Jul;39(7 Suppl):30–3.

38. Audelin AM, Lohse N, Obel N, Gerstoft J, Jørgensen LB. The incidence rate of HIV type-1 drug resistance in patients on antiretroviral therapy: a nationwide population-based Danish cohort study 1999-2005. Antivir Ther. 2009;14(7):995–1000.

39. Region Hovedstadens Apotek [Internet]. Klinisk framaceutisk service. 2013. Available from: www.apotek-regionh.dk

40. May MT, Ingle SM, Costagliola D, Justice AC, de Wolf F, Cavassini M, et al. Cohort profile: Antiretroviral Therapy Cohort Collaboration (ART-CC). Int J Epidemiol. 2014 Jun;43(3):691–702.

41. Chêne G, Phillips A, Costagliola D, Sterne JAC, Furrer H, Del Amo J, et al. Cohort Profile: Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. Int J Epidemiol. 2017 Jun 1;46(3):797-797n.

42. Marubini E, Valsecchi MG. Analysing survival data from clinical trials and observational studies. Chichester: John Wiley; 2005.

43. Cox DR. Regression Models and Life-Tables. J R Stat Soc Ser B Methodol. 1972;34(2):187–220.

44. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. J Am Stat Assoc. 1958 Jun;53(282):457.

45. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc. 1999 Jun;94(446):496.

46. Berry SD, Ngo L, Samelson EJ, Kiel DP. Competing Risk of Death: An Important Consideration in Studies of Older Adults: COMPETING RISK OF DEATH IN STUDIES OF OLDER ADULTS. J Am Geriatr Soc. 2010 Apr;58(4):783–7.

47. Centers for Disease Control (CDC). Pneumocystis pneumonia--Los Angeles. MMWR Morb Mortal Wkly Rep. 1981 Jun 5;30(21):250–2.

48. Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science. 1983 May 20;220(4599):868–71.

49. Bacellar H, Muñoz A, Hoover DR, Phair JP, Besley DR, Kingsley LA, et al. Incidence of clinical AIDS conditions in a cohort of homosexual men with CD4+ cell counts < 100/mm3. Multicenter AIDS Cohort Study. J Infect Dis. 1994 Nov;170(5):1284–7.

50. Hanson DL, Chu SY, Farizo KM, Ward JW. Distribution of CD4+ T lymphocytes at diagnosis of acquired immunodeficiency syndrome-defining and other human immunodeficiency virus-related illnesses. The Adult and Adolescent Spectrum of HIV Disease Project Group. Arch Intern Med. 1995 Jul 24;155(14):1537–42.

51. Mocroft AJ, Johnson MA, Sabin CA, Lipman M, Elford J, Emery V, et al. Staging system for clinical AIDS patients. Royal Free/Chelsea and Westminster Hospitals Collaborative Group. Lancet Lond Engl. 1995 Jul 1;346(8966):12–7.

52. Mocroft A, Katlama C, Johnson A, Pradier C, Antunes F, Mulcahy F, et al. AIDS across Europe, 1994–98: the EuroSIDA study. The Lancet. 2000 Jul;356(9226):291–6.

53. Saah AJ, Hoover DR, Peng Y, Phair JP, Visscher B, Kingsley LA, et al. Predictors for failure of Pneumocystis carinii pneumonia prophylaxis. Multicenter AIDS Cohort Study. JAMA. 1995 Apr 19;273(15):1197–202.

54. Schneider MME, Hoepelman AIM, Schattenkerk JKME, Nielsen TL, van der Graaf Y, Frissen JPHJ, et al. A Controlled Trial of Aerosolized Pentamidine or Trimethoprim–Sulfamethoxazole as Primary Prophylaxis against *Pneumocystis carinii* Pneumonia in Patients with Human Immunodeficiency Virus Infection. N Engl J Med. 1992 Dec 24;327(26):1836–41.

55. Hoover DR, Saah AJ, Bacellar H, Phair J, Detels R, Anderson R, et al. Clinical manifestations of AIDS in the era of pneumocystis prophylaxis. Multicenter AIDS Cohort Study. N Engl J Med. 1993 Dec 23;329(26):1922–6.

56. Bozzette SA, Finkelstein DM, Spector SA, Frame P, Powderly WG, He W, et al. A randomized trial of

three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. N Engl J Med. 1995 Mar 16;332(11):693–9.

57. Nightingale SD, Cameron DW, Gordin FM, Sullam PM, Cohn DL, Chaisson RE, et al. Two Controlled Trials of Rifabutin Prophylaxis against Mycobacterium avium Complex Infection in AIDS. N Engl J Med. 1993 Sep 16;329(12):828–33.

58. Shafran SD, Singer J, Zarowny DP, Phillips P, Salit I, Walmsley SL, et al. A Comparison of Two Regimens for the Treatment of *Mycobacterium avium* Complex Bacteremia in AIDS: Rifabutin, Ethambutol, and Clarithromycin versus Rifampin, Ethambutol, Clofazimine, and Ciprofloxacin. N Engl J Med. 1996 Aug 8;335(6):377–84.

59. Klein NC, Duncanson FP, Lenox TH, Forszpaniak C, Sherer CB, Quentzel H, et al. Trimethoprim-sulfamethoxazole versus pentamidine for Pneumocystis carinii pneumonia in AIDS patients: results of a large prospective randomized treatment trial. AIDS Lond Engl. 1992 Mar;6(3):301–5.

60. Martin DF, Sierra-Madero J, Walmsley S, Wolitz RA, Macey K, Georgiou P, et al. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. N Engl J Med. 2002 Apr 11;346(15):1119–26.

61. Carr A, Marriott D, Field A, Vasak E, Cooper DA. Treatment of HIV-1-associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. Lancet Lond Engl. 1998 Jan 24;351(9098):256–61.

62. Oz HS, Hughes WT. Search for Pneumocystis carinii DNA in upper and lower respiratory tract of humans. Diagn Microbiol Infect Dis. 2000 Jul;37(3):161–4.

63. Santoro C, Goldberg I, Bridey F, Figgie MP, Karila-Israel D, Haviland K, et al. Successful hip arthroplasty in an adult male with severe factor XI deficiency using Hemoleven®, a factor XI concentrate. Haemoph Off J World Fed Hemoph. 2011 Sep;17(5):777–82.

64. Zaman MK, Wooten OJ, Suprahmanya B, Ankobiah W, Finch PJ, Kamholz SL. Rapid noninvasive diagnosis of Pneumocystis carinii from induced liquefied sputum. Ann Intern Med. 1988 Jul 1;109(1):7–10.

65. Martin-Carbonero L, Barrios A, Saballs P, Sirera G, Santos J, Palacios R, et al. Pegylated liposomal doxorubicin plus highly active antiretroviral therapy versus highly active antiretroviral therapy alone in HIV patients with Kaposi's sarcoma. AIDS Lond Engl. 2004 Aug 20;18(12):1737–40.

66. Phair J, Muñoz A, Detels R, Kaslow R, Rinaldo C, Saah A, et al. The Risk of *Pneumocystis carinii* Pneumonia among Men Infected with Human Immunodeficiency Virus Type 1. N Engl J Med. 1990 Jan 18;322(3):161–5.

67. Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med. 2006 Nov 30;355(22):2283–96.

68. INSIGHT START Study Group, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015 Aug 27;373(9):795–807.

69. Yeni PG, Hammer SM, Carpenter CCJ, Cooper DA, Fischl MA, Gatell JM, et al. Antiretroviral Treatment for Adult HIV Infection in 2002: Updated Recommendations of the International AIDS Society-USA Panel. JAMA. 2002 Jul 10;288(2):222.

70. When To Start Consortium, Sterne JAC, May M, Costagliola D, de Wolf F, Phillips AN, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet Lond Engl. 2009 Apr 18;373(9672):1352–63.

71. TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015 Aug 27;373(9):808–22.

72. Antiretroviral Therapy Cohort Collaboration. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. Lancet HIV. 2017 Aug;4(8):e349–56.

73. May MT, Vehreschild J-J, Trickey A, Obel N, Reiss P, Bonnet F, et al. Mortality According to CD4 Count at Start of Combination Antiretroviral Therapy Among HIV-infected Patients Followed for up to 15 Years After Start of Treatment: Collaborative Cohort Study. Clin Infect Dis Off Publ Infect Dis Soc Am. 2016 15;62(12):1571–7.

74. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet Lond Engl. 2008 Jul 26;372(9635):293–9.

75. Hernández-Ramírez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. Lancet HIV. 2017;4(11):e495–504.

76. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep. 1992 Dec 18;41(RR-17):1–19.

77. Thorsteinsson K, Ladelund S, Jensen-Fangel S, Katzenstein TL, Johansen IS, Pedersen G, et al. Incidence of cervical dysplasia and cervical cancer in women living with HIV in Denmark: comparison with the general population. HIV Med. 2016 Jan;17(1):7–17.

78. Legarth R, Helleberg M, Kronborg G, Larsen CS, Pedersen G, Pedersen C, et al. Anal carcinoma in HIV-infected patients in the period 1995-2009: a Danish nationwide cohort study. Scand J Infect Dis. 2013 Jun;45(6):453–9.

79. Rubinstein PG, Aboulafia DM, Zloza A. Malignancies in HIV/AIDS: from epidemiology to therapeutic challenges. AIDS. 2014 Feb;28(4):453–65.

80. Mocroft A, Kirk O, Clumeck N, Gargalianos-Kakolyris P, Trocha H, Chentsova N, et al. The changing pattern of Kaposi sarcoma in patients with HIV, 1994-2003: the EuroSIDA Study. Cancer. 2004 Jun 15;100(12):2644–54.

81. Farizo KM, Buehler JW, Chamberland ME, Whyte BM, Froelicher ES, Hopkins SG, et al. Spectrum of disease in persons with human immunodeficiency virus infection in the United States. JAMA. 1992 Apr 1;267(13):1798–805.

82. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Study Group, Bohlius J, Schmidlin K, Costagliola D, Fätkenheuer G, May M, et al. Incidence and risk factors of HIV-related non-Hodgkin's lymphoma in the era of combination antiretroviral therapy: a European multicohort study. Antivir Ther. 2009;14(8):1065–74.

83. Bedimo R, Chen RY, Accortt NA, Raper JL, Linn C, Allison JJ, et al. Trends in AIDS-defining and non-AIDS-defining malignancies among HIV-infected patients: 1989-2002. Clin Infect Dis Off Publ Infect Dis Soc Am. 2004 Nov 1;39(9):1380–4.

84. Burgi A, Brodine S, Wegner S, Milazzo M, Wallace MR, Spooner K, et al. Incidence and risk factors for the occurrence of non-AIDS-defining cancers among human immunodeficiency virus-infected individuals. Cancer. 2005 Oct 1;104(7):1505–11.

85. Massad LS, Hessol NA, Darragh TM, Minkoff H, Colie C, Wright RL, et al. Cervical cancer incidence after up to 20 years of observation among women with HIV. Int J Cancer. 2017 15;141(8):1561–5.

86. Abraham AG, D'Souza G, Jing Y, Gange SJ, Sterling TR, Silverberg MJ, et al. Invasive cervical cancer risk among HIV-infected women: a North American multicohort collaboration prospective study. J Acquir Immune Defic Syndr 1999. 2013 Apr 1;62(4):405–13.

87. Delmas MC, Larsen C, van Benthem B, Hamers FF, Bergeron C, Poveda JD, et al. Cervical squamous intraepithelial lesions in HIV-infected women: prevalence, incidence and regression. European Study Group on Natural History of HIV Infection in Women. AIDS Lond Engl. 2000 Aug 18;14(12):1775–84.

88. Piketty C, Selinger-Leneman H, Bouvier A-M, Belot A, Mary-Krause M, Duvivier C, et al. Incidence of HIV-related anal cancer remains increased despite long-term combined antiretroviral treatment: results from the french hospital database on HIV. J Clin Oncol Off J Am Soc Clin Oncol. 2012 Dec 10;30(35):4360–6.

89. Rodger AJ, Lodwick R, Schechter M, Deeks S, Amin J, Gilson R, et al. Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the

general population. AIDS Lond Engl. 2013 Mar 27;27(6):973–9.

90. Helleberg M, Kronborg G, Larsen CS, Pedersen G, Pedersen C, Gerstoft J, et al. Causes of death among Danish HIV patients compared with population controls in the period 1995-2008. Infection. 2012 Dec;40(6):627–34.

91. Palella FJ, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 1999. 2006 Sep;43(1):27–34.

92. Calabresi A, Ferraresi A, Festa A, Scarcella C, Donato F, Vassallo F, et al. Incidence of AIDS-defining cancers and virus-related and non-virus-related non-AIDS-defining cancers among HIV-infected patients compared with the general population in a large health district of Northern Italy, 1999-2009. HIV Med. 2013 Sep;14(8):481–90.

93. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576–82.

94. Ceccarelli M, Rullo EV, Facciolà A, Madeddu G, Cacopardo B, Taibi R, et al. Head and neck squamous cell carcinoma and its correlation with human papillomavirus in people living with HIV: a systematic review. Oncotarget [Internet]. 2018 Mar 30 [cited 2019 Apr 25];9(24). Available from: http://www.oncotarget.com/fulltext/24660

95. White MK, Pagano JS, Khalili K. Viruses and Human Cancers: a Long Road of Discovery of Molecular Paradigms. Clin Microbiol Rev. 2014 Jul 1;27(3):463–81.

96. Shcherba M, Shuter J, Haigentz M. Current questions in HIV-associated lung cancer. Curr Opin Oncol. 2013 Sep;25(5):511–7.

97. Cutrell J, Bedimo R. Non-AIDS-defining cancers among HIV-infected patients. Curr HIV/AIDS Rep. 2013 Sep;10(3):207–16.

98. Guiguet M, Boué F, Cadranel J, Lang J-M, Rosenthal E, Costagliola D, et al. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. Lancet Oncol. 2009 Dec;10(12):1152–9.

99. Kirk GD, Merlo C, O'Driscoll P, Mehta SH, Galai N, Vlahov D, et al. HIV Infection Is Associated with an Increased Risk for Lung Cancer, Independent of Smoking. Clin Infect Dis. 2007 Jul 1;45(1):103–10.

100. Clifford GM, Lise M, Franceschi S, Egger M, Bouchardy C, Korol D, et al. Lung cancer in the Swiss HIV Cohort Study: role of smoking, immunodeficiency and pulmonary infection. Br J Cancer. 2012 Jan 31;106(3):447–52.

101. Simard EP, Engels EA. Cancer as a cause of death among people with AIDS in the United States. Clin Infect Dis Off Publ Infect Dis Soc Am. 2010 Oct 15;51(8):957–62.

102. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med. 2008 May 20;148(10):728–36.

103. Silverberg MJ, Chao C, Leyden WA, Xu L, Tang B, Horberg MA, et al. HIV infection and the risk of cancers with and without a known infectious cause. AIDS Lond Engl. 2009 Nov 13;23(17):2337–45.

104. Engels EA, Brock MV, Chen J, Hooker CM, Gillison M, Moore RD. Elevated incidence of lung cancer among HIV-infected individuals. J Clin Oncol Off J Am Soc Clin Oncol. 2006 Mar 20;24(9):1383–8.

105. Engels EA, Brock MV, Chen J, Hooker CM, Gillison M, Moore RD. Elevated incidence of lung cancer among HIV-infected individuals. J Clin Oncol Off J Am Soc Clin Oncol. 2006 Mar 20;24(9):1383–8.

106. Shepherd L, Ryom L, Law M, Petoumenos K, Hatleberg CI, d'Arminio Monforte A, et al. Cessation of Cigarette Smoking and the Impact on Cancer Incidence in HIV-positive Persons: The D:A:D Study. Clin Infect Dis Off Publ Infect Dis Soc Am. 2018 Jun 14;

107. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004 Jun 26;328(7455):1519.

108. Godtfredsen NS, Prescott E, Osler M. Effect of smoking reduction on lung cancer risk. JAMA. 2005 Sep 28;294(12):1505–10.

109. Ebbert JO, Yang P, Vachon CM, Vierkant RA, Cerhan JR, Folsom AR, et al. Lung Cancer Risk Reduction After Smoking Cessation: Observations From a Prospective Cohort of Women. J Clin Oncol. 2003 Mar;21(5):921–6.

110. Reddy KP, Kong CY, Hyle EP, Baggett TP, Huang M, Parker RA, et al. Lung Cancer Mortality Associated With Smoking and Smoking Cessation Among People Living With HIV in the United States. JAMA Intern Med. 2017 Nov 1;177(11):1613.

111. Helleberg M, May MT, Ingle SM, Dabis F, Reiss P, Fätkenheuer G, et al. Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America. AIDS Lond Engl. 2015 Jan 14;29(2):221–9.

112. Park LS, Hernández-Ramírez RU, Silverberg MJ, Crothers K, Dubrow R. Prevalence of non-HIV cancer risk factors in persons living with HIV/AIDS: a meta-analysis. AIDS Lond Engl. 2016 Jan;30(2):273–91.

113. Mdodo R, Frazier EL, Dube SR, Mattson CL, Sutton MY, Brooks JT, et al. Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. Ann Intern Med. 2015 Mar 3;162(5):335–44.

114. Kirk GD, Merlo C, O' Driscoll P, Mehta SH, Galai N, Vlahov D, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. Clin Infect Dis Off Publ Infect Dis Soc Am. 2007 Jul 1;45(1):103–10.

115. Reekie J, Kosa C, Engsig F, Monforte A d'Arminio, Wiercinska-Drapalo A, Domingo P, et al. Relationship between current level of immunodeficiency and non-acquired immunodeficiency syndrome-defining malignancies. Cancer. 2010 Nov 15;116(22):5306–15.

116. Monforte A d'Arminio, Abrams D, Pradier C, Weber R, Reiss P, Bonnet F, et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. AIDS Lond Engl. 2008 Oct 18;22(16):2143–53.

117. Frisch M, Biggar RJ, Engels EA, Goedert JJ, AIDS-Cancer Match Registry Study Group. Association of cancer with AIDS-related immunosuppression in adults. JAMA. 2001 Apr 4;285(13):1736–45.

118. Clifford GM, Rickenbach M, Polesel J, Dal Maso L, Steffen I, Ledergerber B, et al. Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma. AIDS Lond Engl. 2008 Oct 18;22(16):2135–41.

119. Shiels MS, Althoff KN, Pfeiffer RM, Achenbach CJ, Abraham AG, Castilho J, et al. HIV Infection, Immunosuppression, and Age at Diagnosis of Non-AIDS-Defining Cancers. Clin Infect Dis Off Publ Infect Dis Soc Am. 2017 15;64(4):468–75.

120. Sigel K, Wisnivesky J, Crothers K, Gordon K, Brown ST, Rimland D, et al. Immunological and infectious risk factors for lung cancer in US veterans with HIV: a longitudinal cohort study. Lancet HIV. 2017 Feb;4(2):e67–73.

121. Marcus JL, Leyden WA, Chao CR, Horberg MA, Klein DB, Quesenberry CP, et al. Immunodeficiency, AIDS-related pneumonia, and risk of lung cancer among HIV-infected individuals. AIDS Lond Engl. 2017 24;31(7):989–93.

122. Hleyhel M, Hleyhel M, Bouvier AM, Belot A, Tattevin P, Pacanowski J, et al. Risk of non-AIDS-defining cancers among HIV-1-infected individuals in France between 1997 and 2009: results from a French cohort. AIDS Lond Engl. 2014 Sep 10;28(14):2109–18.

123. Shiels MS, Islam JY, Rosenberg PS, Hall HI, Jacobson E, Engels EA. Projected Cancer Incidence Rates and Burden of Incident Cancer Cases in HIV-Infected Adults in the United States Through 2030. Ann Intern Med. 2018 Jun 19;168(12):866–73.

124. Helleberg M, Kronborg G, Larsen CS, Pedersen G, Pedersen C, Obel N, et al. CD4 Decline Is Associated With Increased Risk of Cardiovascular Disease, Cancer, and Death in Virally Suppressed Patients With HIV. Clin Infect Dis. 2013 Jul 15;57(2):314–21.

125. Shebl FM, Engels EA, Goedert JJ, Chaturvedi AK. Pulmonary infections and risk of lung cancer among persons with AIDS. J Acquir Immune Defic Syndr 1999. 2010 Nov;55(3):375–9.

126. Sogaard OS, Lohse N, Gerstoft J, Kronborg G, Ostergaard L, Pedersen C, et al. Hospitalization for pneumonia among individuals with and without HIV infection, 1995-2007: a Danish population-based, nationwide cohort study. Clin Infect Dis Off Publ Infect Dis Soc Am. 2008 Nov 15;47(10):1345–53.

127. Brenner DR, Boffetta P, Duell EJ, Bickeböller H, Rosenberger A, McCormack V, et al. Previous lung diseases and lung cancer risk: a pooled analysis from the International Lung Cancer Consortium. Am J Epidemiol. 2012 Oct 1;176(7):573–85.

128. Almirall J, Bolíbar I, Balanzó X, González CA. Risk factors for community-acquired pneumonia in adults: a population-based case-control study. Eur Respir J. 1999 Feb;13(2):349–55.

129. Coghill AE, Shiels MS, Suneja G, Engels EA. Elevated Cancer-Specific Mortality Among HIV-Infected Patients in the United States. J Clin Oncol Off J Am Soc Clin Oncol. 2015 Jul 20;33(21):2376–83.

130. Zucchetto A, Virdone S, Taborelli M, Grande E, Camoni L, Pappagallo M, et al. Non-AIDS-Defining Cancer Mortality: Emerging Patterns in the Late HAART Era. J Acquir Immune Defic Syndr 1999. 2016 01;73(2):190–6.

131. Vaccher E, Serraino D, Carbone A, De Paoli P. The evolving scenario of non-AIDS-defining cancers: challenges and opportunities of care. The Oncologist. 2014 Aug;19(8):860–7.

132. Mehanna H, Beech T, Nicholson T, El-Hariry I, McConkey C, Paleri V, et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer--systematic review and meta-analysis of trends by time and region. Head Neck. 2013 May;35(5):747–55.

133. O'Sullivan B, Huang SH, Su J, Garden AS, Sturgis EM, Dahlstrom K, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. Lancet Oncol. 2016;17(4):440–51.

134. Heck JE, Berthiller J, Vaccarella S, Winn DM, Smith EM, Shan'gina O, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int J Epidemiol. 2010 Feb;39(1):166–81.

135. Herrero R, Castellsagué X, Pawlita M, Lissowska J, Kee F, Balaram P, et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst. 2003 Dec 3;95(23):1772–83.

136. Smith EM, Ritchie JM, Summersgill KF, Klussmann JP, Lee JH, Wang D, et al. Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers. Int J Cancer. 2004 Feb 20;108(5):766–72.

137. Kreimer AR, Alberg AJ, Daniel R, Gravitt PE, Viscidi R, Garrett ES, et al. Oral Human Papillomavirus Infection in Adults Is Associated with Sexual Behavior and HIV Serostatus. J Infect Dis. 2004 Feb 15;189(4):686–98.

138. Beachler DC, Sugar EA, Margolick JB, Weber KM, Strickler HD, Wiley DJ, et al. Risk Factors for Acquisition and Clearance of Oral Human Papillomavirus Infection Among HIV-Infected and HIV-Uninfected Adults. Am J Epidemiol. 2015 Jan 1;181(1):40–53.

139. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst. 2009 Aug 19;101(16):1120–30.

140. Beachler DC, Abraham AG, Silverberg MJ, Jing Y, Fakhry C, Gill MJ, et al. Incidence and risk factors of HPV-related and HPV-unrelated Head and Neck Squamous Cell Carcinoma in HIV-infected individuals. Oral Oncol. 2014 Dec;50(12):1169–76.

141. D'souza G, Carey TE, William WN, Nguyen ML, Ko EC, Riddell J, et al. Epidemiology of head and neck squamous cell cancer among HIV-infected patients. J Acquir Immune Defic Syndr 1999. 2014 Apr 15;65(5):603–10.

142. Silverberg MJ, Chao C, Leyden WA, Xu L, Horberg MA, Klein D, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2011 Dec;20(12):2551–9.

143. Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, et al. Cancer risk in people infected

with human immunodeficiency virus in the United States. Int J Cancer. 2008 Jul 1;123(1):187–94.

144. Rasmussen LD, Omland LH, Pedersen C, Gerstoft J, Kronborg G, Jensen J, et al. Risk of myocardial infarction in parents of HIV-infected Individuals: a population-based Cohort Study. BMC Infect Dis. 2010 Jun 14;10:169.

145. Zuckerman M, Kuhlman DM. Personality and Risk-Taking: Common Bisocial Factors. J Pers. 2000 Dec;68(6):999–1029.

146. Gilman SE, Rende R, Boergers J, Abrams DB, Buka SL, Clark MA, et al. Parental smoking and adolescent smoking initiation: an intergenerational perspective on tobacco control. Pediatrics. 2009 Feb;123(2):e274-281.

147. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord, Lewden C, Bouteloup V, De Wit S, Sabin C, Mocroft A, et al. All-cause mortality in treated HIV-infected adults with CD4 ≥500/mm3 compared with the general population: evidence from a large European observational cohort collaboration. Int J Epidemiol. 2012 Apr;41(2):433–45.

148. Goncalves PH, Montezuma-Rusca JM, Yarchoan R, Uldrick TS. Cancer prevention in HIV-infected populations. Semin Oncol. 2016 Feb;43(1):173–88.

149. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med. 2011;62:141–55.

150. Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet Lond Engl. 1998 Nov 28;352(9142):1725–30.

151. Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998 Mar 26;338(13):853–60.

152. Smith CJ, Sabin CA, Lampe FC, Kinloch-de-Loes S, Gumley H, Carroll A, et al. The potential for CD4 cell increases in HIV-positive individuals who control viraemia with highly active antiretroviral therapy. AIDS Lond Engl. 2003 May 2;17(7):963–9.

153. Mocroft A, Phillips AN, Gatell J, Ledergerber B, Fisher M, Clumeck N, et al. Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study. Lancet Lond Engl. 2007 Aug 4;370(9585):407–13.

154. Guihot A, Tubiana R, Breton G, Marcelin A-G, Samri A, Assoumou L, et al. Immune and virological benefits of 10 years of permanent viral control with antiretroviral therapy. AIDS Lond Engl. 2010 Feb 20;24(4):614–7.

155. Hughes RA, May MT, Tilling K, Taylor N, Wittkop L, Reiss P, et al. Long terms trends in CD4+ cell counts, CD8+ cell counts, and the CD4+ : CD8+ ratio. AIDS Lond Engl. 2018 19;32(10):1361–7.

156. Kaufmann GR, Perrin L, Pantaleo G, Opravil M, Furrer H, Telenti A, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. Arch Intern Med. 2003 Oct 13;163(18):2187–95.

157. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. Clin Infect Dis Off Publ Infect Dis Soc Am. 2007 Feb 1;44(3):441–6.

158. Baker JV, Peng G, Rapkin J, Krason D, Reilly C, Cavert WP, et al. Poor initial CD4+ recovery with antiretroviral therapy prolongs immune depletion and increases risk for AIDS and non-AIDS diseases. J Acquir Immune Defic Syndr 1999. 2008 Aug 15;48(5):541–6.

159. Ingle SM, May MT, Gill MJ, Mugavero MJ, Lewden C, Abgrall S, et al. Impact of risk factors for specific causes of death in the first and subsequent years of antiretroviral therapy among HIV-infected patients. Clin Infect Dis Off Publ Infect Dis Soc Am. 2014 Jul 15;59(2):287–97.

160. Grabar S, Le Moing V, Goujard C, Leport C, Kazatchkine MD, Costagliola D, et al. Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral

therapy. Ann Intern Med. 2000 Sep 19;133(6):401–10.

161. Piketty C, Weiss L, Thomas F, Mohamed AS, Belec L, Kazatchkine MD. Long-term clinical outcome of human immunodeficiency virus-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen. J Infect Dis. 2001 May 1;183(9):1328–35.

162. Moore DM, Hogg RS, Yip B, Wood E, Tyndall M, Braitstein P, et al. Discordant immunologic and virologic responses to highly active antiretroviral therapy are associated with increased mortality and poor adherence to therapy. J Acquir Immune Defic Syndr 1999. 2005 Nov 1;40(3):288–93.

163. Tan R, Westfall AO, Willig JH, Mugavero MJ, Saag MS, Kaslow RA, et al. Clinical outcome of HIV-infected antiretroviral-naive patients with discordant immunologic and virologic responses to highly active antiretroviral therapy. J Acquir Immune Defic Syndr 1999. 2008 Apr 15;47(5):553–8.

164. Gilson RJC, Man S-L, Copas A, Rider A, Forsyth S, Hill T, et al. Discordant responses on starting highly active antiretroviral therapy: suboptimal CD4 increases despite early viral suppression in the UK Collaborative HIV Cohort (UK CHIC) Study. HIV Med. 2010 Feb;11(2):152–60.

165. Dronda F, Moreno S, Moreno A, Casado JL, Pérez-Elías MJ, Antela A. Long-term outcomes among antiretroviral-naive human immunodeficiency virus-infected patients with small increases in CD4+ cell counts after successful virologic suppression. Clin Infect Dis Off Publ Infect Dis Soc Am. 2002 Oct 15;35(8):1005–9.

166. Engsig FN, Gerstoft J, Kronborg G, Larsen CS, Pedersen G, Røge B, et al. Long-term mortality in HIV patients virally suppressed for more than three years with incomplete CD4 recovery: a cohort study. BMC Infect Dis. 2010 Nov 2;10:318.

167. Loutfy MR, Genebat M, Moore D, Raboud J, Chan K, Antoniou T, et al. A CD4+ cell count <200 cells per cubic millimeter at 2 years after initiation of combination antiretroviral therapy is associated with increased mortality in HIV-infected individuals with viral suppression. J Acquir Immune Defic Syndr 1999. 2010 Dec;55(4):451–9.

168. van Lelyveld SFL, Gras L, Kesselring A, Zhang S, De Wolf F, Wensing AMJ, et al. Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. AIDS Lond Engl. 2012 Feb 20;26(4):465–74.

169. Helleberg M, Kronborg G, Larsen CS, Pedersen G, Pedersen C, Obel N, et al. Poor CD4 response despite viral suppression is associated with increased non-AIDS-related mortality among HIV patients and their parents. AIDS Lond Engl. 2013 Mar 27;27(6):1021–6.

170. Trickey A, May MT, Vehreschild J, Obel N, Gill MJ, Crane H, et al. Cause-Specific Mortality in HIV-Positive Patients Who Survived Ten Years after Starting Antiretroviral Therapy. PloS One. 2016;11(8):e0160460.

171. Florence E, Lundgren J, Dreezen C, Fisher M, Kirk O, Blaxhult A, et al. Factors associated with a reduced CD4 lymphocyte count response to HAART despite full viral suppression in the EuroSIDA study. HIV Med. 2003 Jul;4(3):255–62.

172. Hunt PW, Deeks SG, Rodriguez B, Valdez H, Shade SB, Abrams DI, et al. Continued CD4 cell count increases in HIV-infected adults experiencing 4 years of viral suppression on antiretroviral therapy. AIDS Lond Engl. 2003 Sep 5;17(13):1907–15.

173. Gaardbo JC, Hartling HJ, Gerstoft J, Nielsen SD. Incomplete immune recovery in HIV infection: mechanisms, relevance for clinical care, and possible solutions. Clin Dev Immunol. 2012;2012:670957.

174. Gazzola L, Tincati C, Bellistrì GM, Monforte A d'Arminio, Marchetti G. The absence of CD4+ T cell count recovery despite receipt of virologically suppressive highly active antiretroviral therapy: clinical risk, immunological gaps, and therapeutic options. Clin Infect Dis Off Publ Infect Dis Soc Am. 2009 Feb 1;48(3):328–37.

175. Interleukin-2 Therapy in Patients with HIV Infection. N Engl J Med. 2009 Oct 15;361(16):1548–59.

176. Boatman JA, Baker JV, Emery S, Furrer H, Mushatt DM, Sedláček D, et al. Risk Factors for Low CD4+ Count Recovery Despite Viral Suppression Among Participants Initiating Antiretroviral Treatment

With CD4+ Counts > 500 Cells/mm3: Findings From the Strategic Timing of AntiRetroviral Therapy (START) Trial. J Acquir Immune Defic Syndr 1999. 2019 May 1;81(1):10–7.

177. Collazos J, Valle-Garay E, Carton JA, Montes AH, Suarez-Zarracina T, De la Fuente B, et al. Factors associated with long-term CD4 cell recovery in HIV-infected patients on successful antiretroviral therapy. HIV Med. 2016;17(7):532–41.

178. Riddler SA, Haubrich R, DiRienzo AG, Peeples L, Powderly WG, Klingman KL, et al. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med. 2008 May 15;358(20):2095–106.

179. Costagliola D, Lacombe J-M, Ghosn J, Delaugerre C, Pialoux G, Cuzin L, et al. CD4+ cell count recovery in naïve patients initiating cART, who achieved and maintained plasma HIV-RNA suppression. J Int AIDS Soc. 2014;17(4 Suppl 3):19481.

180. Luz PM, Grinsztejn B, Velasque L, Pacheco AG, Veloso VG, Moore RD, et al. Long-term CD4+ cell count in response to combination antiretroviral therapy. PloS One. 2014;9(4):e93039.

181. O'Connor JL, Smith CJ, Lampe FC, Hill T, Gompels M, Hay P, et al. Failure to achieve a CD4+ cell count response on combination antiretroviral therapy despite consistent viral load suppression. AIDS Lond Engl. 2014 Mar 27;28(6):919–24.

182. Montaner JS, Singer J, Schechter MT, Raboud JM, Tsoukas C, O'Shaughnessy M, et al. Clinical correlates of in vitro HIV-1 resistance ot zidovudine. Results of the Multicentre Canadian AZT Trial. AIDS Lond Engl. 1993 Feb;7(2):189–96.

183. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. Delta Coordinating Committee. Lancet Lond Engl. 1996 Aug 3;348(9023):283–91.

184. Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez C, McMahon D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med. 1997 Sep 11;337(11):734–9.

185. Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez C, McMahon D, et al. Simultaneous vs sequential initiation of therapy with indinavir, zidovudine, and lamivudine for HIV-1 infection: 100-week follow-up. JAMA. 1998 Jul 1;280(1):35–41.

186. Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. Ann Intern Med. 1999 Jul 20;131(2):81–7.

187. Havlir DV, Hellmann NS, Petropoulos CJ, Whitcomb JM, Collier AC, Hirsch MS, et al. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. JAMA. 2000 Jan 12;283(2):229–34.

188. Abram ME, Ferris AL, Shao W, Alvord WG, Hughes SH. Nature, position, and frequency of mutations made in a single cycle of HIV-1 replication. J Virol. 2010 Oct;84(19):9864–78.

189. Coffin JM. HIV population dynamics in vivo: implications for genetic variation, pathogenesis, and therapy. Science. 1995 Jan 27;267(5197):483–9.

190. Collier AC, Coombs RW, Schoenfeld DA, Bassett RL, Timpone J, Baruch A, et al. Treatment of human immunodeficiency virus infection with saquinavir, zidovudine, and zalcitabine. AIDS Clinical Trials Group. N Engl J Med. 1996 Apr 18;334(16):1011–7.

191. Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. N Engl J Med. 1997 Sep 11;337(11):725–33.

192. Cameron DW, Heath-Chiozzi M, Danner S, Cohen C, Kravcik S, Maurath C, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. The Advanced HIV Disease Ritonavir Study Group. Lancet Lond Engl. 1998 Feb 21;351(9102):543–9.

193. Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiest D, Stanford J, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and

lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. N Engl J Med. 1999 Dec 16;341(25):1865–73.

194. Barreiro P, Soriano V, Blanco F, Casimiro C, de la Cruz JJ, González-Lahoz J. Risks and benefits of replacing protease inhibitors by nevirapine in HIV-infected subjects under long-term successful triple combination therapy. AIDS Lond Engl. 2000 May 5;14(7):807–12.

195. FDA. HIV/AIDS Historical Time Line 1995-1999 [Internet]. [cited 2018 May 11]. Available from: https://www.fda.gov/ForPatients/Illness/HIVAIDS/History/ucm151079.htm

196. Sulkowski MS, Mehta SH, Chaisson RE, Thomas DL, Moore RD. Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir. AIDS Lond Engl. 2004 Nov 19;18(17):2277–84.

197. Cardiello PG, Monhaphol T, Mahanontharit A, van Heeswijk RP, Burger D, Hill A, et al. Pharmacokinetics of once-daily saquinavir hard-gelatin capsules and saquinavir soft-gelatin capsules boosted with ritonavir in HIV-1-infected subjects. J Acquir Immune Defic Syndr 1999. 2003 Apr 1;32(4):375–9.

198. Arribas JR. Drugs in traditional drug classes (nucleoside reverse transcriptase inhibitor/nonnucleoside reverse transcriptase inhibitor/protease inhibitors) with activity against drug-resistant virus (tipranavir, darunavir, etravirine). Curr Opin HIV AIDS. 2009 Nov;4(6):507–12.

199. Madruga JV, Berger D, McMurchie M, Suter F, Banhegyi D, Ruxrungtham K, et al. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. Lancet Lond Engl. 2007 Jul 7;370(9581):49–58.

200. Arastéh K, Yeni P, Pozniak A, Grinsztejn B, Jayaweera D, Roberts A, et al. Efficacy and safety of darunavir/ritonavir in treatment-experienced HIV type-1 patients in the POWER 1, 2 and 3 trials at week 96. Antivir Ther. 2009;14(6):859–64.

201. Kirk O, Katzenstein TL, Gerstoft J, Mathiesen L, Nielsen H, Pedersen C, et al. Combination therapy containing ritonavir plus saquinavir has superior short-term antiretroviral efficacy: a randomized trial. AIDS Lond Engl. 1999 Jan 14;13(1):F9-16.

202. Mathez D, Bagnarelli P, Gorin I, Katlama C, Pialoux G, Saimot G, et al. Reductions in viral load and increases in T lymphocyte numbers in treatment-naive patients with advanced HIV-1 infection treated with ritonavir, zidovudine and zalcitabine triple therapy. Antivir Ther. 1997 Jul;2(3):175–83.

203. Walli R, Herfort O, Michl GM, Demant T, Jäger H, Dieterle C, et al. Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1-infected patients. AIDS Lond Engl. 1998 Oct 22;12(15):F167-173.

204. Behrens G, Dejam A, Schmidt H, Balks HJ, Brabant G, Körner T, et al. Impaired glucose tolerance, beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors. AIDS Lond Engl. 1999 Jul 9;13(10):F63-70.

205. Guest JL, Ruffin C, Tschampa JM, DeSilva KE, Rimland D. Differences in rates of diarrhea in patients with human immunodeficiency virus receiving lopinavir-ritonavir or nelfinavir. Pharmacotherapy. 2004 Jun;24(6):727–35.

206. Pillay P, Ford N, Shubber Z, Ferrand RA. Outcomes for efavirenz versus nevirapine-containing regimens for treatment of HIV-1 infection: a systematic review and meta-analysis. PloS One. 2013;8(7):e68995.

207. Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. N Engl J Med. 2006 Jan 19;354(3):251–60.

208. Melikian GL, Rhee S-Y, Varghese V, Porter D, White K, Taylor J, et al. Non-nucleoside reverse transcriptase inhibitor (NNRTI) cross-resistance: implications for preclinical evaluation of novel NNRTIs and clinical genotypic resistance testing. J Antimicrob Chemother. 2014 Jan;69(1):12–20.

209. Shafer RW, Smeaton LM, Robbins GK, De Gruttola V, Snyder SW, D'Aquila RT, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1

infection. N Engl J Med. 2003 Dec 11;349(24):2304–15.

210. Kakuda TN, Schöller-Gyüre M, Hoetelmans RMW. Pharmacokinetic interactions between etravirine and non-antiretroviral drugs. Clin Pharmacokinet. 2011 Jan;50(1):25–39.

211. Cohen C, Wohl D, Arribas JR, Henry K, Van Lunzen J, Bloch M, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs. efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV-1-infected adults. AIDS Lond Engl. 2014 Apr 24;28(7):989–97.

212. Drug Approval Package: PIFELTRO (doravirine) [Internet]. Drugs@FDA. [cited 2019 Feb 26]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210806Orig1s000,210807Orig1s000TOC.cfm

213. Hare CB, Mellors J, Krambrink A, Su Z, Skiest D, Margolis DM, et al. Detection of nonnucleoside reverse-transcriptase inhibitor-resistant HIV-1 after discontinuation of virologically suppressive antiretroviral therapy. Clin Infect Dis Off Publ Infect Dis Soc Am. 2008 Aug 1;47(3):421–4.

214. Mollan KR, Tierney C, Hellwege JN, Eron JJ, Hudgens MG, Gulick RM, et al. Race/Ethnicity and the Pharmacogenetics of Reported Suicidality With Efavirenz Among Clinical Trials Participants. J Infect Dis. 2017 01;216(5):554–64.

215. Antinori A, Zaccarelli M, Cingolani A, Forbici F, Rizzo MG, Trotta MP, et al. Cross-resistance among nonnucleoside reverse transcriptase inhibitors limits recycling efavirenz after nevirapine failure. AIDS Res Hum Retroviruses. 2002 Aug 10;18(12):835–8.

216. Margolis AM, Heverling H, Pham PA, Stolbach A. A review of the toxicity of HIV medications. J Med Toxicol Off J Am Coll Med Toxicol. 2014 Mar;10(1):26–39.

217. Venhoff N, Setzer B, Melkaoui K, Walker UA. Mitochondrial toxicity of tenofovir, emtricitabine and abacavir alone and in combination with additional nucleoside reverse transcriptase inhibitors. Antivir Ther. 2007;12(7):1075–85.

218. DAD Study Group, Friis-Møller N, Reiss P, Sabin CA, Weber R, Monforte A d'Arminio, et al. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med. 2007 Apr 26;356(17):1723–35.

219. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JMAH, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA. 2004 Jul 14;292(2):191–201.

220. Smith KY, Patel P, Fine D, Bellos N, Sloan L, Lackey P, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. AIDS Lond Engl. 2009 Jul 31;23(12):1547–56.

221. Cassetti I, Madruga JVR, Suleiman JMAH, Etzel A, Zhong L, Cheng AK, et al. The safety and efficacy of tenofovir DF in combination with lamivudine and efavirenz through 6 years in antiretroviral-naïve HIV-1-infected patients. HIV Clin Trials. 2007 Jun;8(3):164–72.

222. McManus H, Li P, Nolan D, Bloch M, Kiertiburanakul S, Choi J, et al. Does use of antiretroviral therapy regimens with high central nervous system penetration improve survival in HIV-infected adults?: Effect of neurocART on survival in APHOD. HIV Med. 2011 Nov;12(10):610–9.

223. Obel N, Farkas DK, Kronborg G, Larsen CS, Pedersen G, Riis A, et al. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. HIV Med. 2010 Feb;11(2):130–6.

224. Brown TT, McComsey GA, King MS, Qaqish RB, Bernstein BM, da Silva BA. Loss of Bone Mineral Density After Antiretroviral Therapy Initiation, Independent of Antiretroviral Regimen: JAIDS J Acquir Immune Defic Syndr. 2009 Aug;51(5):554–61.

225. Cooper DA, Heera J, Goodrich J, Tawadrous M, Saag M, Dejesus E, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naive subjects with CCR5-tropic HIV-1 infection. J Infect Dis. 2010 Mar 15;201(6):803–13.

226. Fätkenheuer G, Pozniak AL, Johnson MA, Plettenberg A, Staszewski S, Hoepelman AIM, et al. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1. Nat Med. 2005 Nov;11(11):1170–2.

227. Fuzeon review [Internet]. www.accessdata.fda.gov. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/021481_fuzeon_review.cfm

228. Selzentry review [Internet]. www.accessdata.fda.gov. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022128_selzentry_toc.cfm

229. Lohse N, Obel N, Kronborg G, Laursen A, Pedersen C, Larsen CS, et al. Declining risk of triple-class antiretroviral drug failure in Danish HIV-infected individuals. AIDS Lond Engl. 2005 May 20;19(8):815–22.

230. Pursuing Later Treatment Options II (PLATO II) Project Team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE), Lodwick R, Costagliola D, Reiss P, Torti C, Teira R, et al. Triple-class virologic failure in HIV-infected patients undergoing antiretroviral therapy for up to 10 years. Arch Intern Med. 2010 Mar 8;170(5):410–9.

231. Borges ÁH, Lundh A, Tendal B, Bartlett JA, Clumeck N, Costagliola D, et al. Nonnucleoside Reverse-transcriptase Inhibitor- vs Ritonavir-boosted Protease Inhibitor-based Regimens for Initial Treatment of HIV Infection: A Systematic Review and Metaanalysis of Randomized Trials. Clin Infect Dis Off Publ Infect Dis Soc Am. 2016 15;63(2):268–80.

232. Phillips AN, Leen C, Wilson A, Anderson J, Dunn D, Schwenk A, et al. Risk of extensive virological failure to the three original antiretroviral drug classes over long-term follow-up from the start of therapy in patients with HIV infection: an observational cohort study. Lancet Lond Engl. 2007 Dec 8;370(9603):1923–8.

233. Harrigan PR, Hogg RS, Dong WWY, Yip B, Wynhoven B, Woodward J, et al. Predictors of HIV drug-resistance mutations in a large antiretroviral-naive cohort initiating triple antiretroviral therapy. J Infect Dis. 2005 Feb 1;191(3):339–47.

234. Lampe FC, Gatell JM, Staszewski S, Johnson MA, Pradier C, Gill MJ, et al. Changes Over Time in Risk of Initial Virological Failure of Combination Antiretroviral Therapy: A Multicohort Analysis, 1996 to 2002. Arch Intern Med. 2006 Mar 13;166(5):521.

235. EACS guidelines 2018, Version 1.2 [Internet]. eacsociety.org. [cited 2019 Feb 26]. Available from: http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf

236. Approval Date and History, Labels, Reviews for NDA 210251 [Internet]. Drugs@FDA: FDA Approved Drug Products. [cited 2019 Feb 26]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=210251

237. Drug Approval Package NDA 022145 [Internet]. Drugs@FDA. [cited 2019 Feb 26]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022145_Isentress.cfm

238. Products on NDA 204790 [Internet]. Drugs@FDA: FDA Approved Drug Products. [cited 2019 Feb 26]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=204790

239. Steigbigel RT, Cooper DA, Kumar PN, Eron JE, Schechter M, Markowitz M, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. N Engl J Med. 2008 Jul 24;359(4):339–54.

240. Eron JJ, Cooper DA, Steigbigel RT, Clotet B, Gatell JM, Kumar PN, et al. Efficacy and safety of raltegravir for treatment of HIV for 5 years in the BENCHMRK studies: final results of two randomised, placebo-controlled trials. Lancet Infect Dis. 2013 Jul;13(7):587–96.

241. Sax PE, DeJesus E, Mills A, Zolopa A, Cohen C, Wohl D, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet Lond Engl. 2012 Jun 30;379(9835):2439–48.

242. Stellbrink H-J, Reynes J, Lazzarin A, Voronin E, Pulido F, Felizarta F, et al. Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. AIDS. 2013 Jul;27(11):1771–8.

243. Yazdanpanah Y, Fagard C, Descamps D, Taburet AM, Colin C, Roquebert B, et al. High rate of virologic suppression with raltegravir plus etravirine and darunavir/ritonavir among treatment-experienced patients infected with multidrug-resistant HIV: results of the ANRS 139 TRIO trial. Clin Infect Dis Off Publ Infect Dis Soc Am. 2009 Nov 1;49(9):1441–9.

244. Fagard C, Colin C, Charpentier C, Rami A, Jacomet C, Yeni P, et al. Long-term efficacy and safety of raltegravir, etravirine, and darunavir/ritonavir in treatment-experienced patients: week 96 results from the ANRS 139 TRIO trial. J Acquir Immune Defic Syndr 1999. 2012 Apr 15;59(5):489–93.

245. Cahn P, Kaplan R, Sax PE, Squires K, Molina J-M, Avihingsanon A, et al. Raltegravir 1200 mg once daily versus raltegravir 400 mg twice daily, with tenofovir disoproxil fumarate and emtricitabine, for previously untreated HIV-1 infection: a randomised, double-blind, parallel-group, phase 3, non-inferiority trial. Lancet HIV. 2017 Nov;4(11):e486–94.

246. Bucciardini R, D'Ettorre G, Baroncelli S, Ceccarelli G, Parruti G, Weimer LE, et al. Virological failure at one year in triple-class experienced patients switching to raltegravir-based regimens is not predicted by baseline factors. Int J STD AIDS. 2012 Jul;23(7):459–63.

247. Capetti A, Landonio S, Meraviglia P, Di Biagio A, Lo Caputo S, Sterrantino G, et al. 96 Week follow-up of HIV-infected patients in rescue with raltegravir plus optimized backbone regimens: a multicentre Italian experience. PloS One. 2012;7(7):e39222.

248. Teague A, Scott C, Bower M, Gazzard B, Nelson M, Stebbing J. A single-center cohort experience of raltegravir in salvage patients failing therapy. J Acquir Immune Defic Syndr 1999. 2010 Apr;53(5):666–7.

249. Nozza S, Galli L, Bigoloni A, Gianotti N, Spagnuolo V, Carbone A, et al. Four-year outcome of a PI and NRTI-sparing salvage regimen: maraviroc, raltegravir, etravirine. New Microbiol. 2014 Apr;37(2):145–51.

250. Lennox JL, DeJesus E, Lazzarin A, Pollard RB, Madruga JVR, Berger DS, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet Lond Engl. 2009 Sep 5;374(9692):796–806.

251. Rockstroh JK, DeJesus E, Lennox JL, Yazdanpanah Y, Saag MS, Wan H, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. J Acquir Immune Defic Syndr 1999. 2013 May 1;63(1):77–85.

252. Edwards JK, Cole SR, Hall HI, Mathews WC, Moore RD, Mugavero MJ, et al. Virologic suppression and CD4 cell count recovery after initiation of raltegravir- or efavirenz- containing HIV treatment regimens: AIDS. 2017 Nov;1.

253. d'Arminio Monforte A, Lorenzini P, Cozzi-Lepri A, Mussini C, Castagna A, Baldelli F, et al. Durability and tolerability of first-line regimens including two nucleoside reverse transcriptase inhibitors and raltegravir or ritonavir boosted-atazanavir or -darunavir: data from the ICONA Cohort. HIV Clin Trials. 2018 Mar;1–9.

254. Hill AM, Mitchell N, Hughes S, Pozniak AL. Risks of cardiovascular or central nervous system adverse events and immune reconstitution inflammatory syndrome, for dolutegravir versus other antiretrovirals: meta-analysis of randomized trials. Curr Opin HIV AIDS. 2018;13(2):102–11.

255. Hoffmann C, Welz T, Sabranski M, Kolb M, Wolf E, Stellbrink H-J, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med. 2017;18(1):56–63.

256. Mathias A, West S, Hui J, Kearney B. Dose–Response of Ritonavir on Hepatic CYP3A Activity and Elvitegravir Oral Exposure. Clin Pharmacol Ther. 2009 Jan;85(1):64–70.

257. Menard A, Meddeb L, Tissot-Dupont H, Ravaux I, Dhiver C, Mokhtari S, et al. Dolutegravir and weight gain: an unexpected bothering side effect? AIDS Lond Engl. 2017 Jun 19;31(10):1499–500.

258. Vannappagari V, Thorne C, for APR* and EPPICC. Pregnancy and Neonatal Outcomes Following Prenatal Exposure to Dolutegravir. J Acquir Immune Defic Syndr 1999. 2019 Mar 29;

259. Sax PE, Pozniak A, Montes ML, Koenig E, DeJesus E, Stellbrink H-J, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet Lond Engl. 2017 Nov 4;390(10107):2073–82.

260. Clavel F, Hance AJ. HIV drug resistance. N Engl J Med. 2004 Mar 4;350(10):1023–35.

261. Martin M, Del Cacho E, Codina C, Tuset M, De Lazzari E, Mallolas J, et al. Relationship between adherence level, type of the antiretroviral regimen, and plasma HIV type 1 RNA viral load: a prospective cohort study. AIDS Res Hum Retroviruses. 2008 Oct;24(10):1263–8.

262. Bangsberg DR, Perry S, Charlebois ED, Clark RA, Roberston M, Zolopa AR, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS Lond Engl. 2001 Jun 15;15(9):1181–3.

263. Hogg RS, Heath K, Bangsberg D, Yip B, Press N, O'Shaughnessy MV, et al. Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up. AIDS Lond Engl. 2002 May 3;16(7):1051–8.

264. Wood E, Hogg RS, Yip B, Moore D, Harrigan PR, Montaner JSG. Impact of baseline viral load and adherence on survival of HIV-infected adults with baseline CD4 cell counts > or = 200 cells/microl. AIDS Lond Engl. 2006 May 12;20(8):1117–23.

265. d'Arminio Monforte A, Lepri AC, Rezza G, Pezzotti P, Antinori A, Phillips AN, et al. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naïve patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naïve Patients. AIDS Lond Engl. 2000 Mar 31;14(5):499–507.

266. Yuan Y, L'Italien G, Mukherjee J, Iloeje U. Determinants of discontinuation of initial highly active antiretroviral therapy regimens in a US HIV-infected patient cohort*. HIV Med. 2006 Apr;7(3):156–62.

267. Combivir [Internet]. www.fda.gov. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/20857s030lbl.pdf

268. Pozniak AL, Gallant JE, DeJesus E, Arribas JR, Gazzard B, Campo RE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes--a 96-week analysis. J Acquir Immune Defic Syndr 1999. 2006 Dec 15;43(5):535–40.

269. Elzi L, Marzolini C, Furrer H, Ledergerber B, Cavassini M, Hirschel B, et al. Treatment modification in human immunodeficiency virus-infected individuals starting combination antiretroviral therapy between 2005 and 2008. Arch Intern Med. 2010 Jan 11;170(1):57–65.

270. Horberg MA, Klein DB. An update on the use of Atripla in the treatment of HIV in the United States. HIVAIDS Auckl NZ. 2010;2:135–40.

271. EACS Guidelines 2014, version 7.1 [Internet]. eacssociety.org. Available from: http://www.eacsociety.org/files/guidelines-7.1-english.pdf

272. Patents and licences on antiretrovirals: A snapshot [Internet]. Essential Medicines and Health Products Information Portal A World Health Organization resource; 2014 Apr. Available from: https://apps.who.int/medicinedocs/documents/s21437en/s21437en.pdf

273. Walensky RP, Sax PE, Nakamura YM, Weinstein MC, Pei PP, Freedberg KA, et al. Economic savings versus health losses: the cost-effectiveness of generic antiretroviral therapy in the United States. Ann Intern Med. 2013 Jan 15;158(2):84–92.

274. Hill A, Hill T, Jose S, Pozniak A. Predicted savings to the UK National Health Service from switching to generic antiretrovirals, 2014-2018. J Int AIDS Soc. 2014;17(4 Suppl 3):19497.

275. Restelli U, Scolari F, Bonfanti P, Croce D, Rizzardini G. New Highly Active Antiretroviral

drugs and generic drugs for the treatment of HIV infection: a budget impact analysis on the Italian National Health Service (Lombardy Region, Northern Italy). BMC Infect Dis. 2015 Aug 11;15:323.

276. Pharmacological equivalence and clinical interchangeability of lamivudine and emtricitabine: a review of current literature. 2013. [Internet]. www.who.int. Available from: http://www.who.int/hiv/pub/treatment2/lamivudine_emtricibatine/en/.

277. Ford N, Vitoria M, Doherty M, Gray A. Candidates for inclusion in a universal antiretroviral regimen: are lamivudine and emtricitabine interchangeable? Curr Opin HIV AIDS. 2017 Jul;12(4):334–8.

278. Harzke AJ, Diaz M, Tong E, Baillargeon G, Zepeda S, Koranek A, et al. Substituting Generic Lamivudine for Emtricitabine in Virologically Suppressed HIV-Infected Patients. J Correct Health Care Off J Natl Comm Correct Health Care. 2018;24(4):371–81.

279. Ramjan R, Calmy A, Vitoria M, Mills EJ, Hill A, Cooke G, et al. Systematic review and meta-analysis: Patient and programme impact of fixed-dose combination antiretroviral therapy. Trop Med Int Health TM IH. 2014 May;19(5):501–13.

280. Langebeek N, Gisolf EH, Reiss P, Vervoort SC, Hafsteinsdóttir TB, Richter C, et al. Predictors and correlates of adherence to combination antiretroviral therapy (ART) for chronic HIV infection: a meta-analysis. BMC Med [Internet]. 2014 Dec [cited 2019 Jun 17];12(1). Available from: http://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-014-0142-1

281. Clay PG, Yuet WC, Moecklinghoff CH, Duchesne I, Tronczyński KL, Shah S, et al. A meta-analysis comparing 48-week treatment outcomes of single and multi-tablet antiretroviral regimens for the treatment of people living with HIV. AIDS Res Ther. 2018 30;15(1):17.

282. Altice F, Evuarherhe O, Shina S, Carter G, Beaubrun AC. Adherence to HIV treatment regimens: systematic literature review and meta-analysis. Patient Prefer Adherence. 2019;13:475–90.

283. Læger er hurtige til at følge skiftende anbefalinger for hiv-behandling. 2012 Oct 1; Available from: https://dagensmedicin.dk/lager-er-hurtige-til-at-folge-skiftende-anbefalinger-for-hiv-behandling

284. Dejesus E, Young B, Morales-Ramirez JO, Sloan L, Ward DJ, Flaherty JF, et al. Simplification of antiretroviral therapy to a single-tablet regimen consisting of efavirenz, emtricitabine, and tenofovir disoproxil fumarate versus unmodified antiretroviral therapy in virologically suppressed HIV-1-infected patients. J Acquir Immune Defic Syndr 1999. 2009 Jun 1;51(2):163–74.

285. Marcelin A-G, Delaugerre C, Wirden M, Viegas P, Simon A, Katlama C, et al. Thymidine analogue reverse transcriptase inhibitors resistance mutations profiles and association to other nucleoside reverse transcriptase inhibitors resistance mutations observed in the context of virological failure. J Med Virol. 2004 Jan;72(1):162–5.

286. Svicher V, Alteri C, Artese A, Forbici F, Santoro MM, Schols D, et al. Different evolution of genotypic resistance profiles to emtricitabine versus lamivudine in tenofovir-containing regimens. J Acquir Immune Defic Syndr 1999. 2010 Nov;55(3):336–44.

287. Marcelin AG, Charpentier C, Wirden M, Landman R, Valantin MA, Simon A, et al. Resistance profiles of emtricitabine and lamivudine in tenofovir-containing regimens. J Antimicrob Chemother. 2012 Jun;67(6):1475–8.

288. Rousseau FS, Wakeford C, Mommeja-Marin H, Sanne I, Moxham C, Harris J, et al. Prospective randomized trial of emtricitabine versus lamivudine short-term monotherapy in human immunodeficiency virus-infected patients. J Infect Dis. 2003 Dec 1;188(11):1652–8.

289. McColl DJ, Margot N, Chen S-S, Harris J, Borroto-Esoda K, Miller MD. Reduced emergence of the M184V/I resistance mutation when antiretroviral-naïve subjects use emtricitabine versus lamivudine in regimens composed of two NRTIs plus the NNRTI efavirenz. HIV Clin Trials. 2011 Apr;12(2):61–70.

290. Hardweir V. Abstract O6: The next generiction update [Internet]. 23rd Annual Conference of

BHIVA Presentations; 2017 Apr 5. Available from: https://www.bhiva.org/170405VenitaHardweir

291. Krentz HB, Campbell S, Lahl M, Gill MJ. De-simplifying single-tablet antiretroviral treatments: uptake, risks and cost savings. HIV Med. 2019 Mar;20(3):214–21.

292. Krentz HB, Campbell S, Gill VC, Gill MJ. Patient perspectives on de-simplifying their single-tablet co-formulated antiretroviral therapy for societal cost savings. HIV Med. 2018 Apr;19(4):290–8.

293. Jacomet C, Allavena C, Peyrol F, Pereira B, Joubert LM, Bagheri H, et al. Perception of antiretroviral generic medicines: one-day survey of HIV-infected patients and their physicians in France. PloS One. 2015;10(2):e0117214.

294. Rwagitinywa J, Sommet A, Palmaro A, Montastruc J-L, Lapeyre-Mestre M. Utilization and costs of HIV antiretroviral drugs in Europe during the last ten years: Impact of generic antiretroviral drugs on cost reduction. Health Policy [Internet]. 2018 Jan [cited 2018 Mar 15]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0168851018300046

295. Olalla J, Pérez-Stachowski J, Tortajada B, Del Arco A, Márquez E, De la Torre J, et al. Efficacy and safety of the switch of Triumeq® to generic (abacavir + lamivudine) + Tivicay®: data at 24 weeks. BMC Pharmacol Toxicol. 2018 Oct 10;19(1):63.

296. Engelhard EAN, Smit C, Vervoort SCJM, Smit PJ, Nieuwkerk PT, Kroon FP, et al. Patients' Willingness to Take Multiple-Tablet Antiretroviral Therapy Regimens for Treatment of HIV. Drugs - Real World Outcomes. 2016 Jun;3(2):223–30.

297. Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan [Internet]. Europeans Medicines Agency. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/efavirenzemtricitabinetenofovir-disoproxil-mylan

298. Emtricitabine/Tenofovir disoproxil Zentiva [Internet]. European Medicines Agency. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/emtricitabinetenofovir-disoproxil-zentiva

299. Vernazza P, Hirschel B, Bernasconi E, Flepp M. Les personnes séropositives ne souffrant d'aucune autre MST et suivant un traitement antirétroviral efficace ne transmettent pas le VIH par voie. Bull Med Suisses. 2008;89.

300. Melo MG, Santos BR, De Cassia Lira R, Varella IS, Turella ML, Rocha TM, et al. Sexual transmission of HIV-1 among serodiscordant couples in Porto Alegre, southern Brazil. Sex Transm Dis. 2008 Nov;35(11):912–5.

301. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med. 2000 Mar 30;342(13):921–9.

302. Castilla J, Del Romero J, Hernando V, Marincovich B, García S, Rodríguez C. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. J Acquir Immune Defic Syndr 1999. 2005 Sep 1;40(1):96–101.

303. Barreiro P, del Romero J, Leal M, Hernando V, Asencio R, de Mendoza C, et al. Natural pregnancies in HIV-serodiscordant couples receiving successful antiretroviral therapy. J Acquir Immune Defic Syndr 1999. 2006 Nov 1;43(3):324–6.

304. Porco TC, Martin JN, Page-Shafer KA, Cheng A, Charlebois E, Grant RM, et al. Decline in HIV infectivity following the introduction of highly active antiretroviral therapy. AIDS Lond Engl. 2004 Jan 2;18(1):81–8.

305. Adam BD, Corriveau P, Elliott R, Globerman J, English K, Rourke S. HIV disclosure as practice and public policy. Crit Public Health. 2015 Aug 8;25(4):386–97.

306. Barré-Sinoussi F, Abdool Karim SS, Albert J, Bekker L-G, Beyrer C, Cahn P, et al. Expert consensus statement on the science of HIV in the context of criminal law. J Int AIDS Soc. 2018 Jul;21(7):e25161.

307. Cohen MS. HIV Treatment as Prevention and "The Swiss Statement": in for a Dime, in for a Dollar? Clin Infect Dis. 2010 Dec;51(11):1323–4.

308. Cu-Uvin S, DeLong AK, Venkatesh KK, Hogan JW, Ingersoll J, Kurpewski J, et al. Genital tract HIV-1 RNA shedding among women with below detectable plasma viral load. AIDS Lond Engl. 2010 Oct 23;24(16):2489–97.

309. Dornadula G, Zhang H, VanUitert B, Stern J, Livornese L, Ingerman MJ, et al. Residual HIV-1 RNA in blood plasma of patients taking suppressive highly active antiretroviral therapy. JAMA. 1999 Nov 3;282(17):1627–32.

310. Nunnari G, Otero M, Dornadula G, Vanella M, Zhang H, Frank I, et al. Residual HIV-1 disease in seminal cells of HIV-1-infected men on suppressive HAART: latency without on-going cellular infections. AIDS Lond Engl. 2002 Jan 4;16(1):39–45.

311. Zhang H, Dornadula G, Beumont M, Livornese L, Van Uitert B, Henning K, et al. Human immunodeficiency virus type 1 in the semen of men receiving highly active antiretroviral therapy. N Engl J Med. 1998 Dec 17;339(25):1803–9.

312. Mocroft A, Ruiz L, Reiss P, Ledergerber B, Katlama C, Lazzarin A, et al. Virological rebound after suppression on highly active antiretroviral therapy. AIDS Lond Engl. 2003 Aug 15;17(12):1741–51.

313. Smith CJ, Phillips AN, Dauer B, Johnson MA, Lampe FC, Youle MS, et al. Factors associated with viral rebound among highly treatment-experienced HIV-positive patients who have achieved viral suppression. HIV Med. 2009 Jan;10(1):19–27.

314. Geretti AM, Smith C, Haberl A, Garcia-Diaz A, Nebbia G, Johnson M, et al. Determinants of virological failure after successful viral load suppression in first-line highly active antiretroviral therapy. Antivir Ther. 2008;13(7):927–36.

315. Benzie AA, Bansi LK, Sabin CA, Portsmouth S, Hill T, Johnson M, et al. Increased duration of viral suppression is associated with lower viral rebound rates in patients with previous treatment failures: AIDS. 2007 Jul;21(11):1423–30.

316. Lampe FC, Smith CJ, Madge S, Kinloch-de Loes S, Tyrer M, Sabin CA, et al. Success of clinical care for human immunodeficiency virus infection according to demographic group among sexually infected patients in a routine clinic population, 1999 to 2004. Arch Intern Med. 2007 Apr 9;167(7):692–700.

317. May MT, Sterne JAC, Costagliola D, Sabin CA, Phillips AN, Justice AC, et al. HIV treatment response and prognosis in Europe and North America in the first decade of highly active antiretroviral therapy: a collaborative analysis. Lancet Lond Engl. 2006 Aug 5;368(9534):451–8.

318. Ballif M, Ledergerber B, Battegay M, Cavassini M, Bernasconi E, Schmid P, et al. Impact of previous virological treatment failures and adherence on the outcome of antiretroviral therapy in 2007. PloS One. 2009 Dec 14;4(12):e8275.

319. Smith CJ, Phillips AN, Hill T, Fisher M, Gazzard B, Porter K, et al. The Rate of Viral Rebound after Attainment of an HIV Load <50 Copies/mL According to Specific Antiretroviral Drugs in Use: Results from a Multicenter Cohort Study. J Infect Dis. 2005 Oct 15;192(8):1387–97.

320. O'Connor J, Smith C, Lampe FC, Johnson MA, Chadwick DR, Nelson M, et al. Durability of viral suppression with first-line antiretroviral therapy in patients with HIV in the UK: an observational cohort study. Lancet HIV. 2017;4(7):e295–302.

321. Donnell D, Baeten JM, Kiarie J, Thomas KK, Stevens W, Cohen CR, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet Lond Engl. 2010 Jun 12;375(9731):2092–8.

322. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. N Engl J Med. 2016 01;375(9):830–9.

323. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, van Lunzen J, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. JAMA. 2016 Jul 12;316(2):171–81.

324. Jean K, Gabillard D, Moh R, Danel C, Fassassi R, Desgrées-du-Loû A, et al. Effect of early antiretroviral therapy on sexual behaviors and HIV-1 transmission risk among adults with diverse heterosexual partnership statuses in Côte d'Ivoire. J Infect Dis. 2014 Feb 1;209(3):431–40.

325. Hoornenborg E, Coyer L, Achterbergh RCA, Matser A, Schim van der Loeff MF, Boyd A, et al. Sexual behaviour and incidence of HIV and sexually transmitted infections among men who have sex with men using daily and event-driven pre-exposure prophylaxis in AMPrEP: 2 year results from a demonstration study. Lancet HIV. 2019 Jun 6;

326. Fonner VA, Dalglish SL, Kennedy CE, Baggaley R, O'Reilly KR, Koechlin FM, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. AIDS Lond Engl. 2016 31;30(12):1973–83.

327. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. The Lancet. 2016 Jan;387(10013):53–60.

328. Molina J-M, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med. 2015 Dec 3;373(23):2237–46.

329. Molina J-M, Charreau I, Spire B, Cotte L, Chas J, Capitant C, et al. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV. 2017 Sep;4(9):e402–10.