



Consequences of HBV infection in HIV-positive individuals in Sub Saharan Africa during the era of early antiretroviral therapy

Menan Gérard Kouame

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POUR OBTENIR LE GRADE DE

DOCTEUR DE
L'UNIVERSITÉ DE BORDEAUX

ÉCOLE DOCTORALE
SPÉCIALITÉ DE LA SANTÉ PUBLIQUE

Par Menan Gérard KOUAME

**CONSÉQUENCES DE L'INFECTION PAR LE VHB CHEZ LES
PERSONNES VIH-POSITIVES EN AFRIQUE
SUBSAHARIENNE A L'ÈRE DU TRAITEMENT
ANTIRÉTROVIRALE PRÉCOCE**

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Présenté le 31 mars 2021

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Aux membres du jury

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ABBREVIATIONS

3TC: lamivudine

Ag: antigen

Anti-HBcAb: antibody against hepatitis B core antigen

Anti-HBsAb: antibody against Hepatitis B surface antigen

Anti-HBeAb: antibody against Hepatitis B surface antigen

cccDNA: covalently closed circular deoxyribonucleic acid

DBS: Dried Blood Spot

DNA: deoxyribonucleic acid

EPI: Expanded Programme on Immunization

ESLD: End Stage of Liver Disease

HBeAg: hepatitis B envelop antigen

HBsAg: hepatitis B surface antigen

HBV: hepatitis B virus

HepB_BD: hepatitis B birth-dose vaccination in newborns (within first 24 hours of life)

HepB3: hepatitis B vaccination with 3 doses in infants

HIV: human immunodeficiency virus

IDUs: injection drug uses

INH: Isoniazid

MSM: men who have sex with men

NAs: Nucleoside/nucleotide analogs

NCD: non communicable disease

PeP: post exposition prophylaxis

PrEP: Pre Exposure Prophylaxis

POC: point of care

PWID: people who inject drugs

PLWH: People Living with HIV

RNA: ribonucleic acid

STI: sexually transmitted infection

SVR: sustained virological response

TDF : tenofovir disoproxil fumarate

TAF : tenofovir alafenamide

TasP: treatment as prevention

UNAIDS: Joint United Nations Programme on HIV/AIDS

VL: viral load

WHO: World Health Organization.

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RESUME

Introduction :

En 2018, il y avait 37,9 millions [32,7-44,0] de personnes infectées par le VIH dans le monde, dont 36,2 millions [31,3-42,0] étaient des adultes. 1,7 million de personnes ont été nouvellement infectées et le nombre annuel de nouvelles infections chez les adultes dans le monde a diminué de 13% depuis 2010.

La prévalence de l'infection par le virus de l'hépatite B (VHB) varie selon les régions. Sur la base de la prévalence relative dans le monde, différents degrés « d'endémicité » ont été définis. Il existe généralement quatre niveaux d'endémicité de la prévalence positive de l'AgHBs, qui sont décrits comme faible (<2%), intermédiaire inférieur (2-4%), élevé intermédiaire (5-7%) et élevé $\geq 8\%$. L'Afrique Sub Saharienne, autrefois considérée comme ayant une endémicité élevée est maintenant classée comme une zone intermédiaire élevée avec une prévalence globale estimée des individus AgHBs positifs à 6,1% (4,6–8,5). Des études ont établi l'augmentation des taux de vaccination comme raison de cette baisse de la prévalence. Nonobstant ces baisses, il convient de noter qu'il y a eu une augmentation du nombre total absolu d'individus AgHBs positifs de 240 millions en 2005 à 350 millions en 2015.

Le Virus de l'Immunodéficience Humaine (VIH) et le Virus de l'Hépatite B (VHB) partagent la même voie de transmission ; ce qui explique la forte prévalence de la co-infection VIH/VHB. L'Afrique subsaharienne a la prévalence la plus élevée de co-infection par le virus de l'hépatite B (VHB) et le virus de l'immunodéficience humaine (VIH) par rapport au reste du monde. Parmi les personnes infectées par le virus de l'immunodéficience humaine (VIH) en Afrique subsaharienne, environ 5 à 10% sont co-infectées par le VHB. Cette prévalence est inquiétante car le diagnostic de l'infection par le VHB est souvent retardé et les services médicaux afférents ne sont pas toujours disponibles.

Dans un certain nombre d'études menées en Europe, aux États-Unis et en Australie, on sait que la co-infection VIH-VHB augmente le risque de morbidité et de mortalité par rapport à la mono-infection à VIH. L'augmentation du risque de morbidité et de mortalité globale au cours de la co-infection VIH-VHB a été largement confirmée chez les patients d'Afrique subsaharienne. Dans des études chez des personnes infectées par le VIH en Afrique subsaharienne, on a observé un risque accru de mortalité toutes causes confondues chez les personnes co-infectées par le VHB malgré l'initiation d'un traitement antirétroviral. Néanmoins, la plupart de ces études ont utilisé des schémas thérapeutiques antirétroviraux avec des agents anti-VHB peu puissants et ont inclus des patients sévèrement immunodéprimés, ou au stade SIDA. On ne sait pas si le risque accru de décès est également observé chez les patients co-infectés débutant un traitement antirétroviral à base de TDF / XTC à des taux de lymphocytes T CD4 plus élevés. De plus, il existe des données limitées concernant l'influence du traitement antirétroviral sur l'évolution de l'hépatite B chez les patients co-infectés.

Dans la mono-infection par le VHB, les patients commencent par une sérologie positive à l'antigène e de l'hépatite B (AgHBe) après l'infection et deviennent négatifs à mesure qu'ils développent des réponses immunitaires contre le virus. Lorsque les patients seroconvertissent et deviennent AgHBe négatif, la charge virale B est indétectable et les transaminases ainsi que le niveau de fibrose sont faibles. Cette phase du VHB est appelée « infection » chronique AgHBe-négatif. Au fil du temps, certains patients entrent dans une forme de maladie plus active, appelée « hépatite chronique AgHBe-négatif », dans laquelle la charge virale B et les taux de transaminases sont beaucoup plus élevés et la fibrose hépatique plus prononcée. Ces phases AgHBe négatif aident à différencier le degré d'activité du VHB. Etant donné que le risque de développer un carcinome hépatocellulaire (CHC), ou la morbidité liée au foie, est toujours présent au cours de l'hépatite AgHBe-négatif, cette classification pourrait guider les cliniciens dans l'initiation du traitement antiviral.

Considérant que les réponses anti-VHB sont nécessaires pour contrôler l'activité du VHB et pourraient être altérées en raison de l'immunosuppression induite par le VIH, les patients co-

infectés par le VIH-VHB pourraient présenter une évolution de la maladie AgHBe-négatif sensiblement différente de celle des patients mono-infectés par le VHB. Cependant, il y a peu d'études sur l'histoire naturelle de l'infection par le VHB lors de la co-infection. Des mesures répétées de la charge virale du VHB et l'alanine amino transférase (ALT) chez les personnes co-infectées AgHBe négatif sans traitement antirétroviral pourrait permettre d'étudier la progression de « l'infection » AgHBe négatif en « hépatite » dans cette population.

Avec l'instauration d'une thérapie antirétrovirale puissante (TAR), la plupart des personnes séropositives au VIH devraient avoir une augmentation substantielle du nombre de lymphocytes T CD4 jusqu'à ce que leur taux se stabilise en plateau. Lorsque le traitement antirétroviral est initié à un nombre de cellules CD4 bas, la restauration immunitaire est plus rapide et un gain supplémentaire est nécessaire pour atteindre ce plateau. De nombreux facteurs sont associés à l'augmentation rapide du nombre de lymphocytes CD4, notamment un âge avancé, une augmentation de l'indice de masse corporelle et une durée plus longue de l'infection incontrôlée à VIH.

La co-infection par le VIH et le virus de l'hépatite B (VHB) a également été impliquée dans une reconstitution immunitaire plus lente, entraînant un gain moindre du nombre de lymphocytes CD4 pendant le traitement antirétroviral à long terme. Néanmoins, cette association n'a pas été confirmée de manière cohérente dans la littérature, même si l'on considère le niveau de charge virale du VHB au début du traitement antirétroviral. Ces écarts pourraient être dus à des degrés variables d'immunosuppression plus sévère chez les patients co-infectés VIH-VHB par rapport aux patients mono-infectés par le VIH. Les différences de reconstitution immunitaire entre les patients co- et mono-infectés pourraient se dissiper à mesure que les individus commencent le traitement antirétroviral à un nombre de lymphocytes CD4 plus élevé (par exemple au-dessus de $500 / \text{mm}^3$), mais aucune étude à ce jour n'a examiné ce phénomène chez les personnes séropositives très peu immuno déprimées.

Entre 2008-2015, nous avons mené un essai contrôlé randomisé pour évaluer les avantages du traitement antirétroviral immédiat basé sur le TDF / XTC et du traitement préventif à l'isoniazide (TPI) de 6 mois pour la tuberculose chez les adultes infectés par le VIH ayant un taux élevé de CD4 en Côte d'Ivoire, Afrique de l'Ouest, l'essai Temprano ANRS12136. Le critère d'évaluation de l'essai était une morbidité sévère à 30 mois. L'analyse finale a montré que le traitement antirétroviral immédiat conduisait à des taux de morbidité sévère plus faibles que lorsque le traitement antirétroviral était différé. Une fois que les participants ont atteint 30 mois de suivi dans l'essai, ils ont continué le suivi dans une phase post-essai (PTP : Post Trial Phase)

Nous avons analysé les données de cet essai contrôlé randomisé en Côte d'Ivoire pour étudier l'histoire naturelle de la co-infection par le VIH et le VHB chez les patients naïfs de traitement antirétroviral, la morbi-mortalité et la réponse immunitaire sur un suivi à long terme sous ARV.

Méthodes :

Dans ce projet, nous avons étudié la problématique la co-infection VIH / VHB à partir des données de l'essai Temprano en collaboration avec l'équipe scientifique du service des maladies infectieuses de l'hôpital St Antoine à Paris et le laboratoire de virologie de Lyon (UMR Inserm 1252), et l'hôpital Saint Louis de Paris où les analyses virologiques du VHB ont été réalisées. L'essai Temprano ANRS 12136 visait à évaluer les avantages et les risques d'une thérapie antirétrovirale précoce et d'une chimio prophylaxie antituberculeuse INH de 6 mois en Côte d'Ivoire.

Les participants ont été répartis au hasard dans 1 des 4 bras : 2 bras «TAR différé » (bras 1 et 2), dans lesquels l'initiation du TAR a été différée jusqu'à ce que les patients présentent les critères de mise sous traitement selon les recommandations de l'OMS en vigueur ; et 2 bras «TAR immédiat » (bras 3 et 4), dans lesquels le TAR a été initié immédiatement à l'inclusion. Dans les bras 2 et 4, les participants ont reçu une prophylaxie isoniazide de 6 mois contre la tuberculose. Le schéma thérapeutique de première intention contenait du TDF / emtricitabine

avec le troisième agent de préférence de l'éfavirenz ou, en cas de contre-indication, de la zidovudine ou du lopinavir / ritonavir.

Tous les participants ont eu une radiographie thoracique à l'inclusion. Des tests sanguins comprenant le taux de CD4, la charge virale plasmatique du VIH-1, les transaminases sériques ont été effectués au départ et tous les six mois.

La sérologie de l'Ag HBs a été réalisée au départ en utilisant un test ELISA (Monolisa® Bio-Rad, Marnes la Coquette, France). À partir d'échantillons congelés conservés à -80 ° C, l'antigène e de l'hépatite B (AgHBe) et les anticorps anti-HBe (AC anti-HBe) ont été détectés au départ en utilisant le test Elecsys (Roche Diagnostics, Meylan, France). Les charges virales d'ADN du VHB ont été quantifiées au départ à l'aide d'un test interne basé sur la réaction en chaîne par polymérase (PCR) (kit QuantiFast SYBR® Green PCR, limite de détection : 12 copies / ml ; Qiagen, Courtaboeuf, France ; Light Cycler 480 ; Roche, Boulogne-Billancourt, France) ou un test PCR disponible dans le commerce (COBAS®Amplicor HBV Monitor, limite de détection : 60 UI / ml ; Roche Diagnostics, Meylan, France). Pour assurer la comparabilité entre les dosages, les charges virales ont été rapportées en UI / ml [facteur de conversion : 1 UI / ml = 2,8 copies / ml.

Tous les participants à l'essai Temprano ont été suivis pendant 30 mois. Le premier participant à l'étude Temprano a effectué 30 mois de suivi en septembre 2010. À partir de cette date, tous les patients ayant atteint la visite de 30 mois ont été invités à poursuivre le suivi dans une phase post-essai (PTP) jusqu'à ce que le dernier patient ait terminé sa visite d'essai à 30 mois de suivi (date de clôture : 5 janvier 2015). L'étude Temprano et la PTP avaient des procédures similaires: les patients avaient des visites trimestrielles dans leur centre de santé et étaient invités à se présenter pour des visites supplémentaires chaque fois qu'ils rencontraient un événement médical; le taux de CD4 et la charge virale plasmatique du VIH de type 1 (VIH-1) ont été mesurés tous les 6 mois; les consultations, la numération des CD4, la charge virale et les médicaments antirétroviraux étaient gratuits; et les patients qui ne se sont pas présentés

lors d'une visite d'essai ont été recherchés par des travailleurs sociaux expérimentés. Les patients affectés aux bras traitement antirétroviral différés qui n'avaient pas commencé le TAR pendant l'essai ont commencé le traitement antirétroviral pendant le PTP à chaque fois qu'ils atteignaient les critères OMS d'initiation du TAR les plus récents. Les patients qui n'atteignaient pas les critères de l'OMS avant la date de clôture n'ont pas commencé le traitement antirétroviral, que ce soit pendant l'essai ou pendant la PTP.

Il y avait 2 différences entre l'étude Temprano et PTP. Premièrement, le transport pour les visites imprévues, les consultations, l'hospitalisation et les médicaments non antirétroviraux étaient gratuits lorsque des événements de morbidité se produisaient pendant l'essai. Dans la PTP, les patients devaient payer de leur poche, comme les autres patients suivis en soins de routine dans le même centre. Deuxièmement, le critère de jugement principal était la morbidité sévère (y compris la mortalité toutes causes confondues) dans l'essai Temprano et seulement la mortalité toutes causes confondues dans l'étude PTP.

Nous avons donc fait trois analyses principales pour mieux comprendre les défis liés à la co-infection VIH-VHB :

1- Etude de la mortalité en fonction du taux de charge virale B

Nous avons analysé l'association entre le statut VHB, le TAR immédiat et la mortalité pendant l'essai Temprano et le suivi post-essai à l'aide de la régression à risques proportionnels multivariés de Cox. Le critère d'évaluation principal était la mortalité toutes causes. Le critère secondaire était le décès ou la perte de vue (LTFU). LTFU a été défini par le fait que les patients ne se sont pas présentés à leur dernière visite trimestrielle prévue et qu'aucune information supplémentaire sur leur état vital n'était disponible dans les 6 mois précédant la date de clôture.

Les patients ont été regroupés en tant que mono infectés pour le VIH (tous les participants AgHBs négatifs) ou co-infectés par le VIH / VHB (tous les participants AgHBs positifs), ce dernier étant stratifié sur l'ADN du VHB plasmatique <2000 UI / ml (faible charge virale du

VHB) et le plasma ADN du VHB ≥ 2000 UI / ml (charge virale VHB élevée) à l'inclusion. Le seuil de 2000 UI / ml a été choisi en fonction des taux correspondant à l'infection active et à l'indication du traitement chez les personnes mono infectées par le VHB. Des tests de Mantel-Haenszel χ^2 ou de Fisher exacts ont été utilisés pour comparer les caractéristiques de base entre ces groupes. La distribution des variables continues a été comparée à l'aide du test de Kruskal-Wallis.

Lors de la stratification sur ces groupes, nous avons utilisé la méthode de Kaplan-Meier pour estimer la probabilité cumulative de décès et de décès ou perdu de vue (PDV), et estimé les taux d'incidence en divisant le nombre de premiers événements par le temps cumulé à risque. La période à risque a commencé lors de la randomisation et s'est terminée au décès, PDV, ou le 5 janvier 2015, selon la première éventualité.

Les modèles de risques proportionnels de Cox ont été utilisés pour comparer les risques liés à l'atteinte de chaque critère d'évaluation entre les patients AgHBs négatifs et AgHBs-positifs (analyse en 2 groupes), et entre les patients AgHBs-négatifs, AgHBs -positifs avec une charge virale du VHB <2000 UI / mL et AgHBs -positifs avec un ADN du VHB ≥ 2000 UI / ml (analyse en 3 groupes). Dans l'analyse multivariée, les rapports de risque (HR) ont été ajustés a priori pour les variables suivantes : stratégie Temprano traitement antirétroviral (Temprano TAR immédiat vs différé), stratégie Temprano IPT (IPT vs pas IPT), nombre de CD4 de base, sexe et charge virale ARN VIH-1 initiale. Les interactions entre les variables ont été testées. L'hypothèse des risques proportionnels a été examinée.

Toutes les valeurs de p rapportées étaient bilatérales et aucun ajustement pour des comparaisons multiples n'a été appliqué. Les analyses statistiques ont été effectuées avec le logiciel SAS 9.4 (SAS Institute, Cary, Caroline du Nord).

2- L'activité du virus de l'hépatite B chez les patients co-infectés naïfs de traitement

Afin d'étudier les facteurs influençant la variabilité des deux marqueurs définissant l'activité du VHB, nous avons utilisé la régression par intervalle interquartile (IQR). La date de visite

d'inclusion a été définie comme référence. La durée de suivi de chaque patient du temps mis pour atteindre un des évènements suivants sans traitement : (i) la dernière visite de suivi, (ii) le début du traitement antirétroviral (iii) le décès.

Des profils longitudinaux d'activité du VHB ont été établis en fonction du fait que les patients présentaient systématiquement une « infection » AgHBe négatif (charge virale indétectable et transaminases normales), fluctuaient entre une « infection » AgHBe négatif charge virale détectable et transaminases élevées) et une « hépatite » ou présentaient systématiquement une « hépatite AgHBe négatif ». Les caractéristiques de base et de suivi ont été comparées entre les groupes d'activité du VHB à l'aide du test de Kruskal – Wallis pour les variables continues et du test de Pearson χ^2 ou du test exact de Fisher pour les variables catégorielles. Afin d'étudier les déterminants de la dispersion dans les deux marqueurs définissant l'activité du VHB, nous avons utilisé la régression par intervalle interquartile (IQR). En bref, deux modèles quantiles sont utilisés pour étudier les déterminants sur les 75^e et 25^e percentiles des niveaux de charge virale B et des transaminases lors des mesures au cours du temps. La différence entre les deux centiles modélisés, $\text{diff} (p_{75}, p_{25})$, est donnée par unité d'augmentation du facteur de risque et les intervalles de confiance (IC) à 95% ont été calculés à partir des erreurs standards obtenues en utilisant 200 échantillons bootstrap. Seuls la charge virale VIH, la charge virale VHB et les transaminases à l'inclusion ont été utilisés dans cette analyse. Toutes les analyses ont été effectuées à l'aide de STATA version 12.1 (StataCorp, College Station, TX, USA) et la signification a été déterminée par une valeur $p < 0,05$.

3- La mortalité en fonction du taux de CD4

A l'aide d'une régression non linéaire à effets mixtes, nous avons modélisé une augmentation du nombre de CD4 sous forme de fonction racine carrée au fil du temps. Les patients ont été regroupés en tant que mono-infectés par le VIH (tous les participants AgHBs négatifs) ou co-infectés par le VIH / VHB (tous les participants AgHBs positifs), ce dernier étant stratifié sur la charge virale plasmatique du VHB < 2000 UI / ml et charge virale plasmatique du VHB ≥ 2000

UI / ml à l'inclusion. Le seuil de 2000 UI / ml a été choisi en fonction des taux correspondant à l'infection active et à l'indication du traitement chez les individus mono-infectés par le VHB.

Sauf indication contraire, le temps à risque dans cette analyse a commencé au moment de la randomisation et s'est terminé au décès, lors du statut « perdue de vue », à la dernière mesure du taux de CD4, ou le 5 janvier 2015, selon la première éventualité.

Nous avons utilisé des états spécifiques du taux de CD4 comme critère de jugement, défini comme ≤ 350 / mm^3 ,] 350-500] / mm^3 et > 500 / mm^3 . Étant donné que les patients pouvaient avoir des fluctuations entre les niveaux de CD4, nous avons modélisé les transitions entre les états à l'aide d'un modèle de Markov multi-états homogène dans le temps, en temps continu. Ce modèle calcule le taux instantané par an d'une transition se produisant, défini comme l'intensité de transition (TI). Les TI entre chacun des états ont été estimés conjointement en maximisant la probabilité des données observées. Le modèle suppose que les individus avec des transitions observées de < 350 à > 500 / mm^3 ou de > 500 à < 350 / mm^3 entre les visites doivent passer par l'état 350-500 / mm^3 . Les rapports de risque (HR) comparant l'IT entre les niveaux du groupe infecté par le VHB et leurs intervalles de confiance (IC) à 95% ont été estimés. Étant donné que la présence d'un traitement antirétroviral a un effet très influent sur les transitions entre le taux CD4, nous avons stratifié l'analyse sur le temps avant le TAR et pendant le TAR en incluant le TAR concomitant et l'interaction entre le traitement antirétroviral et le groupe infecté par le VHB dans le modèle de Markov. Le HR spécifique de la strate a été obtenu à partir de ce modèle et donné à la fois non ajusté et ajusté a priori pour la charge virale du VIH ($> 5,0$ contre $\leq 5,0$ log10 copies / ml), l'âge (> 35 contre ≤ 35 ans) et le sexe.

Nous nous sommes ensuite concentrés sur la période pendant le traitement antirétroviral pour évaluer l'augmentation continue du taux de CD4 en tant que critère d'évaluation. En utilisant une régression non linéaire à effet mixte, nous avons modélisé l'augmentation du nombre de CD4 sous forme de fonction racine carrée au cours du temps. Des estimations spécifiques à la strate ont été obtenues en incluant un terme d'interaction entre le groupe infecté par le VHB

et le temps de suivi. L'interception aléatoire et le coefficient aléatoire pour le temps ont été utilisés pour tenir compte de la variation entre les individus en ce qui concerne le nombre de lymphocytes T CD4 au début du traitement antirétroviral et pendant le suivi, avec une covariance non structurée entre l'interception aléatoire et le coefficient aléatoire. Les modèles étaient à la fois non ajustés et ajustés pour le nombre de cellules CD4 au début du traitement antirétroviral, le niveau de charge virale du VIH à l'inclusion ($> 5,0$ contre $\leq 5,0$ \log_{10} copies / ml), l'âge (> 35 contre ≤ 35 ans), le sexe et le traitement antirétroviral précoce versus différé. En utilisant les strates de comptage de cellules CD4 ci-dessus, nous avons déterminé le temps passé dans une strate de cellules CD4 donnée, en supposant que les CD4 sont constants entre 2 mesures. Nous avons estimé les taux d'incidence (IR) de la mortalité toutes causes spécifiques au taux de CD4 actuels pour 100 personnes-années en divisant le nombre de premiers événements donnés survenus dans chaque strate de CD4 par le temps passé dans la strate correspondante (pour les patients n'ayant pas eu l'événement) ou le temps entre l'entrée dans la strate et le premier événement (pour les patients ayant subi l'événement). Les intervalles de confiance (IC) à 95% des taux d'incidences (TI) ont été calculés en supposant une distribution de Poisson si le nombre d'événements était inférieur à 50 et une approximation normale dans le cas contraire. Les TI ont été comparés entre les groupes infectés par le VHB dans les strates de numération des cellules CD4 par un modèle de régression de Poisson utilisant des estimations médianes sans biais avec la règle de la valeur P moyenne et le temps de suivi. Les rapports des taux d'incidence (RTI) ont été estimés à partir de ce modèle et ont été donnés à la fois non ajustés et ajustés a priori, pour le taux de charge virale du VIH ($> 5,0$ contre $\leq 5,0$ \log_{10} copies / ml), l'âge (> 35 contre ≤ 35 ans), le sexe et bras d'étude (TAR précoce ou différé).

Toutes les valeurs p rapportées étaient bilatérales et aucun ajustement pour des comparaisons multiples n'a été appliqué. Les analyses statistiques ont été effectuées à l'aide de SAS (v9.4, Cary, Caroline du Nord), STATA (v15.0, College Station, Texas) et R (v3.5.2, Vienne, Autriche).

Résultats :

Sur les 2056 participants analysés dans l'essai Temprano, 2052 (99,8%) ont été inclus dans cette analyse, 1862 (91%) étaient mono infectés par le VIH et 190 (9%) co-infectés par le VIH / VHB. Parmi ces derniers, 135 (71%) avaient une charge virale du VHB <2 000 UI / ml et 55 (29%) \geq 2 000 UI / ml.

Etude de la mortalité en fonction du taux de charge virale B

À la date de clôture de l'étude, 1760 participants étaient vivants et en suivi actif, 206 ont été perdus de vue et 86 étaient décédés. Sur les 86 décès, 47 (54,6%) sont survenus pendant l'essai et 39 (45,4%) pendant le PTP. Sur les 206 perdus de vue, 57 (27,7%) se sont produits pendant l'essai et 149 (72,3%) pendant le PTP (**figure 1**).

Le taux médian de CD4 était de 464 (intervalle interquartile [IQR], 369–573) cellules / μ l, et l'ARN du VIH plasmatique médian était de 4,7 (IQR, 4,0–5,3) log₁₀ copies / ml. Il n'y avait aucune différence dans les caractéristiques de base entre les bras. Le nombre de décès était de 74 (4,0%) chez les patients mono infectés par le VIH, 5 (3,7%) chez les patients co-infectés par le VIH / VHB avec un faible ADN du VHB et 7 (12,7%) chez les patients co-infectés par le VIH / VHB avec un ADN du VHB élevé. Le nombre de perdus de vue était de 183 (9,8%) chez les patients mono infectés par le VIH, 15 (11,1%) chez les patients co-infectés par le VIH / VHB avec un faible taux d'ADN du VHB au départ et 8 (14,5%) chez les patients co-infectés par le VIH / VHB avec un ADN du VHB de base élevé.

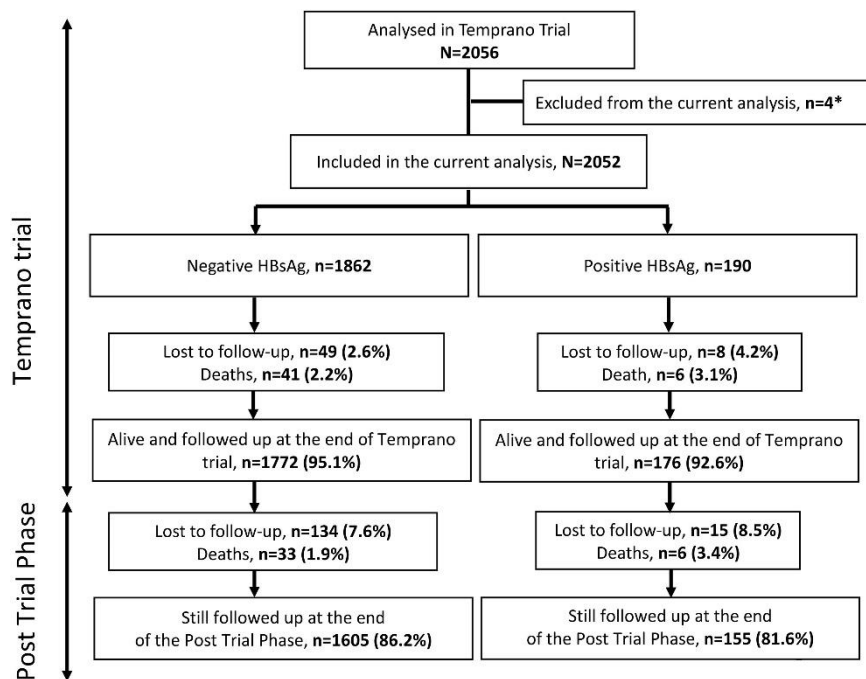
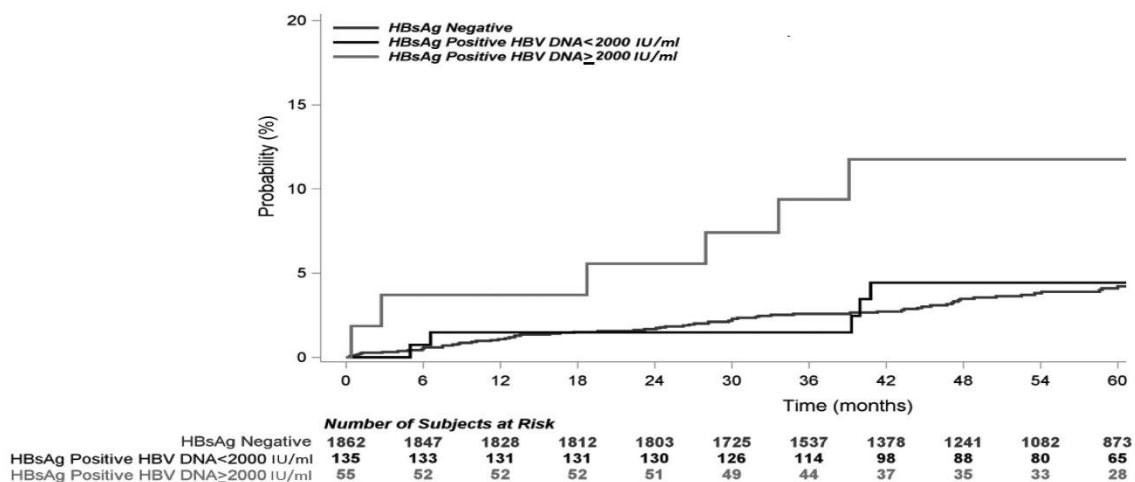


Figure 1 : Diagramme de flux

La probabilité de décès à 60 mois était de 11,8% [5,4% à 24,5%] chez les patients co-infectés avec une charge virale B $\geq 2\,000$ UI / ml ; 4,4% [1,9% à 10,4%] chez les patients co-infectés avec une charge virale B <2000 UI / ml ; et 4,2% [3,3% à 5,4%] chez les patients mono infectés par le VIH. En ajustant sur la stratégie de traitement antirétroviral, le rapport de risque de décès était de 2,74 [1,26 à 5,97] chez les patients co-infectés avec une charge virale B ≥ 2000 UI / ml et de 0,90 [0,36 à 2,24] chez patients co-infectés avec une charge virale B <2000 UI / ml par rapport aux patients mono infectés par le VIH. (**Figure 2**)

A



B

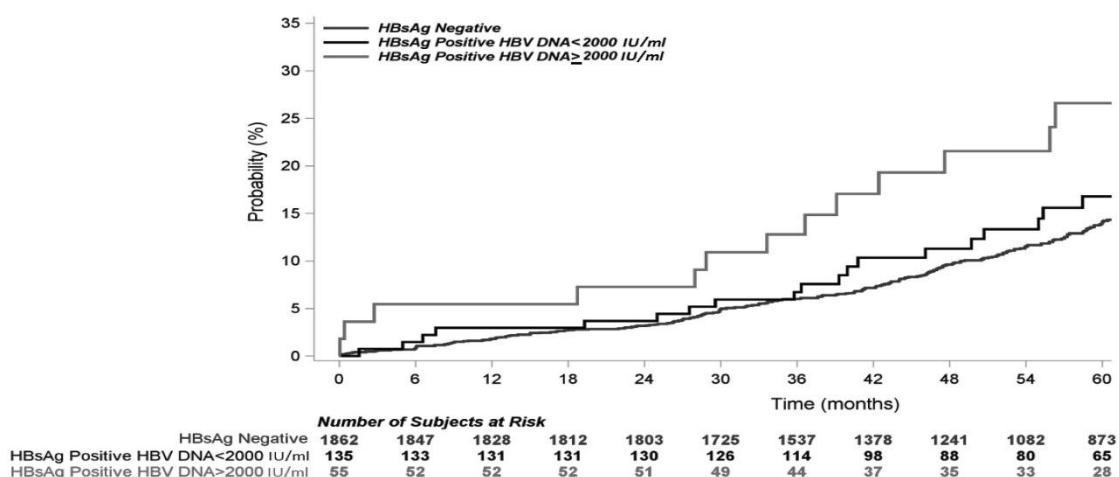


Figure 2 : Probabilité de décès et de décès ou de perte de vue, selon le statut du virus de l'hépatite B (VHB). Probabilité cumulative calculée par la méthode de Kaplan-Meier

Donc, les patients co-infectés VIH-VHB qui ont une forte charge virale VHB > 2000 UI/ml ont une mortalité trois fois plus élevée comparée aux patients non co-infectés, ou avec une charge virale B VHB < 2000 UI/ml.

Etude de l'activité du virus de l'hépatite B chez les patients co-infectés naïfs de traitement

L'activité de l'hépatite B a été étudiée chez 47 patients de l'essai Temprano co-infectés VIH-VHB AgHBe négatif et ne recevant pas de traitement antirétroviral. Le suivi médian a été de 25 mois (IQR 19–31), ce qui correspond à une médiane de 5 visites (IQR 4–6) par patient. La distribution des profils longitudinaux de l'activité du VHB AgHBe négatif était la suivante :

systématiquement une « infection » chronique AgHBe négative (n = 17) (3 figures de gauche), fluctuant entre une « infection » chronique AgHBe négative et une « hépatite » (n = 21) (3 figures du milieu) et une AgHBe systématiquement « hépatite » chronique négative (n = 5) (3 figures de droite) (figure 3). Chez les patients présentant des profils d'activité du VHB fluctuants, une « infection » chronique et une « hépatite » AgHBe-négatif ont été identifiées respectivement dans 45,8% et 54,2% du total des visites d'étude. Aucun patient n'est devenu AgHBe positif au cours du suivi.

Comme le montre la figure 3A, l'intervalle médian intra-patient (la différence entre le minimum et le maximum) des taux de charge virale du VHB observés pendant le suivi était plus important chez les patients fluctuant entre une « infection » chronique et une « hépatite » AgHBe-négatif (3,11 log₁₀ copies / ml [IQR 2,63–3,97]), suivis par les patients systématiquement classés avec une « hépatite » chronique AgHBe négative (2,59 [IQR 0,52–3,02]) et systématiquement avec une « infection » chronique AgHBe négatif (1,67 [IQR 1,00–2,32]) (p = 0,03). Seuls 3 patients (7,0%) avaient des taux de charge virale du VHB indétectable à tous les moments du suivi. La quantification de l'AgHBs était stable pendant le suivi pour la plupart des patients, quel que soit le profil d'activité AgHBe-négatif du VHB (figure 3B). Le taux de transaminase (ALT) était très variable au cours du suivi (figure 3C), la majorité des poussées d'ALT supérieures à deux fois la limite supérieure de la normale (> 70 UI / L) survenant chez des patients systématiquement classés avec une « hépatite » chronique AgHBe négative (60,0 %) ou celles oscillant entre « infection » chronique AgHBe négatif et « hépatite » (38,1%).

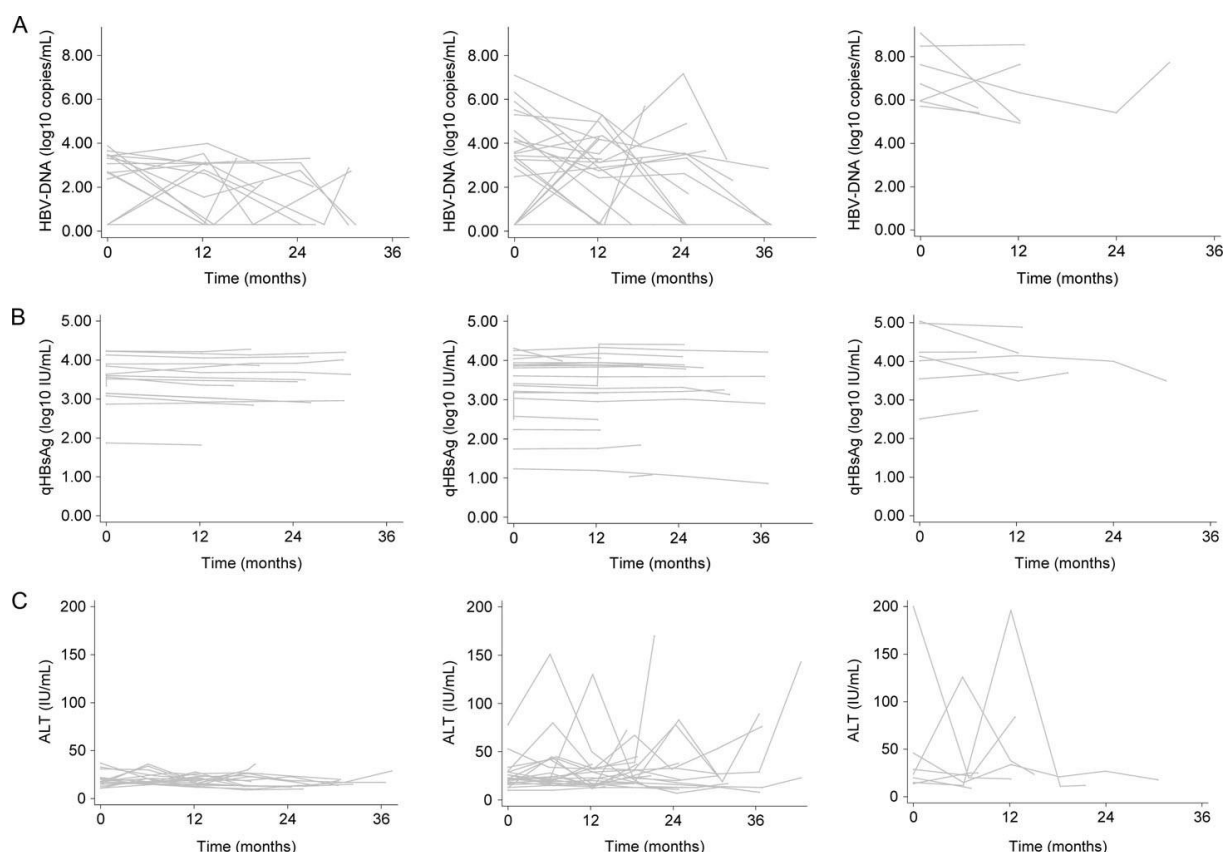


Figure 3 : Marqueurs de réplication du VHB pendant le suivi. Cette figure se lit en ligne : **A** fluctuation de la charge virale B ; **B** fluctuation la quantité de l'AgHBs ; **C** fluctuation du taux de transaminases ; et en colonne : **gauche** infection chronique AgHBe négatif ; **milieu** fluctuation entre infection chronique et hépatite chronique AgHBe négatif et à **droite** hépatite chronique AgHBe négatif.

Etude de la mortalité en fonction du taux de CD4

Au départ, le taux de CD4 initiaux n'était pas significativement différent entre les patients AgHBs négatifs et AgHBs positifs ($p = 0,58$). Les patients AgHBs positifs ayant un taux de CD4 initial $<350 / \text{mm}^3$ représentaient 26%, 23% et 21% pour les patients respectivement AgHBs positifs avec une charge virale VHB $\geq 2000 \text{ UI / ml}$, AgHBs positifs avec charge virale du VHB $< 2000 \text{ UI / ml}$, et AgHBs négatifs. Cette différence n'était pas statistiquement significative.

Les patients ont été suivis pendant une durée médiane de 58 mois (IQR = 40-69). Le suivi médian n'était pas différent entre les patients AgHBs négatifs (58 mois, IQR = 41-69) et les patients AgHBs positifs (60 mois, IQR = [38-69], $p = 0,77$), même avec une charge virale VHB

de base < 2000 UI / ml (60 mois, IQR = [39-69], $p = 0,89$) ou ≥ 2000 UI / ml (60 mois, IQR = [37-70], $p = 0,87$).

971 patients sans traitement antirétroviral, avaient au moins 2 mesures de la numération des cellules CD4 alors qu'ils n'étaient pas sous TAR et n'étaient pas randomisés en TAR précoce. Le suivi médian hors TAR était de 18 mois (IQR = 11-31) dans ce groupe. Le taux d'incidence pour la diminution du nombre de cellules CD4 de 350-500/mm³ à <350mm³ et de >500 à 350-500/mm³ était le suivant : de 350-500 / mm³ à moins de 350, 1,36 / PA (IC à 95% = 1,22-1,50) et de plus 500 / mm³ à 350-500, 1,24 / PA (95 IC% = 1,34-1,37).

1729 patients ont initié un TAR et ont eu au moins 2 mesures du nombre de cellules CD4 pendant le TAR. Le suivi médian sous TAR était de 55 mois (IQR = 37-61) dans ce groupe. Le TI d'augmentation de CD4 au-dessus des seuils de 350 et 500/mm³ étaient respectivement : de <350 à 350-500 / mm³, 2,28 / PA (IC à 95% = 2,10-2,47) et de 350-500 à > 500 / mm³, 1,71 / PA (95 % CI = 1,62-1,82).

Nous nous sommes ensuite concentrés sur les valeurs absolues de CD4 chez les patients sous TAR. Chez les patients AgHBs négatifs, le nombre moyen de CD4 était de 405 / mm³ (IC à 95% = [397-413]) au début du traitement, augmentant à 578 / mm³ (IC à 95% = [568-588]) après 12 mois et de 672 / mm³ (95% IC = [658-686]) à la fin du suivi sous TAR. Chez les patients AgHBs positifs, le nombre moyen de CD4 était de 392 / mm³ (IC à 95% = [369-414]) et a augmenté de manière similaire à 562 / mm³ (IC à 95% = [529-594]) après 12 mois et à 644 / mm³ (IC à 95%) = [605-683]) à la fin du suivi sous TAR. Sur la base du modèle de régression non linéaire à effets mixtes, il n'y avait pas de différence significative dans l'augmentation des cellules CD4 pendant le traitement entre les patients AgHBs-négatifs et AgHBs-positifs, tous deux non ajustés ($p = 0,26$) et ajustés pour le taux de CD4 initiaux, le niveau de charge virale du VIH initial, âge, sexe et TAR précoce versus différé ($p = 0,26$) (**figure 4A**).

Lors du regroupement des patients AgHBs positifs sur la base de la charge virale du VHB <2000 UI / ml et ≥ 2000 UI / ml, respectivement, le nombre moyen de CD4 était de $401 / \text{mm}^3$ (IC 95% = [373-429]) et $369 / \text{mm}^3$ (IC 95% = [329-408]) au début du traitement, augmentant à $563 / \text{mm}^3$ (IC à 95% = [526-601]) et $558 / \text{mm}^3$ (IC à 95% = [491-625]) à 12 mois de traitement, et $653 / \text{mm}^3$ (IC à 95% = [607-698]) et $622 / \text{mm}^3$ (IC à 95% = [542-701]) à la fin du suivi sous TAR. Il n'y avait pas de différence significative dans l'augmentation des cellules CD4 + entre les patients AgHBs négatifs et les patients AgHBs positifs avec une charge virale du VHB <2000 UI / ml (p non ajusté = 0,23 et p = 0,81) ou avec une charge virale du VHB ≥ 2000 UI / ml (p non ajusté = 0,25 et p ajusté = 0,76) (**figure 4B**).

Au cours du suivi, il y a eu 86 décès (IR = 0,92 / 100 personnes-années, IC à 95% = 0,72-1,11). Comme le montre le **tableau 1**, l'incidence ajustée de la mortalité était comparable entre les individus AgHBs positifs et AgHBs négatifs lorsque le nombre de cellules CD4 + était $>500 / \text{mm}^3$ (RTI ajusté = 0,85, IC à 95% = 0,13-2,95). Cette différence est devenue plus apparente lorsque le nombre de CD4 + atteignait $350-500 / \text{mm}^3$ (IRR ajusté = 1,51, IC à 95% = 0,34-4,46) ou $<350 / \text{mm}^3$ (IRR ajusté = 2,10, IC 95% = 0,84-4,53). Ces différences étaient encore plus prononcées chez les patients AgHBs positifs avec un ADN HBV initial ≥ 2000 UI / ml versus les patients AgHBs-négatifs : à $350-500 / \text{mm}^3$ CD4 +, IRR ajusté = 3.82 (IC 95% = 1.11-9.70), et à $<350 / \text{mm}^3$ CD4 +, IRR ajusté = 4,37 (IC à 95% = 0,98-13,02).

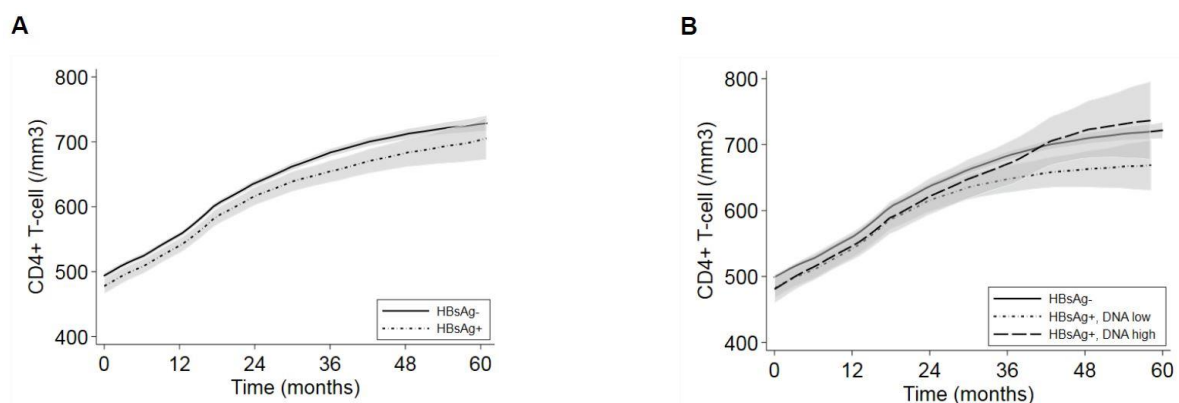


Figure 4 : Modélisation de l'augmentation du nombre de lymphocytes T CD4 + après l'instauration d'un traitement antirétroviral XXIX

Tableau 1 : Incidence des décès selon le statut d'infection par le virus de l'hépatite B dans les strates du taux de CD4

Strate de CD4	Statut de l'infection	Décès, <i>n</i>	P.A. à risque	Taux d'incidence pour 100 P.A. (95%CI)	Taux d'incidence relatif ¹ (95%CI)	
					Non ajusté	ajusté ²
Analyses en 2 groupes						
<350	AgHBs négatif	31	1363	2,27 [1,47-3,08]	Ref	Ref
	AgHBs positif	7	141	4,96 [1,99-10,23]	2,25 [0,90-4,85]	2,10 [0,84-4,53]
350-500	AgHBs négatif	20	2306	0,87 [0,53-1,34]	Ref	Ref
	AgHBs positif	3	239	1,26 [0,26-3,67]	1,50 [0,34-4,40]	1,51 [0,34-4,46]
>500	AgHBs négatif	23	4858	0,47 [0,30-0,71]	Ref	Ref
	AgHBs positif	2	486	0,41 [0,05-1,49]	0,92 [0,14-3,16]	0,85 [0,13-2,95]
Analyses en 3 groupes						
<350	AgHBs négatif	31	1363	2,27 [1,47-3,08]	Ref	Ref
	AgHBs positif, HBV DNA <2000UI/mL	3	96	3,13 [0,64-9,14]	1,48 [0,34-4,16]	1,33 [0,31-3,78]
	AgHBs positif, HBV DNA ≥2000UI /mL	4	46	8,70 [2,37-22,26]	3,98 [1,16-10,11]	3,82 [1,11-9,70]
350-500	AgHBs négatif	20	2306	0,87 [0,53-1,34]	Ref	Ref
	AgHBs positif, HBV DNA <2000UI/mL	0	162	0 [0-2,28]	0,50 [0,00-2,28]	0,52 [0,00-2,40]
	AgHBs positif, HBV DNA ≥2000UI/mL	3	78	3,85 [0,79-11,24]	4,68 [1,06-13,74]	4,37 [0,98-13,02]
>500	AgHBs négatif	23	4858	0,47 [0,30-0,71]	Ref	Ref
	AgHBs positif, HBV DNA <2000UI/mL	2	364	0,55 [0,07-1,98]	1,24 [0,18-4,22]	1,16 [0,17-4,02]
	AgHBs positif, HBV DNA ≥2000UI/mL	0	123	0 [0-3,00]	1,21 [0,00-5,52]	1,07 [0,00-4,91]

Conclusion :

En Afrique subsaharienne, nous avons montré que les adultes infectés par le VIH et atteints d'hépatite B chronique restent une population à risque accru de mortalité malgré un traitement antirétroviral précoce, même pour ceux qui sont traités à un stade précoce de l'infection par le VIH.

Avec les données disponibles sur la réplication du VIH et du VHB chez les participants à l'essai Temprano, nous nous sommes d'abord intéressés à étudier l'effet de la mortalité globale chez les patients co-infectés par le VIH et le VHB à un stade précoce de l'infection par le VIH. Notre étude est, à notre connaissance, la première à évaluer cette question de recherche à un stade précoce de l'infection à VIH et, plus important encore, à l'initiation précoce du traitement antirétroviral. Nous avons observé que malgré un traitement efficace et précoce du VIH, il y avait un excès de mortalité chez les patients co-infectés avec une charge virale VHB élevée (> 2000 UI / ml) par rapport aux participant mono infectés VIH ou co-infectés VIH-VHB avec une charge virale B indétectable. Le risque de mortalité associé à la co-infection VIH-VHB avec une charge virale B élevée est apparu plus évident lorsque le nombre de CD4 était inférieur à $500 / \text{mm}^3$. Chez les patients co-infectés par le VIH-VHB non traités par le traitement antirétroviral, la chute des CD4 en dessous de $350/\text{mm}^3$ est plus fréquente chez les patients avec une charge virale VHB $>2000\text{UI/l}$. La mortalité chez les personnes co-infectées par le VIH et le VHB peut être liée au VIH, au VHB ou aux deux. Une hypothèse serait que le VHB contribue au risque plus élevé de mortalité chez les patients co-infectés par le VIH-VHB avec une charge virale du VHB élevé à l'inclusion. Comme les participants à l'essai Temprano n'ont pas été testés pour des lésions hépatiques infracliniques hors les transaminases, il est difficile de confirmer cette hypothèse. Dans l'essai Temprano, la cause la plus fréquente de morbidité était liée à des maladies bactériennes et une sous-étude précédente de l'essai Trivacan (essai

d'évaluation des Interruptions Programmées de TAR) a également montré un risque plus élevé de maladies bactériennes pour les personnes co-infectées par le VIH-VHB avec une charge virale B initiale élevée et ayant reçu un TAR contenant un anti-VHB. La plus grande fréquence des infections bactériennes chez les patients co-infectés avec une répllication élevée de la charge virale du VHB, pourrait être associée à certains facteurs liés au VIH.

Ces résultats intrigants nous ont conduit à nous interroger sur les raisons de la surmortalité malgré un traitement efficace contre le VIH et le VHB. Nous avons démontré que les patients co-infectés par le VIH-VHB et mono-infectés par le VIH n'étaient pas différents du point de vue de l'immunodépression ni de la réponse immunitaire lorsqu'ils prenaient un traitement antirétroviral. Conformément aux résultats d'autres études menées chez des patients présentant un nombre de cellules CD4 relativement élevé en Afrique Sub Saharienne, la co-infection chronique par le VHB ne semble pas modifier les réponses immunitaires après l'initiation d'un TAR. Néanmoins, ce constat contraste avec d'autres études, où les patients étaient plus immunodéprimés et il y avait une prévalence beaucoup plus élevée d'individus avec une sérologie AgHBe positive et des niveaux plus élevés de répllication de charge virale du VHB. Il a été montré chez les personnes infectées par le VIH avec une immunosuppression sévère, que la co-infection VIH-VHB était associée à une apoptose accrue des lymphocytes T CD4 par une activation accrue des lymphocytes T par rapport à la mono-infection par le VIH. Enfin, lorsque le TAR n'est pas administré aux co-individus VIH-VHB, on pourrait supposer que l'activité du VHB changerait avec une diminution accrue du nombre de cellules CD4. Nous avons donc évalué l'histoire naturelle, c'est-à-dire l'activité de la charge virale du VHB et des transaminases, de l'infection chronique par le VHB chez les participants naïfs de TAR randomisés dans les bras de TAR différés de l'essai Temprano. Nous avons montré qu'environ la moitié des patients présentaient des fluctuations entre « infection » chronique et « hépatite

» AgHBe-négatif, ce qui souligne les degrés élevés de variation de l'activité du VHB chez ces patients. En partie liée à la réplication du VIH, la fluctuation entre les phases AgHBe-négatif du VHB est préoccupante en termes de risque de développer une complication hépatique chez les personnes co-infectées par le VIH-VHB en Afrique Sub saharienne sans traitement. Étant donné que nous avons démontré un risque de mortalité plus élevé, même lorsque des patients co-infectés par le VIH-VHB avec une charge virale élevée du VHB ont commencé le TAR tôt, il reste un certain nombre de questions qui doivent être clarifiées pour la population co-infectée par le VIH-VHB en Afrique Sub Saharienne. Du fait que le paysage du traitement antirétroviral évolue encore, il existe de nombreux défis auxquels les personnes co-infectées par le VIH-VHB pourraient être confrontées à l'avenir.

En effet, il existe très peu d'études qui ont exploré la fréquence et l'ampleur de la fibrose hépatique et de la cirrhose chez les individus co-infectés par le VIH-VHB traités par le TDF en Afrique Sub Saharienne, et il n'existe pratiquement aucune étude sur la progression du carcinome hépatocellulaire (CHC) et des complications hépatiques chez ces patients. On sait que le risque de CHC diffère considérablement entre les gènes du VHB, l'origine ethnique et l'exposition à d'autres agents hépatotoxiques, tels que l'aflatoxine B1 par exemple. De plus, les études menées à ce jour sur l'impact des génotypes du VHB ont principalement impliqué les génotypes A, B, C et D, et comme le génotype E est prédominant en Afrique de l'Ouest, les implications de ce génotype dans l'apparition d'un cancer hépatocellulaire sont mal connues. Des cohortes de patients co infectés VIH-VHB ou mono infectées VHB aideraient à combler ces lacunes, et à définir des stratégies de surveillance plus efficaces pour ces patients.

L'actualité du traitement antirétroviral est à l'allègement thérapeutique avec le risque que les nouveaux protocoles n'incluent pas de molécules efficaces contre le VHB. Ainsi, tous les individus séropositifs au VIH devraient bénéficier d'un dépistage du VHB d'autant plus que les deux virus partagent les voies de contamination, afin d'éviter de faire des allègements de TAR chez les patients co-infectés.

Comprendre les causes sous-jacentes, à la fois liées au VIH et au VHB, aidera à informer les cliniciens sur les types de comorbidités à rechercher dans les soins de routine. Par ailleurs, les nouvelles stratégies de traitement des personnes séropositives doivent prendre en compte les spécificités requises lors du traitement des patients co-infectés VIH-VHB. En attendant de mieux comprendre tous les mécanismes de cette infection au VHB chez les patients co-infectés VIH –VHB en vue de diminuer leur surmortalité, il est crucial de continuer les traitements efficaces contre l'infection par le VHB par le biais d'un traitement antirétroviral contenant des anti-VHB et d'augmenter la couverture vaccinale.

Mots clés : Co-infection VIH-VHB, activité du VHB, AgHBe, restauration immunitaire, mortalité, Afrique subsaharienne

ABSTRACT

Background: In sub-Saharan Africa, human immunodeficiency virus (HIV) and hepatitis B virus (HBV) represent a real public health problem because of their frequency and severity. HIV-HBV co-infection poses specific research questions, even at a time when antiretroviral therapy is universal. We analyzed data from a randomized controlled trial in Côte d'Ivoire to study the risk of morbidity and mortality and immune responses on long-term follow-up with antiretroviral therapy (ART) and the natural history of co-infection with HIV and HBV in ART-naïve patients.

Methods: In this project, we examined parameters of HBV infection [i.e. hepatitis B surface antigen (HBsAg) and HBV DNA replication] in HIV-positive individuals using data from the Temprano trial in collaboration with the infectious diseases department of Saint-Antoine Hospital (Paris, France) and the virology laboratory of UMR Inserm 1252 (Lyon, France) and Saint-Louis Hospital (Paris, France). The Temprano ANRS 12136 trial aimed to assess the benefits and risks of early antiretroviral therapy and 6-month isoniazid (INH) anti-tuberculosis chemoprophylaxis in Côte d'Ivoire. We then conducted three main analyses to evaluate: (1) the association between HBV status, immediate ART and mortality over the entire trial and post-trial follow-up using Cox multivariate proportional hazards regression, (2) increase in CD4+ cell count between HBV status using mixed-effect linear models and the risk of mortality at levels of CD4+ using Exact Poisson regression, and (3) viral activity through HBV DNA and alanine aminotransferase (ALT) in hepatitis B “e” antigen negative individuals and the dispersion of these two markers using interquartile range (IQR) regression.

Findings: Of 2052 adults followed, 1862 (91%) were monoinfected with HIV and 190 (9%) co-infected with HIV-HBV. Of these, 135 (71%) had an HBV viral load <2000 IU/mL and 55 (29%)

≥ 2000 IU/mL. The probability of death at 60 months was 11.8% (95%CI=5.4% to 24.5%) in co-infected patients with an HBV DNA viral load ≥ 2000 IU/mL; 4.4% (95%CI=1.9% to 10.4%) in co-infected patients with an HBV DNA viral load < 2000 IU/ml; and 4.2% (95%CI=3.3% to 5.4%) in patients monoinfected with HIV. After adjustment, the hazards ratio for death was 2.74 (95%CI=1.26 to 5.97) in co-infected patients with an HBV DNA ≥ 2000 IU/mL and 0.90 (95%CI=0.36 to 2.24) in co-infected patients with an HBV DNA viral load < 2000 IU/mL compared to patients monoinfected with HIV. After adjustment, HBsAg positive individuals with an HBV DNA viral load ≥ 2000 IU/ml showed greater differences in all-cause mortality compared to HIV mono-infected individuals at $< 350/\text{mm}^3$ (adjusted IRR=3.82, 95%CI=1.11-9.70) and at 350-500/ mm^3 (adjusted IRR=4.37, 95%CI 0.98-13.02). In HBeAg negative patients without treatment, 17 (40%) patients consistently had 'infection', 5 (12%) consistently had 'hepatitis' and 21 (48%) fluctuated between phases. A wider dispersion of HBV DNA viral load over time was associated with a higher baseline HIV viral load ($p=0.02$), while a wider dispersion of ALT was associated with an HIV RNA viral load ($p<0.001$) and baseline HBsAg levels $> 4.0 \log_{10}$ IU/mL ($p=0.02$).

Conclusion: HIV-positive adults in sub-Saharan Africa with chronic hepatitis B remain a population at increased risk of death, particularly when their HBV DNA viral loads are elevated at ART-initiation, despite early ART and being at an early stage of HIV infection. The risk of mortality associated with HIV-HBV co-infection with a high viral load appeared more evident when the CD4+ cell count was below $500/\text{mm}^3$. HBV activity can be variable during HBeAg-negative infection in the absence of ART. The data presented in this project help inform the clinical management of treated HIV-HBV co-infected patients in the era of early ART.

Key words: HIV-HBV co-infection, HBV activity, immune recovery, mortality, sub-saharan Africa

INTRODUCTION

In Sub-Saharan Africa (SSA), the prevalence of the human immunodeficiency virus (HIV) and hepatitis B virus (HBV) is higher compared to other regions of the world and given their pathogenesis and disease burden, they represent a real public health problem. The burden of the HIV epidemic, in terms of number infected, has been the largest of any other region early on in the epidemic. HBV is endemic in SSA and has remained so for the past several decades. Since the prevalence of both these infections is high, it is unsurprising that the largest number of HIV-HBV co-infected individuals also lives on the continent, affecting 2.6 million individuals in SSA (1,2). In the treatment of HIV-infection, there has been a dramatic shift towards earlier treatment of antiretroviral therapy (ART). This poses a number of specific research questions for the HIV-HBV co-infected population, which we will develop in this thesis.

This thesis discusses issues related to the implications of HBV during HIV infection, particularly related to treatment. In order to provide some context of HIV and HBV infection individually, as well as HIV-HBV co-infection, the natural history of these infections in the absence and presence of treatment will be discussed, along with the types of antiviral treatments that are available and the clinical monitoring that is recommended during infection. There will also be additional discussion on the epidemiology of these infections, which includes the common modes of transmission and prevalence. Finally, the types of prevention strategies against both infections, even when an individual is infected with one of the viruses, will be elaborated, as these will have implications for further research. Particular attention will be given to SSA and specifically the national situation in Côte d'Ivoire.

1.1. Natural history of HIV and HBV infections in the absence and presence of treatment

1.1.1. HIV infection

With almost 33 million lives lost due to infection as of 2019, HIV continues to be a major global public health issue (3). The general progression of HIV disease is illustrated in Figure 1. Early after HIV-1 infection, there is a substantial increase in HIV RNA viral load for roughly twelve weeks, which then decreases as anti-HIV immunity is established (4). HIV RNA levels then increase with the progressive loss of immune function, marked by depletion of the CD4+ T-lymphocytes, which then leads to individuals developing opportunistic infections and malignancies characteristic of the acquired immunodeficiency syndrome (AIDS). Although both host and viral determinants influence disease progression, the median time from initial infection to the development of AIDS-defining illness among untreated patients ranges from 8 to 10 years (4–6). In the absence of treatment, almost all HIV-infected patients progress to AIDS and with the emergence of opportunistic infections, will eventually die from their infection.

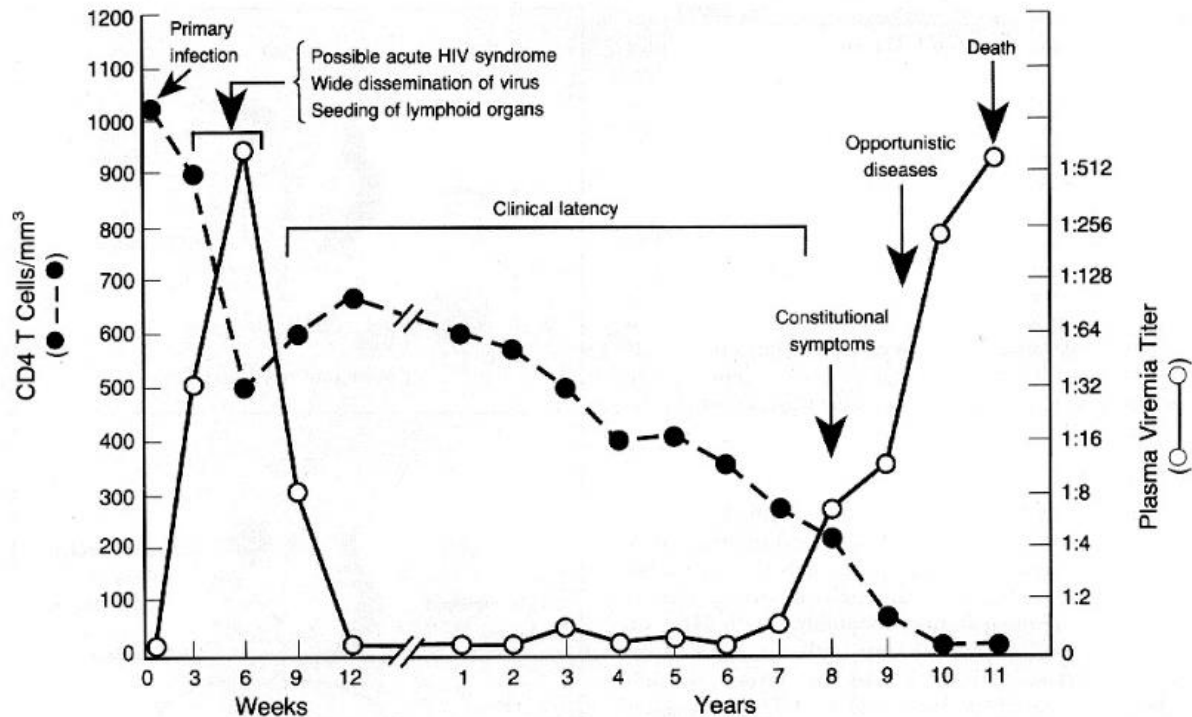
In the years without effective treatment, diagnosis of HIV-infection was synonymous with a dire, short-term prognosis. It took several years after the first diagnoses of AIDS before the first effective treatments against HIV were developed. In the late 1980s, zidovudine brought about momentary hope of controlling HIV replication, which was followed by other antiretroviral agents, such as didanosine and lamivudine (7). In 1996, another class of antiretrovirals became available, protease inhibitors, which gave way to ART regimens containing three antiretroviral agents active against HIV. Treatment with highly potent ART extensively diminished the rates of AIDS-related mortality. Furthermore, AIDS-related morbidity, such as pneumocystis, tuberculosis or cryptococcosis, witnessed dramatic declines (8,9). As AIDS-related diseases have decreased, the prevalence of non-AIDS co-morbidities, including

metabolic disorders, cardiovascular diseases and non-AIDS related cancers, have increased in parallel and have been more frequently observed in HIV-positive individuals (10–12). Nevertheless, emerging evidence has demonstrated the benefit of starting ART earlier with a high CD4+ cell (13,14). Taken together, the natural history and course of HIV-infection has changed since the introduction of combined ART (15–17).

The natural history of HIV-infection is highly similar for HIV-positive individuals in SSA, despite differences in the genetic variability of HIV on the continent (18). However, many of the gains in reducing HIV-related morbidity/mortality that have been observed in other parts of the world have not been readily observed in SSA. The limited number of patients on effective ART and individuals still unaware of their HIV status and who often present at late stages of HIV-infection when diagnosed mostly contribute to the increased prevalence of HIV-related disease in this region (19,20). A large study from South Africa has shown that about 32% of individuals newly diagnosed with HIV between 2014 and 2015 had a recorded baseline CD4+ cell count ≤ 200 cells/mm³ (21). Meanwhile, a large proportion of HIV-positive individuals has been shown to present with AIDS-defining illnesses in SSA, which, in highly immunocompromised African patients, are dominated by tuberculosis, cerebral toxoplasmosis, neuro-meningeal cryptococcosis, and invasive bacterial infections (9,22). Even if individuals are tested early and diagnosed with HIV-infection, they might not have access to care and treatment for a variety of reasons. Inequalities in accessing healthcare facilities, sociocultural beliefs, such as

denying the existence of HIV, and geopolitical conflicts, such as civil war, are also known to play a role in the ability to provide care for HIV-positive individuals (23).

Figure 1: Typical course of HIV infection



The above figure was obtained from (4). The natural evolution of HIV-disease is depicted by changes in CD4+ T cell counts and plasma viremia titers. Major prognostic events are also labeled at various points during HIV-infection.

1.1.2. HBV infection

HBV is a hepatotropic virus, meaning that it infects the liver and maintains persistence in liver cells, i.e., hepatocytes. Symptoms after acquiring HBV infection are not pathognomonic and many are often mistaken for more common illnesses, such as influenza or gastroenteritis. Recently infected individuals can experience fever, tiredness, general aches and pains, malaise, yellowing of skin or eyes, and dark urine (24). HBV infection is either

cleared usually within 6-12 months [i.e., clearing hepatitis B surface antigen (HBsAg) and developing anti-HBs antibodies (anti-HBsAb)] or develops into chronic infection (25,26). The risk of developing chronic infection is inversely related to an individual's age, meaning that infected children will generally develop chronic infection, whereas adults are generally able to clear HBV during the acute phase of infection (27). Progression to chronic HBV infection has also been associated with geographic area, which is likely a direct result of the local epidemiology of average age at HBV transmission, and HBV genotype (28).

The natural history of chronic HBV infection is schematically broken down into several phases. Viral replication is not *per se* cytopathogenic, but rather interactions between viral replication and the immune system of the host, which are intended to control viral replication, are responsible for hepatic damage. The 2017 clinical practice guidelines of the European Association for the Study of the Liver (EASL) has defined these phases of chronic HBV infection (29), whereby the fundamental distinction is between phases of "chronic infection" and "chronic hepatitis" and serological status of hepatitis B "e" antigen (HBeAg). Because of the dynamic nature of chronic HBV infection, it is sometimes difficult to classify a patient on the basis of a single sample and optimal management often requires longitudinal monitoring of the main markers of HBV replication and infection (30). Chronic HBV infection evolves in five phases (summarized in Figure 2), which have been defined in the EASL guidelines:

- **HBeAg-positive, chronic infection:** This phase (formerly termed "immunotolerance") is characterized by HBeAg-positive serology, a high HBV DNA viral load, and few hepatic lesions. This phase is more frequently found after perinatal transmission of HBV infection and generally lasts longer with decreasing age at infection (30–33). Due to the high levels of circulating HBV DNA, these patients are highly contagious. The

rate of spontaneous HBeAg seroclearance (i.e. loss of HBeAg) is very low in this phase and HBsAg-seroclearance (i.e. loss of HBsAg) very rarely occurs (34).

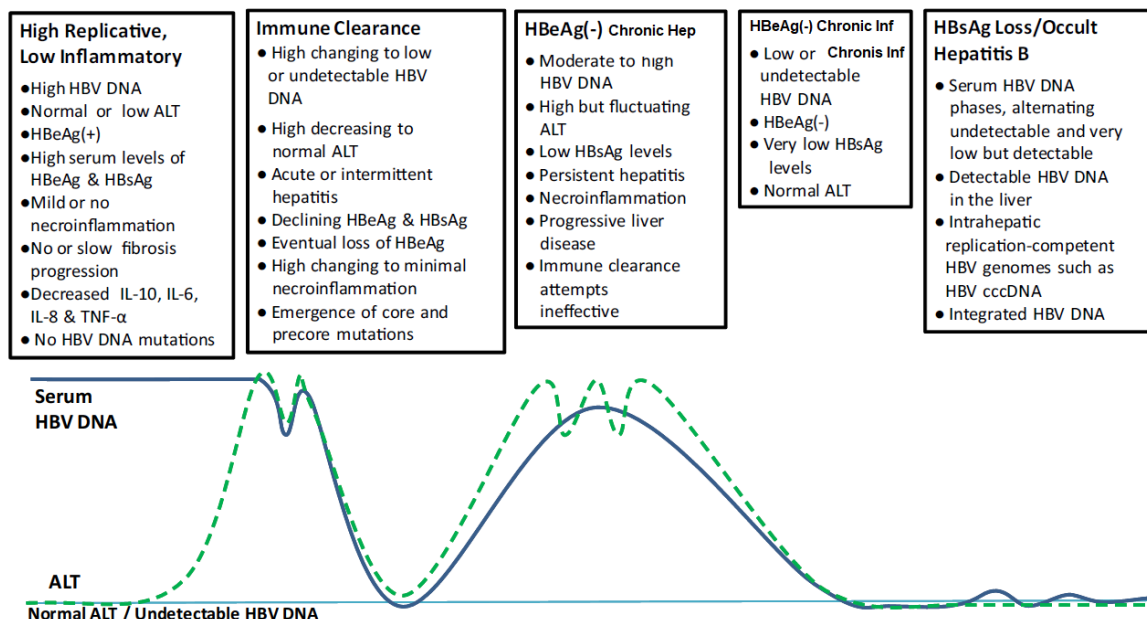
- **HBeAg-positive, chronic hepatitis:** This phase corresponds to what was previously termed “immune clearance”. It can be distinguished from the previously mentioned phase by a relatively lower level of HBV DNA replication. Nevertheless, there are usually increases in transaminases and necro-inflammation associated with the exacerbation of the host immune response and therefore, an increased risk of evolution towards fibrosis and cirrhosis with longer duration in this phase. The outcome of this phase is variable. Most patients can achieve HBeAg seroconversion (i.e. HBeAg loss and acquisition of anti-HBeAb) and HBV DNA suppression, which lead to the subsequent phase of HBV infection, ‘HBeAg-negative chronic hepatitis’. Roughly 8-15% of individuals in this phase annually will spontaneously seroconvert to HBeAg-negative/anti-HBsAb positive status (30,35–38). Other patients might develop mutations on the *precore* or basal core promotor, which abrogate HBeAg production despite the presence of high HBV DNA viral loads (39). HBsAg seroclearance may occur in some individuals who are able to control and sustain HBV replication (29,40).
- **HBeAg-negative, chronic infection:** This phase usually begins after HBeAg seroconversion. During this stage, transaminase levels are normal and HBV DNA replication in serum is low (<2,000 IU/mL) or undetectable (as measured using a sensitive PCR-based assay). The rate of spontaneous HBsAg-seroclearance and HBsAg-seroconversion during this phase is in the order of 1-3% per year. In contrast, about 4-20% of individuals in this phase return to the HBeAg-positive, chronic hepatitis phase (30,41)
- **HBeAg-negative, chronic hepatitis:** This phase is also characterized by the absence of HBeAg and usually the appearance of anti-HBeAb. In the majority of patients

belonging to this phase, mutations on the *precore* gene (i.e. the G1896A nucleotide substitution) and basal core promoter (i.e. the A1762T/G1764A nucleotide substitution) are commonly observed. This phase is manifested by periodic fluctuations in HBV DNA viral replication, transaminases, and lesions of necro-inflammation and fibrosis, and is associated with low rates of spontaneous reversion to HBeAg-positive chronic hepatitis. Individuals able to acquire anti-HBeAb are more frequently able to control HBV replication (42). Individuals in this phase rarely exhibit HBsAg-seroclearance and HBsAg-seroconversion.

- **“Occult” HBV infection (OBI):** Some individuals exhibit loss of HBsAg with the appearance of anti-Hepatitis B core (HBc) antibodies (anti-HBcAb) and persistent HBV replication at low levels. Most often viral DNA is undetectable in the serum or plasma, but detectable in the liver. These individuals are classified as having “occult” hepatitis B infection (OBI) (43). Although this status has never been defined as a separate phase in American or European guidelines, others have viewed OBI as a sort of fifth phase of infection (44,45). Based on the antibody status, OBI may be further categorized into two OBI groups: *seropositive OBI* with anti-HBsAb positive serology and *seronegative OBI* with anti-HBsAb negative serology (43). The prevalence of OBI varies across patient populations owing to numerous factors, such as geographic location, assay characteristics, host immune response, coinfection with other viruses, and vaccination status(46). For individuals with OBI, the risk of HBV reactivation is relatively high and some have suggested that onward HBV transmission could occur (29). OBI has also been implicated in the development of hepatocellular carcinoma (HCC). The proposed pathogenetic mechanisms of OBI-related HCC include the influence of HBV DNA integration on the hepatocyte cell cycle, production of pro-oncogenic proteins, and persistent low-grade necroinflammation (46).

There is a clear association between higher HBV DNA viral loads and liver fibrosis, HCC and liver-related mortality, which can be explained by the increased levels of liver damage from host immune responses, as evidenced by high alanine aminotransferase (ALT) levels (47). Considering that the risk of cirrhosis or HCC is contingent on the HBV DNA and ALT levels, as well as the cumulative duration under higher levels over time, and that this information is used to determine the phase of chronic HBV infection, each phase has their own risk of developing liver-related morbidity and mortality. The 5-year risk for a variety of hard clinical outcomes is highest for untreated individuals with HBeAg-negative chronic hepatitis: cumulative risk of 8% to 20% with cirrhosis, cumulative risk of 10 to 15% with HCC, risk of cirrhotic decompensation of 20%, and probability of survival between 14% and 35% (48,49). The risk for these events is substantially lower in individuals with HBeAg-negative infection and OBI. There have also been other studies in largely HBeAg-positive, Asian populations that have found higher rates of HCC in individuals chronically infected with HBV genotype C when compared to genotype B (50,51).

Figure 2: Major phases of chronic hepatitis B virus infection



This figure has been adopted from (52). Phases of HBV infection are illustrated with serum HBV DNA and ALT levels. Hallmarks of these infection phases, including HBeAg and HBsAg status, are also described in the boxes above.

The overarching goal of treatment is to eventually bring individuals to phases of low risk of liver-related morbidity and mortality, as will be discussed in Chapter 1.2. Indeed, effective anti-HBV treatment has been able to effectively suppress HBV DNA levels to undetectable levels, normalize liver enzyme levels, sometimes induce HBeAg-seroclearance and more infrequently, HBsAg-seroclearance, and finally to decrease necroinflammation and lessen liver fibrosis levels (53–55). Accordingly, preliminary evidence has shown that treatment can reduce the risk of HCC to very low levels; however, this risk still persists after years of effective HBV suppression (56).

In SSA, individuals are usually infected with HBV early in life compared to other regions of the world (57). After infection, roughly 50-60% of individuals before the age of 5 are HBeAg-positive, but this proportion declines rapidly with increasing age and a rate of spontaneous HBeAg-seroclearance at 5-15% per year (58). This finding explains why adults chronically infected with HBV from SSA are more frequently in HBeAg-negative phases of disease. Furthermore, most chronically infected individuals in SSA harbor HBV genotypes A and E, which are known to have a low rate of developing HCC (59,60), thereby explaining the low frequency of HCC and end stage liver disease (ESLD) observed on the continent.

1.1.3. HIV-HBV co-infection

In the presence of HIV and HBV, both appear to affect the natural history of one another. Chronic HBV infection has been observed, albeit inconsistently, to have a negative effect on the immunologic response of HIV in HIV-positive individuals (61). Part of this finding could be explained by the impaired HBV-specific T-cell immune response during HIV-HBV co-infection (62,63). However, the vast majority of studies have shown that progression of HIV-related disease is not more rapid in individuals infected with HBV (64).

HIV-infection is also known to bear a certain influence on resolving HBV infection, such as decreasing the probability of HBsAg-seroconversion during acute infection and increasing the rate of progressing to chronic infection (61). Co-infection with HIV also alters the natural history of chronic hepatitis B, with increased serum HBV DNA levels and increased liver enzyme levels in particularly those with low CD4+ cell counts and naïve of ART (65). Accordingly, the negative consequences during co-infection parallels faster progression of HBV-related liver disease. For instance, liver cirrhosis has been more commonly reported in HIV-HBV coinfecting individuals despite lower ALT levels than those with HBV mono-infection, which may be more

closely related to lower CD4+ T cell counts (66,67). Individuals with HBV infection who are HIV-positive also tend to have more severe liver fibrosis, progress more rapidly to ESLD, have a higher risk of liver-related death, and more likely progress to HCC than patients without HIV (68–70).

Fortunately, several antiretroviral agents for HIV are also effective for HBV, which means that viral suppression of both HIV and HBV through combined ART can mitigate the progression of the natural course of disease. ART containing a potent anti-HBV agent is known to be associated with normalization of ALT levels and can induce HBeAg and HBsAg seroconversion when HIV RNA viral load suppression is sustained (40,69,71). Consequently, the risk of progressing to severe complications due to chronic HBV infection is decreased during ART containing anti-HBV and anti-HIV agents (72). However, several studies have shown that all-cause mortality still remains high in this population and higher than in HIV mono-infected patients (73–76). Most of these studies involved patients with very low CD4+ cell counts despite effective ART. Recently, it has been shown that the risk of death from both AIDS- and non-AIDS related death has dramatically decreased in HIV-HBV co-infected patients ever since the advent of TDF-containing ART (77). On the other hand, little is known about mortality in the context of early treatment, as well as the factors influencing morbidity and mortality for early treatment initiators.

In the setting of SSA, the majority of co-infected individuals have already acquired HBV during youth and adolescence (78). Thus, they had been chronically infected with HBV when acquiring HIV-infection during adulthood, as discussed in Chapter 1.4. Given that the most common HBV phase observed on the continent is HBeAg-negative chronic infection, it would be assumed that HIV-HBV co-infected patients from SSA would likely be in a post HBeAg

seroconversion phase with low or undetectable HBV DNA. To what extent HIV would influence HBV infection and *vice versa* can only be speculated, as most studies on the natural progression of co-infection involved HBeAg-positive individuals with mainly sexually-acquired infections during adulthood (66,79,80) and there are virtually no studies in co-infected patients within this specific epidemiology.

1.2. Antiviral treatment for HIV and HBV infections

1.2.1. HIV infection

As discussed in Chapter 1.1, the main goal of ART is to prevent progression to AIDS and death by lowering HIV RNA viral load and consequently, maintaining or restoring immunity (81). There are 4 major classes of antiretroviral treatment available in SSA:

- **Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs):** This is the oldest class of antiretroviral agents. NRTIs inhibit the HIV enzyme, reverse transcriptase, responsible for transforming viral RNA into DNA, which allows it to integrate into the DNA of the host cell. This class of antiretrovirals includes mainly: zidovudine (AZT), lamivudine (3TC), emtricitabine (FTC), and tenofovir (TDF). With the exception of FTC, all these drugs are available in Côte d'Ivoire.
- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs):** This class of antiretrovirals also inhibits reverse transcriptase, yet the target is on a different portion of the enzyme compared to NRTIs. Nevirapine (NVP) and efavirenz (EFV) are the most commonly used NNRTIs in SSA. NVP is only used to prevent mother to child HIV transmission and no longer to treat HIV-positive adults in Côte d'Ivoire. EFV-based regimens were formerly used as first-line treatment, but is still available as part of the therapeutic arsenal.

- **Protease inhibitors (PIs):** HIV protease inhibitors are all small protein-like chains designed to mimic a peptide (peptidomimetics). They bind to the active site of the viral protease and prevent it from catalyzing the cleavage of the polypeptides of the virus. From this class, ritonavir-boosted (/r) lopinavir (LPV/r), darunavir (DRV/r) and atazanavir (ATV/r and without /r) are the PI agents currently used in Côte d'Ivoire as part of second- and third-line ART regimens.
- **Integrase strand transfer inhibitors (INSTIs):** This class of agents inhibits the catalytic activity of integrase, an enzyme encoded by HIV necessary for viral replication. Integrase inhibition prevents covalent insertion, or integration, of the HIV genome into the host cell genome. This class includes raltegravir (RAL) and dolutegravir (DTG). Currently, DTG-based regimens are used as first-line ART in Côte d'Ivoire.

From these classes, different drugs are combined to define the ART regimen line. In Côte d'Ivoire, the current first-line regimen usually consists of 2 NNRTIs and 1 INSTI, such as TDF/3TC/DTG.

The major impediment to effective ART is the development of HIV resistant variants. In the early 2000s, when HIV treatment was scaled up in SSA, ART was almost exclusively based on NRTIs and NNRTIs with oftentimes a low genetic barrier to resistance. As a result, it was common to find strains resistant to these classes in treated HIV-positive individuals in SSA (82,83). These resistant strains can be transmitted to a newly infected person. A meta regression-analysis of Transmission Drug Resistance (TDR) surveillance studies in low and middle income countries (LMIC) conducted until 2010 showed a significant increase of primary NNRTI TDR over time in SSA. The increase was steepest in east Africa, reaching a prevalence of 7.4% after the rollout of ART. A recent update in 2016, including individuals with both TDR

and other reasons of pretreatment resistance (PDR), confirmed this trend and predictions of the prevalence of NNRTI PDR for 2016 ranged from 7.2% to 15.5% across Africa (82,84,85). The emergence and transmission of HIV resistant strains renders the choice of effective antiretrovirals limited and could have consequences at the population level. This line of reasoning led the World Health Organization (WHO) to recommend non-NNRTI-containing first-line ART regimens in countries where NNRTI PDR exceeds 10% (86).

As ART became more effective during the 2000s yet was still associated with a number of severe side-effects, such as cardiovascular disease, changes in lipid metabolism, etc. (87,88), it had been debated whether ART should be initiated shortly after HIV-diagnosis or delayed until CD4 cell counts were below a certain threshold. Several criteria of starting ART have been implemented under the aegis of the WHO, taking into account the research of available regimens at the time (89). Before 2015, HIV-positive individuals were treated according to CD4 levels. Results from two large, randomized clinical trials showed a benefit in morbidity and mortality when ART is initiated early in HIV-positive individuals. In those who immediately start ART, serious AIDS-related events were reduced by 70% and the risk of death or severe HIV-related illness was lower than in individuals who were deferred ART according to a CD4+ cell count threshold (13,90). This led the WHO to recommend ART to all HIV-positive individuals without any CD4+ criterion (91).

Access to treatment remains one of the most important elements of reducing morbidity and mortality and preventing onwards transmission of HIV. The Joint United Nations Programme on HIV/AIDS (UNAIDS) is one of the largest international programs to help ensure that care and treatment are provided for people living with HIV around the world. In 2018, 19.0 billion US dollars were invested for the response to HIV/AIDS in LMIC. Additionally, around 56% of

the total resources for HIV in LMIC in 2018 were from domestic sources (19), while this co-financing structure makes it possible to provide care and treatment of HIV-positive individuals free-of-charge. These services have helped increase access to treatment from 7.7 million in 2010 to 26 million HIV-positive individuals in 2020 (3,92). Overall, an estimated 68% of adults and 53% of children living with HIV globally were receiving lifelong ART in 2019 (3). With the 90-90-90 goals, in which 90% of HIV-positive individuals are aware of their infection, 90% of them are treated with ART, and 90% of them have undetectable HIV RNA, UNAIDS believed in 2016 that 26.2 billion US dollars will be required to achieve these goals in 2020 (19).

1.2.2. HBV infection

The therapeutic goals of therapy for chronic HBV infection are the reduction of circulating viremia and amelioration of liver function, with the expectation that these would lead to prevent or reduce the risk of progression to cirrhosis, liver decompensation, and HCC. To this end, various endpoints for treatment have been recommended, which include virological (i.e. achieving undetectable HBV DNA levels), serological (i.e. achieving HBeAg-seroclearance or seroconversion for HBeAg-positive individuals and achieving HBsAg-seroclearance or seroconversion for all chronically infected patients), biochemical (i.e. normalization of ALT), and histologic (i.e. reduced necroinflammation or reversion of fibrosis) responses (93). HBV DNA suppression ensures that treatment is effective, especially for nucleoside/nucleotide analogues (94). Nevertheless, the ideal endpoint is HBsAg-seroconversion (i.e. no longer chronically infected) (95), which is infrequently achievable with the currently available anti-HBV agents.

Eight therapeutics are currently licensed for the use against HBV by the US Food and Drug Administration and comprise two classes of agents: 6 oral nucleoside/nucleotide analogues

(NA) and standard or pegylated (peg) IFN- α . Some of the NAs, such as 3TC, TDF and tenofovir alafenamide (TAF) are also active against HIV (48).

- **Nucleoside/nucleotide analogs (NAs):** This class of agents targets the reverse transcriptase function of the HBV polymerase and therefore interferes with the synthesis of viral DNA from pregenomic RNA. NAs are administered orally and are very well tolerated. NAs approved for the treatment of HBV fall into three groups: L-nucleosides, including 3TC and telbivudine; acyclic phosphonates, including TDF, TAF and adefovir; and deoxyguanosine analogues, including entecavir (ETV). ETV and TDF (and likely TAF) have more potent antiviral activity and have been associated with higher rates of HBV DNA viral suppression, ALT normalization and histologic improvement (96). In HBeAg-positive patients, NAs lead to HBeAg-seroconversion in approximately 20% of patients at 48–52 weeks of therapy; however, when treatment is stopped, up to 50% of patients revert back to HBeAg-positive serology within 6 months (97). In HBeAg-positive patients, rates of HBsAg-seroclearance following 12 months of treatment were 1% with 3TC, 0% with adefovir, 2% with ETV, 0.5% with telbivudine, and 3% with TDF (98–103). This rate was 0% for all NAs agents in HBeAg-negative patients (102–105). HBsAg-seroclearance occurs for the most part at a constant rate in HBeAg-positive individuals, with roughly 3-5% achieving this endpoint after 3–5 years of NA therapy (106). HBsAg loss is rarely observed during a similar timeframe in HBeAg-negative patients (107–109).
- **Alpha interferons (IFN- α):** These agents are pleiotropic cytokines with antiviral, anti-proliferative, and immune modulatory effects. Upon binding of IFN- α to its receptor, multiple interactions between Janus kinases and signal transducers and activators of transcription cause a variety of signaling responses, including induction of a diverse set of IFN-stimulated genes and many antiviral proteins (110,111). It promotes CD8+

T cell responses, induces macrophage activity, NK cell cytotoxicity, cytotoxic lymphocyte activity and decreases in neutrophil activation (112). In HBeAg-positive patients, rates of HBsAg-seroclearance following 12 months of treatment were 3-7% with peg-IFN- α (113,114). After completing IFN/peg-IFN- α therapy, HBsAg-seroclearance is more likely to occur in patients with sustained off-treatment virological response (115–117) and, if combined with NAs, prolonged duration of NA therapy (106,107,118,119). In HBeAg-negative patients, rates of HBsAg-seroclearance 6-months after following a 12-month course of treatment with peg-IFN-2a were 3% (120). HBsAg-seroclearance increased to 9% at 3 years and 12% at 5 years following discontinuation of peg-IFN-2a therapy (48,120). In a retrospective evaluation of HBeAg-positive patients treated with IFN, HBsAg-seroclearance occurred in 23% of patients during a median follow-up of 8.8 years (116).

In the early 1990s, IFN- α was licensed for the treatment of chronic HBV infection in most countries. Its advantages are a finite treatment period (6 months to 1 year) and inability of resistant mutant variants of HBV to emerge. The efficacy of IFN- α is determined by both virological (HBV DNA <2,000 IU/mL) and serological response (HBeAg- or HBsAg-seroconversion) (121). The major disadvantage of IFN- α is a variety of side-effects, which limit dosing and thus can reduce therapeutic efficacy. These side effects include flu-like symptoms, fatigue, anorexia, and depression, which may be mild or severe (122). Furthermore, it requires weekly injections to be administered. These drawbacks have made treatment with NAs more favorable for many settings.

NAs only suppress viral replication by inhibiting HBV reverse transcriptase, but do not directly suppress viral transcription and translation or more importantly, do not diminish the pool of

covalently-closed circular (ccc-DNA), which is the viral template for all proteins involved in HBV replication (123–125). This means that HBV remains latent in hepatocytes despite NA-induced suppression of circulating virus. Thus, NA treatment is considered to be of indefinite duration for the vast majority of patients. It has been therefore estimated that the median time to HBsAg-seroclearance would be 36 years for HBeAg-positive and 39 years for HBeAg-negative patients with chronic HBV infection (126). There are some additional concerns with the use of TDF, particularly centered around reports of renal and bone toxicity and subclinical reductions in kidney function (127) and bone mineral density (128). TAF would appear to be less toxic to the kidney and bones compared to TDF (129).

Similar to HIV, effective suppression of HBV DNA can be mitigated by the emergence of mutant HBV resistant strains, whose risk increases substantially with longer periods of treatment for some NAs. The rate at which resistant mutants are selected is also related to serum HBV DNA levels prior to treatment, the time taken to suppress HBV DNA and prior exposure to other NA therapies (resulting in compensatory mutations) (130). 3TC is associated with the highest rates of emerging resistance, with 14% to 24% of HBeAg-positive and 6–18% of HBeAg-negative patients developing genotypic resistance after one year of therapy and >70% of both HBeAg-positive and HBeAg-negative patients after 8 years of continuous therapy (98,101,114,131–134). Resistance to ETV is very uncommon and is usually due to compensatory mutations from previous exposure to 3TC (131,132). The rates of developing TDF or TAF-resistant HBV is virtually null, while no documented resistance has been observed to date (135,136). One case report has described a patient who was naïve of NA treatment and showed complete viral suppression before developing supposed TDF resistance (137). Genotypic sequencing showed 9 mutation sites, most of which had never been described as conferring resistance to TDF. For these reasons, only ETV, TDF and TAF

are included as the mainstay treatments in clinical practice guidelines for HBV mono-infection (29). These potent NAs with a high genetic barrier to resistance offers a predictably high, long-term antiviral efficacy in the vast majority of patients adhering to their therapy (29).

The criteria to initiate either IFN or NAs-based therapies is relatively more complex than in HIV mono-infection. Current guidelines recommend treating chronically HBV infected patients with elevated circulating levels of viral HBV DNA, ALT and aspartate aminotransferase (AST), as they are at the greatest risk of developing progressive liver disease and HCC (138). There is much discussion as to if and when individuals with HBeAg-positive chronic infection or HBeAg-negative chronic infection should even initiate therapy. NAs can be safely used in any HBV-infected patient and represent the only treatment option for several patient subgroups, which include those with decompensated liver disease, liver transplant, extra hepatic manifestations, or severe chronic HBV exacerbation (136,139).

In SSA, TDF and 3TC are becoming more and more accessible for the management HBV infection, but only in the context of HIV infection (i.e. for HIV-HBV co-infected individuals). This is mainly with the financial assistance provided by national and international HIV programs. Efforts still need to be made to widen TDF access to individuals with HBV mono-infection. Generic tenofovir is widely available at a low cost for many LMICs, particularly as part of their national ART programmes, although the annual cost per person may range from 50 to 350 US dollars (140). HBV mono-infected individuals almost always have to pay out-of-pocket for treatment, as well as monitoring HBV DNA suppression and drug toxicity, which significantly increases the annual cost of care. These costs are completely free of charge for HIV-HBV co-infected individuals.

1.2.3. HIV-HBV co-infection

As mentioned earlier, some antiretroviral treatments, such as 3TC, TDF and TAF, have effective antiviral activity on both HBV and HIV, which makes it possible to treat both infections simultaneously. The same therapeutic issues for these infections individually mostly apply to HIV-HBV co-infected individuals. The WHO has recommended that people with active chronic HBV infection, defined by an APRI score >2 , elevated transaminases, HBeAg-positive and elevated HBV DNA viral load and living with HIV start ART containing 300 mg TDF, regardless of their CD4 count (141). In contrast, the European AIDS Clinical Society (EACS) guidelines recommend that all HIV-HBV co-infected individuals initiate ART with either TDF or TAF, unless these agents cannot be tolerated (142). The optimal treatment duration for the anti-HBV active agent included in the ART regimen has not yet been determined and similar to HBV mono-infection, it is likely to be life-long. For individuals whose anti-HBV active agent needs to be modified, anti-HBV therapy may be stopped cautiously in non-cirrhotic HIV-positive individuals who have achieved HBeAg-seroconversion for at least one year or after confirmed HBsAg-seroconversion in those who are HBeAg-negative (29). In HIV-positive individuals with liver cirrhosis, discontinuing effective anti-HBV treatment is not recommended in order to avoid severe flares in liver enzymes and liver decompensation following HBV reactivation (143). Peg-IFN has been entertained as an intensifying agent to increase the rate of HBeAg-seroclearance in HBeAg-positive HIV-HBV co-infected patients, but one cohort study demonstrated no increase in rates of HBeAg- or HBsAg-seroclearance during peg-IFN intensification, despite faster declines of antigen levels while on peg-IFN (144).

Similar considerations on developing resistant variants during treatment for each infection individually also applies to HIV-HBV co-infection. The WHO recommends preferential use of NAs with a high genetic barrier to drug resistance, which would exclude 3TC (140). However,

from studies in HIV-HBV co-infected individuals, the rates of developing 3TC resistance are somewhat lower in settings where HBV DNA viral loads are very low and HBeAg is negative (145,146). Interestingly, ETV has demonstrated *in vitro* and *in vivo* anti-HIV activity (147), but can induce the M184V mutation in HIV and is hence not recommended for HIV-HBV co-infection unless given with concomitant TDF- or TAF- containing ART (148).

In terms of treatment outcomes, TDF suppresses HBV to undetectable levels for the majority of HIV-HBV coinfecting patients. The proportion with fully suppressed HBV steadily increases during continuous treatment, with 57.4%, 79.0% and 85.6% at one, two and three years of TDF-containing ART, respectively (149). However, roughly 10% of patients are expected to exhibit persistent HBV viremia (i.e., ongoing HBV replication, usually at low-levels) despite HIV suppression and 5-years of TDF-based ART (150). An analysis of TDF concentrations in dried blood spots (DBS) of HIV-HBV co-infected individuals with persistent viremia demonstrated lower tenofovir concentrations than expected (150,151). This suggests that lower ART adherence may be partly responsible for persistent HBV viremia and that the threshold for ART adherence is different for suppression of HBV than HIV (152). In cohorts of ART-treated HIV-HBV-co-infected individuals, 39.7% of HBeAg-positive individuals are expected to have HBeAg-seroclearance, while anywhere from 5% to 22% of all individuals are expected to have HBsAg-seroclearance after 3 years of treatment (153–156). Interestingly, HBsAg-seroclearance/-seroconversion is associated with lower baseline CD4+ cell count at ART-initiation, greater increases in CD4+ cell count from ART-initaiton, and having an AIDS-defining illness (157–159). This raises questions about the potential role of immune reconstitution on HBsAg-seroclearance (160,161). However, other cohorts of individuals with HIV-HBV co-infection and baseline CD4+ count below 200 cells/mm³ have not substantiated these findings (152).

1.3. Clinical monitoring during HIV and HBV infections

1.3.1. HIV infection

There are several guidelines, such as those from the EACS (142) and WHO (89), on the monitoring involved in HIV-positive individuals. Their recommendations are highly extensive and will not be summarized in this thesis. Instead, guidelines for the clinical management of HIV-positive individuals from Côte d'Ivoire (162), which are largely based on those from the WHO, will be summarized.

After individuals initiate ART, HIV-positive individuals are monitored biologically and clinically every six months. The aim is to evaluate the efficacy and safety of their treatment regimen. Measuring HIV RNA viral loads remains the gold standard for assessing the effectiveness of treatment. Two HIV RNA viral load measurements are recommended at 6 and 12 months after initiating ART in adult patients. After 12 months, HIV RNA viral load measurements are carried out once a year (163,164). Kidney and liver function tests are measured by determining transaminase and creatinine levels, mainly in order to assess treatment tolerance. Additionally, vomiting, weight loss, or skin lesions will also be examined, which are also suggestive of treatment intolerance or an opportunistic disease.

Successful management of PLWH goes beyond simply providing effective ART, with increasing focus being placed on the appropriate management of co-morbidities in order to ensure high quality of life for people living with HIV (PLWH). Recognized co-morbidities that disproportionately affect PLWH include cardiovascular disease, pulmonary, hepatic, metabolic, neoplastic, renal, bone, central nervous system disorders, as well as sexual dysfunction (142). Many of these conditions are expected to become more prevalent as HIV-

positive individuals grow older (165,166). Guidelines suggests HIV-specific age cut-offs at which screening for many of these co-morbidities should take place, as well as introducing new sections to offer guidance on screening for frailty in older PLWH (143,167). Unfortunately, the management of co-morbidities is not accounted for in the Ivorian guidelines, at least not as well detailed as those for opportunistic infections. Another challenge in their management is that each patient has to pay out-of-pocket or through a private health insurance plan for care related to almost all of these co-morbidities, which can limit the access to these services for HIV-positive individuals with co-morbidities.

1.3.2. HBV infection

In general, almost all country-level recommendations for monitoring patients with chronic HBV infection are drawn from those provided by the WHO in 2015 (168). Exceptions include recommendations from high-income countries, such as those from the American Association for the Study of Liver Diseases (AASLD) in 2019 (169) and EASL in 2017(29). Each country or region adapts their recommendations depending, to a certain extent, on the services that can be provided and the local epidemiology. Monitoring patients chronically infected with HBV is naturally based on aspects related to disease progression, such as HBsAg, HBeAg, HBV DNA, ALT, liver fibrosis assessment and treatment toxicity. It also depends on whether patients are on treatment. The WHO recommends monitoring, at least annually, of the following:

- ALT level, HBsAg, HBeAg, and HBV DNA levels when HBV DNA testing is available;
- Non-invasive test (APRI or FibroScan) to assess for the presence of liver cirrhosis, for those without a previous diagnosis of cirrhosis;
- If on NA-based therapy, adherence should be monitored regularly and at each clinical visit. Furthermore, monitoring the markers above should be performed at least every 3 months for the first year. In all persons prior to initiation of antiviral therapy,

measurement of baseline renal function and assessment of baseline risk for renal dysfunction should be considered. Renal function should be monitored annually in persons on long-term TDF or ETV therapy (140).

Currently, in Côte d'Ivoire, patient monitoring is in function of HBeAg status and whether the patient is cirrhotic or not. As mentioned previously, HBV mono-infected patients are required to pay for their HBV-related care out-of-pocket. Ivorian HBV monitoring criteria have been adapted from the WHO guidelines, per available healthcare facilities and technical capacity. These criteria are summarized below.

For patients who are not receiving treatment, monitoring focuses on assessing criteria for treatment initiation. Non-treated patients with HBeAg-positive chronic HBV infection who are younger than 30 years should be followed at least every 3–6 months. Those with HBeAg-negative chronic HBV infection and serum HBV DNA <2,000 IU/ml should be followed every 6–12 months. Finally, those with HBeAg-negative chronic HBV infection and serum HBV DNA \geq 2,000 IU/ml should be followed every 3 months for the first year after entering care and every 6 months thereafter (29).

Monitoring for patients with chronic HBV infection undergoing treatment is considerably different. In patients receiving IFN-based treatment, HBV DNA viral loads and HBsAg are monitored at treatment initiation and at 12 and 24 weeks of treatment, while ALT levels are evaluated monthly. In those taking NAs-based treatments, ALT and HBV DNA viral loads are monitored at treatment initiation, every 6 months (HBeAg-positive) or every 3 months (HBeAg-negative) and HBsAg at treatment initiation and once a year. Treatment continuation and discontinuation criteria are as follows (170):

- When treated with peg-IFN, treatment stop criterion are:
 - If no decline in HBsAg levels $>1 \log_{10}$ at 12 weeks or if HBsAg levels $>25,000$ IU/mL or positive HBV DNA viral load at 24 weeks or any major side effects, peg-IFN should be discontinued and TDF should be initiated.
 - If HBV DNA viral load and HBsAg levels drop $>1 \log_{10}$ at 12 weeks or HBV DNA viral load becomes undetectable at 24 weeks, pegylated interferon should be continued for the complete course of 48 weeks.
- When treated with NA-based treatments:
 - In the absence of cirrhosis, discontinuation is possible if HBV DNA viral load is undetectable for at least 2 years and HBsAg levels are <100 IU/mL, HBsAg is negative, or HBsAg-seroconversion occurred. HBV DNA viral loads should be determined every 3-4 months and if they become detectable again, NA therapy should be re-initiated.

In the event of cirrhosis: treatment should be continued unless issues with treatment tolerance develop.

1.3.3. HIV-HBV co-infection

HIV-HBV co-infected patients are usually monitored and treated according to the guidelines of the respective infections individually. The EACS has provided a more detailed description of the specific tests required for this patient population. PLWH in general should be screened for HBV, usually for anti-HBcAb and HBsAg. Those who are anti-HBcAb positive, in particular those with elevated liver transaminases, should be screened for HBV-DNA to rule out OBI (142,171). All HBsAg-positive persons should be screened for hepatitis D virus (HDV). Liver blood tests should be performed every 3 months during the first year of ART initiation and every 6-12 months thereafter. HBV-DNA viral load should be determined every 3-6 months

during the first year of ART initiation and every 12 months thereafter. HBsAg should be assessed yearly until HBsAg-seroclearance (143).

In Côte d'Ivoire, there are no standardized monitoring guidelines for HIV-positive individuals who are chronically infected with HBV. ALT is the only HBV-related marker, which is monitored every 6 months, that is offered free-of-charge. All other markers of HBV activity will be assessed when symptoms occur, and this is performed at the patient's expense.

1.4. Common modes of transmission for HIV and HBV infection

1.4.1. HIV infection

HIV infection is predominately transmitted via sexual contact across mucosal surfaces, contact with infected blood, mother-to-child transmission, and percutaneous inoculation (172,173). Heterosexual transmission accounts for nearly 70% of HIV infections worldwide, with the remainder of infections attributed to MSM, mother-to-child transmission, and injecting drug use (IDU) (173). Some routes of transmission are more frequently observed than others, depending on the region (173). Table 1 summarizes the relative frequency of the different routes of HIV transmission according to LMIC and HIC. Sexual contact, particularly in men who had sex with men (MSM), and injecting drug use are more likely to be the main routes of transmission in HIC. While in LMIC, sexual contact, mostly heterosexual, and mother-to-child transmission seem to be the predominant routes of HIV transmission.

1.4.2. HBV infection

HBV infection is commonly transmitted via sexual transmission, mother-to-child transmission, and direct exposure to infected blood or saliva (174,175). Similar to HIV, there are substantial differences in the frequency of HBV transmission routes depending on region, while the relative frequency of the different routes of HBV transmission according to LMIC and HIC is summarized in Table 1. Sexual transmission of hepatitis B is known to occur particularly in unvaccinated MSM and persons with multiple sex partners or contact with sex workers (176). In the 1990s, HBV transmission was found to be rather common in MSM in HIC (Table 1), which then declined substantially with targeted and/or universal vaccination programs (177,178). Horizontal transmission is the most common mode of HBV transmission in SSA (179,180). Studies in western or southern Africa show that around 30% to 40% of children under the age of 5 are either currently infected (HBsAg+) with or previously exposed to HBV (HBcAb) (181). Nevertheless, a study in repeat blood donors from Côte d'Ivoire found a rate of newly HBsAg-positive individuals at 700 per 100,000 inhabitants per year, suggesting that acute infections and ongoing transmission of HBV are still occurring despite the fact that vaccination via the Expanded Program of Immunization has been available since 2002 (182,183).

1.4.3. HIV-HBV co-infection

HIV and HBV share very similar routes of transmission. The frequency of these transmission routes for HIV-HBV co-infected individuals are summarized in Table 1. Oftentimes, these infections are acquired at different moments during life, depending on the regional epidemiology. In settings where HBV is highly endemic, HBV is acquired during or after birth through perinatal transmission (predominantly in east and south-east Asia) or in young children through close household contact or through medical or traditional scarification

procedures (predominantly in Africa) (69). In these regions, HIV is mostly acquired later during adulthood through sexual intercourse. Some research in LMIC has shown that HIV-HBV co-infection potentially increases the risk of perinatal HBV transmission (69,184) and thus without appropriate post-exposure prophylaxis, infants born to these mothers could acquire both viruses at birth. In settings where HBV is less endemic (i.e., North America, Europe, and Australia), HBV and HIV are most often acquired during adolescence or adulthood through sexual transmission or IDU (2). For all settings, as vaccination campaigns have reduced the transmission of HBV, the risk of becoming co-infected with HIV-HBV has also decreased.

Table 1. Main transmission routes of HIV and HBV infections according to region

Transmission types	Low and middle income countries			High-income countries		
	HBV	HIV	HBV-HIV	HBV	HIV	HBV-HIV
Heterosexual	↑↑	↑↑↑	↑↑↑	↑	↑↑	↑↑
MSM	↑	↑	↑	↑↑↑	↑↑↑	↑↑↑
Unsafe Injection [†]	↑	↑	↑	↑↑↑	↑↑↑	↑↑↑
Vertical*	↑↑↑	↑	↑	↓	↓	↓
Horizontal**	↑↑↑	↑	↑	↓	↓	↓

Table uses data from (185). Arrows indicate increased or decreased frequency of modes of transmission with respect to the given infection and country. This is not the same as transmission probability.

*: infection transmitted from mother-to-child. This mostly applies to south-east Asia.

**: infection transmitted within the household. This mostly applies to Africa.

†: unsafe infection is defined by reuse of single-use disposable syringes and needles, multiple injections using a single needle and syringe.

Abbreviations: HBV, hepatitis B virus; HIV, human immunodeficiency virus; MSM, men who have sex with men.

1.5. Prevalence of HIV and HBV infections

1.5.1. *HIV infection*

The prevalence of HIV is known by epidemiological surveys or data collection from national surveillance systems through each country's Ministry of Health. From these sources, there were 37.9 million PLWH worldwide in 2018, of which 36.2 million were adults. In 2018, 1.7 million people were newly infected (3,19) and the annual number of new infections among adults globally has declined 13% since 2010 (186).

For nearly all regions of the world, HIV prevalence is highest in certain groups who share common risk factors (187). These key affected populations include MSM, persons who inject drugs (PWID), people in prisons and other incarcerated individuals, sex workers and transgender people (188). Each of these groups has complex legal and social issues related to their behaviors that contributes to their increased susceptibility to HIV infection and prevents them from accessing prevention and treatment services (189). Given the high prevalence of HIV infection in these populations, they are considered essential partners for an effective response to the pandemic. Infants of HIV-positive mothers are another group considered at high risk of infection, but one of the great success stories of HIV prevention has been the near elimination of mother-to-child transmission when ART is correctly used.

Over two-thirds of all PLWH reside in the African WHO Region, which is the equivalent of 25.7 million individuals (190). While HIV is prevalent in the general population in this region,

an increasing number of new infections has been occurring among key population groups (191,192). Key populations and their sexual partners account for 54% of new HIV infections globally and 64% of new HIV infections in western and central Africa (193,194). MSM accounted for an estimated 17% of new HIV infections globally. The risk of acquiring HIV is 22 times higher in PWIDs than for people who do not inject drugs, 21 times higher for sex workers than adults aged 15–49 years and 12 times higher for transgender women than adults aged 15–49 years (3,186,195).

In Côte d'Ivoire, surveillance of HIV infection relies on surveys of general population and studies conducted in key populations, such as sex workers and MSM (182). Côte d'Ivoire is one of the countries most affected by HIV in the region of west and central Africa, after Nigeria, Cameroon and the Democratic Republic of Congo (DRC). In 2018, HIV prevalence among adults (hereto defined as 15-49 years) was 2.6% (8). The prevalence of HIV is much higher in urban than in rural areas (13,182,196). Importantly, women are disproportionately affected by HIV in Côte d'Ivoire and of the 430,000 adults living with HIV, 260,000 (60.5%) were women. New HIV infections among young women aged 15-24 years were more than three-times higher than those among young men, with 3100 new infections among young women, compared to fewer than 1000 among young men. Given that five other countries neighbor Côte d'Ivoire, there is a large flow of migrants who are also a key population highly susceptible to HIV-infection (198).

1.5.2. HBV infection

Estimates of HBV infection relies on data from clinical trials, national surveillance systems and epidemiological surveys through research institutes, local ministries of health, and non-government organizations. It should be noted that, as opposed to HIV infection where there is

only HIV-positive or HIV-negative status, reports of HBV infection prevalence focus on different aspects of HBV infection, such as being HBsAg-positive, being anti-HBcAb-positive, or having OBI, etc. From these sources, it has been estimated that more than 2 billion people have had HBV infection (i.e., anti-HBcAb-positive), with a strong increase in anti-HBcAb-positive serology as age increases (199,200). Furthermore, 350 million were identified as chronically infected with HBV (i.e., HBsAg-positive) and thus were at high risk of liver cirrhosis and primary HCC (201–203). HBV accounts for an estimated 500,000-700,000 annual deaths worldwide (201–204). Considering that a safe and effective vaccine has been available since 1982, many of these infections and deaths would have been preventable (201,204,205).

The prevalence of HBV is known to vary across different regions. Based on the relative prevalence worldwide, different degrees of “endemicity” have been defined. There are usually four endemicity levels of HBsAg-positive prevalence, which are described as low (<2%), lower intermediate (2-4%), high intermediate (5-7%), and high $\geq 8\%$ (206). SSA was formerly considered as a high endemicity. For example, studies in health workers and medical students in Uganda conducted from November 2000 to January 2001 found that 9.0-12.2% were HBsAg-positive and 45.9-79.6 were anti-HBcAb-positive (207). However, it is now classified as a high intermediate zone with an estimated overall prevalence of HBsAg-positive individuals at 6.1% (4.6–8.5) (175,208,209). Studies have attributed increased vaccination rates as the reason for this decline in prevalence (210). Notwithstanding these decreases, it is noteworthy that there has been an increase in the absolute total of HBsAg-positive individuals from 240 million in 2005 to 350 million in 2015 (202,210).

There have also been studies conducted in order to understand the prevalence of OBI, which are more difficult to execute as they require measuring anti-HBcAb, HBsAg, and HBV DNA.

Normally, anti-HBsAb is also required to distinguish between seropositive and seronegative OBI, as defined in Chapter 1.1.2, but this is infrequently measured in these studies. Reports from different regions worldwide have given a widely varying prevalence, from less than 1% to as high as 87% (211–213). Higher prevalence of OBI is usually found in areas where HBV is highly endemic or risk of parenteral HBV transmission is higher (214,215). As HBV infection is endemic to SSA and a large proportion has had exposure to HBV, it is unsurprising that the prevalence of OBI is high in this region (216,217).

In Côte d'Ivoire, there exist very few data on HBV infection prevalence for the general population. Studies have suggested that the prevalence of HBsAg-positive status is about 8.2% to 13% (182,197). Other estimates can only be inferred from HBV screening studies, which nationally concern specific populations, such as pregnant women, blood donors and in those who have medical complications suspected to be due to HBV infection. Given that these studies only used HBsAg to determine HBV infection status, the inavailability of anti-HBc and HBV DNA do not make it possible to study the prevalence of OBI.

1.5.3. HIV-HBV co-infection

Since HIV and HBV share similar transmission routes, co-infection is frequent (218). Nevertheless, HBV infection is much more commonly observed in HIV-positive individuals, whereas HIV infection is infrequently observed in individuals chronically infected with HBV (219). It is estimated that 5–20% of PLWH have chronic HBV infection (220). Nevertheless, the prevalence of co-infection in HIV-positive individuals is geographically heterogeneous and depends on various factors, such as distribution of key populations, implementation of HBV vaccination programs, and levels of endemicity in the general population (161,185,221). The highest prevalence of HBV infection in PLWH are found in Asia and Africa (2), primarily

affecting key populations of LMIC (222). In specifically SSA, chronic HBV co-infection in PLWH ranges from 3.4% to 28.4%, with the highest prevalence reported in west African and southern African cohorts (223). It should be noted that part of the variation in HBsAg-positive estimates are likely due to the disparities in HBsAg-testing in PLWH across countries and even between clinical centers.

Similar to HBV mono-infection, assessing the prevalence of OBI depends on the availability of data, which rarely include anti-HBsAb. Previous studies in PLWH have shown an estimated prevalence of OBI ranging from 0-18% (224,225). In HIV-positive individuals in SSA, almost all studies only report HBsAg. However, data from HIV-positive individuals screened for a complete HBV serological battery and HBV DNA suggest that 10% have OBI (226), which falls in line with other studies from the continent (227,228).

1.6. Testing for HIV and HBV infections

1.6.1. HIV infection

HIV testing is the gateway to HIV prevention, treatment, care and other support services. Knowledge of HIV status through HIV testing services is crucial to ensure adequate care, reduce transmission, and successfully respond to the HIV epidemic (229). As outlined earlier, the 90-90-90 target goals established by the WHO stipulates that 90% of PLWH should be aware of their status (230). HIV testing is based on a serological test, usually from an enzyme-linked immunosorbant (ELISA)-based assay, aimed at detecting antibodies to the virus. A variety of rapid tests are also available (231), which can be used to facilitate larger screening campaigns. Testing recommendations have been thoroughly described by several organizations, including the WHO (89,142). These recommendations have focused on targeting HIV testing in key populations, i.e. those with high prevalence of HIV. HIV screening

should be conducted to all individuals who are sexually active. Other key populations include sexually-active youth living in settings with high HIV prevalence, partners of PLWH who do not have undetectable viral load, and individuals recently diagnosed with sexually transmitted infection (STI).

In terms of testing frequency, many modeling studies have been conducted to assess how often HIV-negative individuals should be retested for HIV to reduce the incidence of HIV (232). For instance, Yazdanpanah et al have found that one-time screening in addition to risk-based screening is cost-effective; however, more frequent screening in subpopulations of substantially higher risk of HIV, such as MSM or PWID, is justified from a cost-benefit perspective (233). To enable those who have previously tested HIV-negative to remain HIV-negative and to identify those who have become HIV-positive as early as possible so that they can initiate treatment, the WHO recommends annual HIV testing for sexual active persons living in a setting with high HIV prevalence and more often (every 3 to 6 months) in people at high risk of acquiring HIV (230). In Côte d'Ivoire, it is suggested that all individuals have an HIV test at least once in their lifetime.

1.6.2. *HBV infection*

Screening for HBV can involve various serological markers of infection, which depend on the goal of the clinical or epidemiological investigation. HBsAg is used to screen for chronic (or acute) HBV infection, anti-HBcAb are used to determine past exposure of HBV infection, and anti-HBsAb are usually used to determine if vaccination was successful (if both HBsAg and anti-HBcAb are negative) or if past infection was resolved (if HBsAg is negative and anti-HBcAb is positive) (234). These serological markers are generally assessed using an ELISA-based assay, yet these tests can be expensive in some settings and not readily accessible to

every level of healthcare systems (196). There are also many rapid tests marketed for HBsAg (235) with high diagnostic accuracy, but those for anti-HBsAb have very poor performance (236) and those for anti-HBcAb are still in the early phases of development (237). Nonetheless, these rapid tests should only be considered as tools for screening and not diagnosis.

Similar to HIV, HBsAg testing should be based on risk of acquiring HBV. In all settings, vaccination against HBV should be given to those who are non-immune to HBV. In settings with an HBsAg-seroprevalence of $\geq 2\%$ in the general population, all adults should have routine access and be offered HBsAg serological testing with linkage to prevention, care and treatment services (238). HBsAg testing and linkage to these services should also be available to all pregnant women and their partners (239). In contrast to HIV, repeated testing is mostly performed when there is suspected acute HBV infection (29).

In Côte d'Ivoire, screening for HBV infection, usually by detecting HBsAg, is limited to certain populations, such as pregnant women, blood donors, and in patients who are suspected of having complications related to HBV infection. However, HBsAg testing must be paid out-of-pocket. Screening for HBsAg, which is normally recommended during the initial assessment at pregnancy, is not often carried out mainly because of limited financial resources. Insufficient screening leads to a later diagnosis of chronic HBV infection and increased of complications due to untreated HBV infection (29). Studies among pregnant women in west Africa and PLWH report 9-10% of OBI (226,240), which means that HBsAg would not be detected. Assuming that the prevalence of OBI are comparable to HIV-negative individuals, the detection of HBV DNA would be necessary to reduce the risk of HBV transmission during transfusion in SSA (241).

1.6.3. Testing for HIV or HBV infection when already infected with HBV or HIV

Since these two viruses share the same route of transmission, anyone who tests positive for one virus should be screened for the other virus. There are clear HBsAg screening recommendations for HIV-positive individuals in the EACS guidelines (142), as well as HIV screening recommendations for HBsAg-positive individuals in both the AASLD and EASL guidelines (29,45), and these recommendations closely follow each other. The frequency of testing will also depend on frequency of at-risk activities. In SSA, as HBV infection is expected to occur during youth and adolescence, HBsAg screening would likely need to be conducted once and HIV screening more regularly as individuals become sexually active.

Apart from HIV and HBV, anytime HIV and HBV are newly diagnosed, serological (or virological) testing of hepatitis C virus (HCV) or HDV should be conducted, given the considerably high proportion of individuals with tri- and even quad-infection (242,243).

1.7. Prevention strategies against infection

1.7.1. HIV prevention strategies

There is no effective vaccine against HIV; nevertheless, certain preventative measures can be used to reduce the risk of acquiring HIV. For decades, correct condom use has been one of the cornerstones of HIV prevention, as well as for preventing transmission of many other STIs. A previous study in USA and a systematic review have shown that consistent use of condoms can result in an 80% reduction in HIV incidence among heterosexuals and based on self-report, a 70% reduction in incidence in MSM (244,245). The consistency of condom use for

HIV prevention varies across key populations (246–248), while the barriers and psychosocial aspects related to their use are multifarious and will not be discussed in this thesis.

There are also some traditional practices that appear to be effective in HIV prevention. Randomized controlled trials have demonstrated that circumcision was able to reduce HIV acquisition 50-60% in HIV-negative men in SSA compared to those were not circumcized (249,250). There have been several pathophysiological investigations to explain these results. The highly vascularized foreskin mucosa and the mucosa at the frenulum are prone to tearing and bleeding during intercourse. These micro injuries allow HIV to more easily enter into the bloodstream (251). One factor that could further facilitate transmission of the virus is the presence of an ulcerative sexually transmitted infection, such as herpes simplex, chancroid from syphilis, which tends to be more common in uncircumcized men (251–254). However, the supposed preventative benefits of male circumcision does not appear to extend to MSM (255). The WHO recommends that male circumcision be considered as an important component of comprehensive HIV prevention (256).

Another effective way to prevent HIV transmission is providing ART to HIV-positive individuals, i.e., treatment-as-prevention (TasP). HIV RNA viral load is one of the strongest predictors of the risk of sexual transmission of HIV and transmission is exceedingly rare among individuals with HIV RNA levels of <1500 copies/mL (257). A randomized control trial in serodiscordant couples comparing early versus ART given according to recommendations at the time demonstrated a 96% reduction in HIV transmission in those randomized to early ART (258). Several large studies have also assessed the effect of ART on transmission at the community level, showing a strong impact on curbing the HIV-epidemic with more widespread ART use (259). These findings have led the WHO to recommend treatment of HIV-positive individuals

with a stable HIV-negative partner (260); however, given the low proportion of partners who know their HIV status in SSA, these recommendations might only concern a small part of the population (261). It is also important to remind patients who are being treated for HIV infection of the benefit of reduced risk of transmission when HIV RNA viral loads are consistently suppressed.

Antiretroviral agents can also be used in HIV-negative individuals to prevent HIV transmission, i.e., pre-exposure prophylaxis (PrEP). PrEP involves the use of TDF/FTC, which can be given daily or intermittently when an individual engages in at risk activities. There is also evidence that combined TAF/FTC is non-inferior to TDF/FTC for the used PrEP against HIV (262). PrEP is effective in reducing risk of HIV acquisition across different types of sexual exposure and key populations, provided that adherence to PrEP is high (263). PrEP is also effective in women; however, as PrEP usually requires longer periods of time to accumulate in vaginal than rectal tissue, there are special considerations for women. For PrEP to be maximally effective in vaginal tissue, it needs to be taken daily and may require up to 20 days of adherent intake before being fully protective against HIV (264,265). Carbogravir as an injectable form of PrEP has also been shown to be highly effective, and even more effective than TDF/FTC, in preventing HIV for key populations likely to exhibit poor adherence (266).

ART can be used to reduce mother-to-child transmission by reducing the mother's HIV RNA viral load to prevent incoming virus from establishing infection during, at, and after pregnancy. ART containing a triple-agent regimen can be provided during pregnancy and breastfeeding, and is safe and reduces the risk of HIV transmission to infants (267). All pregnant women living with HIV should be immediately provided with lifelong treatment, regardless of their CD4 count. The WHO recommends that mothers living with HIV who are on treatment and are adherent

to their regimen should exclusively breastfeed their infants for the first six months of life, then introduce appropriate complementary foods while continuing to breastfeed for up to 24 months or longer (268).

1.7.2. HBV prevention strategies

As opposed to HIV, there is an effective vaccine against HBV infection. In populations where extensive HBV vaccination has taken place, there has been in parallel a substantial decrease in the number of HBsAg-positive individuals and in the rate of HBV-related morbidity and mortality (269,270). One study from Taiwan in 1997 showed that nationwide universal HBV vaccination was able to reduce the population level incidence of HCC in children 13 years after the introduction of their vaccine program (271). More specifically, the annual incidence of HCC per 100,000 people declined from 0.70 to 0.36 in children 6 to 14 years of age and from 0.52 to 0.13 in those 6 to 9 years of age in the periods before and after universal vaccination, respectively. A study from the Gambia has also showed an 83% reduction in new infections and 95% reduction in HBsAg-positive seroprevalence 9 years after the implementation of large-scale HBV vaccination (272).

All African countries have incorporated HBV vaccination (HepB) in their immunization schedules as part of the Expanded Programme for Immunization (EPI). The vaccine is usually given as three doses of the pentavalent vaccine (diphtheria, tetanus, pertussis, Haemophilus influenza type B, and HepB) at 6, 10, and 14 weeks of age 11. Regional coverage for the third dose of HepB has increased from 5% in 2001 to 76% in 2015 (273). HepB vaccination has been introduced to the list of the EPI for Côte d'Ivoire and is free and mandatory at birth nationally (183).

As discussed in Chapter 1.4, HBV is mainly transmitted perinatally from mother-to-child at the time of birth and through horizontal transmission during early childhood in highly endemic settings. Therefore, WHO recommends universal vaccination with a monovalent dose of hepatitis B vaccine given within 24 hours of birth (HepB-BD), followed by at least two subsequent doses. This strategy is known to be highly effective in reducing the risk of HBV infection, particularly in Africa (274), with 90% effectiveness in preventing perinatal transmission of HBV from HBsAg-positive mothers to their infants. However, few African countries have introduced HepB-BD despite WHO recommendations and vaccination coverage for infants remains generally insufficient for many countries (275,276).

Other strategies are also useful in the prevention of mother-to-child transmission in HBsAg-positive mothers. Through passive immunization, Hepatitis B immunoglobulin (HBIG) is also effective to prevent HBV acquisition even if its administration is not easy (277). Administration of HBIG and HBV vaccine within 24 hours of birth, followed by completion of the vaccine series, is 85%–95% efficacious for prevention of MTCT. Unfortunately, this combination can fail in 5%–15% of infants almost exclusively in HBeAg-positive women with high HBV DNA levels (>200,000 IU/ml) and/or HBsAg level above 4.0-4.5 log₁₀ IU/ml (277,278). HBIG is not available in SSA because of their high costs and difficulties in storage, delivery, and administration.

NAs prophylaxis could be also useful in women with high levels of HBV DNA viremia. One group from Thailand recently shown that HBeAg-positive pregnant Thai women who received TDF at 28 weeks of gestation, in addition to HBIG and HBV vaccination to newborns, had no infants develop HBV infection, compared to 3 newly HBV infected infants in the arm with placebo (152,279,280). Although these results are encouraging, the duration of NA therapy,

as well as the possibility to discontinue NA therapy/prophylaxis is not well-defined in the context of mother-to-child transmission.

For individuals who are HBsAg-positive, they should be counseled regarding potential HBV transmission to others. Because of the increased risk of acquiring HBV infection, household members and sexual partners should be vaccinated if they are non-immunized, as confirmed with a full serological battery of HBV. For casual sex partners or steady partners who have not been tested for HBV or have not completed the full immunization series (if non-immunized), condom use should be encouraged (281).

1.7.3. Preventing HIV when infected with HBV

For individuals who are chronically infected with HBV, the preventative measures needed to protect against HIV infection are similar to those for individuals who are not chronically infected. These mainly include use of condoms, TasP when engaging in condomless anal sex with HIV-positive partners, etc. The only treatment that is currently licenced for PrEP is TDF/FTC and as TDF bears anti-HBV activity, certain considerations are needed if HBsAg-positive individuals wish to use PrEP for HIV. For HBV-infected individuals eligible for treatment, they are protected from HIV infection if initiating a TDF or TAF containing NA-based therapy. However, for HBV-infected individuals who are not yet eligible for treatment, PrEP raises some concerns as a *de facto* HBV treatment (282,283). When assessing whether or not PrEP should be taken, these individuals will likely be faced with the question of initiating lifelong treatment against HBV if they want to take PrEP and whether they can discontinue PrEP without any risk of HBV reactivation (284–286).

1.7.4. Preventing HBV when infected with HIV

Ever since the 1980s, when the effectiveness of the HBV vaccination was demonstrated, has vaccination been the cornerstone of HBV prevention (287). In HIV mono-infected individuals, however, there is a weak response to this vaccine. In a study of HIV-positive children vaccinated against HBV, only 29% were able to produce protective anti-HBsAb titers (288). A modified HBV vaccination schedule using 40 µg IM given at months 0, 1, 2, and 6 is now recommended in HIV-positive, non-immunized patients (289–292) and has been clearly shown to increase anti-HBsAb titers, vaccine response rates, and thus may provide prolonged protection against HBV (293–295).

Nevertheless, even if HBV vaccination is unsuccessful, most ART regimens contain TDF with anti-HBV activity and could also serve as a type of prophylaxis against HBV infection. Indeed, TDF-containing ART has been shown to be effective in preventing HBV infection in HIV-positive individuals (296–298) and reducing mother-to-child transmission of HBV in co-infected mothers (152,279,280). Further HBV prevention strategies would also include the use of condoms during sexual intercourse (295,299) and for PWIDs, complete harm reduction programs and counselling (295).

1.8. Objectives of this thesis

This thesis aims to address certain research questions in the HIV-HBV co-infected population. From previous research, there is a tremendous amount of information about where prevalence of these infections is highest, who should be tested, and how to prevent infection. It is also clearly obvious that the natural history of both HIV and HBV infections are modified during co-infection and that treatment can have a major impact on the course of both these infections.

However, many of the contemporary studies to date in SSA include HIV-HBV co-infected patients who initiate ART at later stages of infection and use non-TDF-containing regimens. The research questions on morbidity/mortality and therapeutic implications of the natural history of infection need to be revisited in individuals receiving immediate ART, which is now considered the standard of care. Hence, this thesis will focus on: (i) the association between HBV status, immediate ART and mortality, (ii) how HIV-HBV co-infection influences changes in CD4+ cell count before and during ART and the risk of death based on CD4+ levels, and (iii) HBV activity in ART naïve individuals who are HBeAg-negative, the most frequent HBV group in SSA.

2. CONSEQUENCES OF HBV INFECTION IN HIV-POSITIVE INDIVIDUALS IN SUB SAHARAN AFRICA DURING THE ERA OF EARLY ANTIRETROVIRAL THERAPY

There is an overwhelming consensus that HIV-positive individuals should be treated as soon as possible for their HIV infection in order to reduce morbidity and mortality and to prevent onward transmission of HIV. Most first-line ART regimens contain TDF, which leaves a number of questions to consider for the HIV-HBV co-infected population. To address these questions, we took advantage of data from the Temprano study. In this chapter, the general design of the Temprano study and the components related to HBV will be described in detail. The specific questions concerning the rates of overall mortality during early ART, its relationship with immunorecovery and CD4+ cell counts, and progression of HBV disease without ART in HIV-HBV co-infected patients will be discussed in the sections thereafter.

2.1. Design of the Temprano trial and post-phase trial

We used data from the Temprano ANRS 12136 trial, which was a randomized trial conducted at 9 clinical monitoring centers in Abidjan, Côte d'Ivoire from 2008 to 2015. The protocol of this trial is available online at the following link <https://clinicaltrials.gov/ct2/show/NCT00495651>. The Temprano ANRS 12136 trial aimed to assess the benefits and risks of early ART and 6-month isoniazid (INH) chemoprophylaxis against tuberculosis infection. At that time, the recommendation for INH prophylaxis in HIV-infected people was recommended by the WHO, but was not adopted in Côte d'Ivoire. The primary endpoint was a combined endpoint of death (from any cause), any AIDS-defining disease, or severe HIV-related and non-AIDS-related disease due to bacterial origin or cancer.

A total of 2056 HIV-infected adults with less than 800 CD4/mm³ and who were not yet indicated to initiate ART, according to concomitant recommendations from the WHO criteria, were included. During the course of the trial, the CD4+ count level in the WHO recommendations used to determine ART eligibility changed three times: <250/mm³ from 2006-2009, <350/mm³ from 2009-2013, and <500/mm³ from 2013 until the end of the trial. The main criterion for non-inclusion was the presence of active tuberculosis at inclusion, while the full list of non-inclusion criteria has been described previously (13). The study was designed as a 2x2 factorial design, whereby participants were randomized into four arms: (i) initiation of ART during follow-up when WHO criteria for ART initiation were met; (ii) six-month prophylaxis with isoniazid 300 mg/day, with the start of ART during follow-up when WHO criteria for ART initiation were met; (iii) immediate ART regardless of WHO criteria; (iv) six-month prophylaxis with isoniazid 300 mg/day and immediate ART initiation regardless of WHO criteria. For strategies (ii) and (iv), INH prophylaxis was initiated one month after inclusion, which allowed investigators to conduct a chest X-ray and liver function tests and to detect signs suggestive of active tuberculosis infection that normally would have gone unnoticed at inclusion. The first-line antiretroviral regimens were: (i) tenofovir-emtricitabine-efavirenz as a priority; (ii) tenofovir-emtricitabine-lopinavir/ritonavir for women who were not taking effective contraception, women who received a 6-month course or less of nevirapine-containing ART to prevent mother-to-child transmission of HIV, and people co-infected with HIV-1 and HIV-2. These regimens contained the potent anti-HBV treatment, tenofovir.

The trial started in March 2008 and ended in December 2014. For all patients who completed their 30-month follow-up visit in the study, extended follow-up was offered to continue their clinical care. These visits continued until the last patient included in the Temprano trial completed their 30-month follow-up visit, i.e. until December 2014. This prolonged follow-up

included quarterly clinic visits, CD4+ counts measured every six months, and a blood draw for blood sample storage at a bio-bank. The major difference from the trial was that apart from the consultation with the investigator doctor, which was free, the patient had to pay out of pocket for any consultation with a specialist or for any other additional examination.

2.2. Assessing HBV infection in the Temprano Study

In countries with a high prevalence of chronic HBV, the WHO recommends screening all HIV-positive adults for HBsAg before initiating antiretroviral therapy. This recommendation has existed since the 2006 WHO guidelines (300). In accordance with these recommendations, all participants of the Temprano trial were screened for HBV infection by assessing HBsAg status. Frozen blood samples of HBsAg-positive patients were then sent to Lyon, France (INSERM, Unité 1052) for HBV-DNA quantification and HBV viral sequencing and then further shipped to Paris, France (Saint-Louis Hospital) for quantification of other viral markers of HBV replication.

For the purposes of this thesis, the three more important markers were HBsAg, HBeAg and HBV-DNA viral load. HBsAg serology was performed at inclusion of the Temprano trial using an ELISA-based assay (Monolisa® Bio-Rad, Marnes la Coquette, France). From frozen samples stored at -80°C, hepatitis B e antigen (HBeAg) was detected at inclusion using the Elecsys® assay (Roche Diagnostics, Meylan, France). HBV DNA viral loads were quantified at inclusion using an in-house polymerase chain reaction (PCR)-based assay (QuantiFast SYBR® Green PCR kit, detection limit: 12 copies/mL; Qiagen, Courtaboeuf, France; Light Cycler 480; Roche, Boulogne-Billancourt, France) (301) or a commercially-available PCR assay (COBAS®Amplicor HBV Monitor, detection limit: 60 IU/mL; Roche Diagnostics, Meylan,

France). To ensure comparability between assays, viral loads were reported in IU/mL [conversion factor: 1 IU/mL=2.8 copies/mL (302)].

2.3. All-cause mortality in HIV-HBV co-infected individuals in the Temprano study

Improving survival in HIV-positive individuals has been one of the biggest priorities for researchers and health workers around the world. The increasingly widespread use of ART with three active antiretroviral agents at the beginning of the 2000s made it possible to considerably reduce the mortality associated with opportunistic diseases and AIDS-related illnesses. However, with the decrease of AIDS-related morbidity and mortality, other causes of chronic diseases seem to play an increasingly important role.

As discussed in Chapters 1.4 and 1.5, HIV and HBV share similar routes of transmission and, as a result, high prevalence of HBsAg-positive serology is often observed in HIV-positive individuals, while liver-related morbidity or mortality from chronic HBV infection appears to becoming more problematic for HIV-HBV co-infected individuals. Indeed, without effective treatment, co-infection with HBV reduces the rate of overall survival in HIV-positive individuals (16,73,303–305).

There is a wide body of literature as to how HIV and HBV affect the progression of their respective infections. In HIV-HBV co infected individuals with low CD4 cell counts, studies have observed that HIV-related rather than HBV-related factors more importantly contributed to mortality (305–308). The deleterious effect of HBV on HIV-related disease in HIV-HBV co-infected patients could also be linked to excessive HBV replication. For instance, Boyd et al.

demonstrated that co-infected patients with elevated HBV-DNA replication (i.e. >2,000 IU/mL) were more susceptible to HIV-related morbidity, especially invasive bacterial diseases (309). On the other hand, HIV-infection has been demonstrated to accelerate HBV-related liver disease progression (i.e. liver fibrosis and cirrhosis) and significantly increase liver-related mortality, especially for those with low CD4+ nadir counts (66,304,310). The underlying theme of these studies would be that suppression of HIV and HBV replication is needed to reduce the impact of both HIV- and HBV-related disease.

In Côte d'Ivoire, and in SSA more generally, there are very little data on the incidence of all-cause morbidity or mortality in people co-infected with HIV-HBV at the early stages of HIV infection. In order to address this major gap in research, we used data from the Temprano study to estimate the rate of mortality in co-infected patients, defined by HBsAg-status at inclusion. We then categorized co-infection status into three classes based on HBsAg-status and levels of HBV DNA viral loads at inclusion: HBsAg-negative, HBsAg-positive with HBV-DNA less than 2000 IU/ml, and HBsAg-positive with more than 2000 IU/ml. We compared the 5-year probability of all-cause mortality between these co-infection groups. The main results from this analysis were published in the journal, *Clinical Infectious Diseases*, and are presented on the following page.

Higher Mortality Despite Early Antiretroviral Therapy in Human Immunodeficiency Virus and Hepatitis B Virus (HBV)–Coinfected Patients With High HBV Replication

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Background. In human immunodeficiency virus (HIV)–infected patients, hepatitis B virus (HBV) coinfection increases the risk of disease progression. Tenofovir plus emtricitabine/lamivudine (TDF/XTC)–based antiretroviral therapy (ART), which suppresses HIV and HBV replication, has the potential for decreasing this risk. Here, we analyze the association between HBV replication, early ART, and mortality in West African adults.

Methods. The Temprano randomized controlled trial assessed the benefits of immediately initiating vs deferring ART in HIV-infected adults with high CD4 counts. After trial completion, participants continued follow-up in a posttrial phase. We analyzed the association between HBV status, immediate ART, and mortality over the entire trial and posttrial follow-up using multivariable Cox proportional hazards regression.

Results. A total of 2052 HIV-infected adults (median baseline CD4 count, 464 cells/ μ L) were followed for 9394 person-years. At baseline, 1862 (91%) were HIV monoinfected and 190 (9%) HIV/HBV coinfecting. Of the latter, 135 (71%) had plasma HBV DNA <2000 IU/mL and 55 (29%) HBV DNA \geq 2000 IU/mL. The 60-month probability of death was 11.8% (95% confidence interval [CI], 5.4%–24.5%) in coinfecting patients with HBV DNA \geq 2000 IU/mL; 4.4% (95% CI, 1.9%–10.4%) in coinfecting patients with HBV DNA <2000 IU/mL; and 4.2% (95% CI, 3.3%–5.4%) in HIV-monoinfected patients. Adjusting for ART strategy (immediate vs deferred), the hazard ratio of death was 2.74 (95% CI, 1.26–5.97) in coinfecting patients with HBV DNA \geq 2000 IU/mL and 0.90 (95% CI, .36–2.24) in coinfecting patients with HBV DNA <2000 IU/mL compared to HIV-monoinfected patients. There was no interaction between ART strategy and HBV status for mortality.

Conclusions. African HIV/HBV-coinfecting adults with high HBV replication remain at heightened risk of mortality in the early ART era. Further studies are needed to assess interventions combined with early ART to decrease mortality in this population.

Clinical Trials Registration. NCT00495651

Keywords. hepatitis B virus; HIV; sub-Saharan Africa; early antiretroviral therapy; viral replication.

Sub-Saharan Africa has the highest prevalence of hepatitis B virus (HBV) and human immunodeficiency virus (HIV) infection compared to the rest of the world [1]. In this setting, HBV infection predominately occurs during early childhood [2]. Chronic HBV infection affects 5%–10% of the overall population, with similar prevalence in HIV-infected and uninfected individuals [3]. This prevalence is worrying as diagnosis of HBV infection is frequently delayed and liver-related medical services are limited [4].

In HIV-infected patients, HBV coinfection increases the rate of morbidity and mortality [5]. Tenofovir + emtricitabine or lamivudine (TDF/XTC)–based antiretroviral therapy (ART), which suppresses both HIV and HBV replication, could counterbalance this association. Studies in HIV-infected individuals from sub-Saharan Africa have observed increased risk of all-cause mortality for those with HBV coinfection despite initiating ART [6–8]. Nevertheless, most of these studies used ART regimens with less-potent anti-HBV agents [5] and included severely immunocompromised patients who are prone to AIDS-related disease and poor immune recovery [9, 10]. Whether increased risk of death is also observed in coinfecting patients initiating TDF/XTC-based ART at higher CD4⁺ T-cell counts is unknown.

Additionally, there are limited data regarding the influence of ART timing on disease outcomes in coinfecting patients. In 2008–2015, we conducted a randomized controlled trial to

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assess the benefits of TDF/XTC-based immediate ART and 6-month isoniazid preventive therapy (IPT) for tuberculosis in HIV-infected adults with high CD4 counts in Côte d'Ivoire, West Africa. The trial endpoint was severe morbidity at 30 months. The final analysis showed that immediate ART led to lower rates of severe morbidity than deferred ART [11]. After participants reached 30 months of follow-up in the trial, they continued follow-up in a posttrial phase. Here, we present results of an analysis on the association between HIV/HBV coinfection, immediate ART, and all-cause mortality at the end of the posttrial phase.

METHODS

Participants and Study Design

All participants in the Temprano ANRS 12136 trial were eligible for updated analysis. Participants with missing data on plasma hepatitis B surface antigen (HBsAg) and HBsAg-positive participants with missing data on plasma HBV DNA levels were excluded.

The Temprano trial was a randomized controlled, 2 × 2 factorial, superiority trial, conducted in 9 clinics in Côte d'Ivoire. The trial design and results have been previously reported [11]. In summary, from March 2008 to July 2012, patients were included based on the following criteria: HIV infection, ≥18 years of age, CD4 count <800 cells/μL, absence of active tuberculosis or severe liver disease, and no criteria for starting ART according to the most recent World Health Organization (WHO) guidelines (2006 guidelines [12] from trial start to November 2009, 2010 guidelines [13] from December 2009 to July 2013, and 2013 guidelines [14] from August 2013 to end of trial). Liver-related exclusion criteria were as follows: plasma aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >4 times the upper limit of normal or any other severe liver disease.

Trial Arms and Treatment

Participants were randomly assigned to 1 of 4 arms: 2 "deferred ART" arms (arms 1 and 2), in which ART initiation was deferred until patients met concurrent WHO starting criteria; and 2 "immediate ART" arms (arms 3 and 4), in which ART was initiated immediately at inclusion. In arms 2 and 4, participants received 6-month isoniazid prophylaxis for tuberculosis. First-line ART regimen contained TDF/emtricitabine with the third agent preferably efavirenz or, if contraindicated, zidovudine or lopinavir/ritonavir.

Follow-up

All participants in the Temprano trial were followed for 30 months. The first Temprano study participant completed 30 months of follow-up in September 2010. From this date, all patients who reached the 30-month visit were asked to continue follow-up in a posttrial phase (PTP) until the last patient

completed their 30-month trial visit (closing date: 5 January 2015). Both the Temprano study and PTP had similar procedures: patients had quarterly visits at their healthcare center and were requested to present for additional visits any time they encountered a medical event; CD4 count and plasma HIV type 1 (HIV-1) RNA were measured every 6 months; consultations, CD4 count, viral load, and antiretroviral drugs were free of charge; and patients who did not present at a trial visit were traced by experienced social workers. Patients assigned to the deferred ART arms who had not started ART during the trial commenced ART during the PTP whenever they reached the most recent ART-initiation WHO criteria. Patients who did not reach WHO criteria before the closing date did not commence ART, be it during the trial or PTP.

There were 2 differences between the Temprano study and PTP. First, transportation for unscheduled visits, consultations, hospitalization, and nonantiretroviral drugs were free of charge when morbidity events occurred during the trial. In PTP, patients were required to pay out-of-pocket, similar to other patients followed in routine care at the same center. Second, the primary outcome was severe morbidity (including all-cause mortality) in the Temprano trial and only all-cause mortality in the PTP.

Study Parameters

All participants had a chest radiograph at inclusion. Blood tests including CD4 count, plasma HIV-1 RNA, and serum aminotransferases were done at baseline and every 6 months.

HBsAg serology was performed at baseline using an enzyme-linked immunosorbent assay (Monolisa Bio-Rad, Marnes la Coquette, France). From frozen samples stored at -80°C, hepatitis B "e" antigen (HBeAg), and anti-HBe antibodies (anti-HBeAb) were detected at baseline using the Elecsys assay (Roche Diagnostics, Meylan, France). HBV DNA viral loads were quantified at baseline using an in-house polymerase chain reaction (PCR)-based assay (QuantiFast SYBR Green PCR kit, detection limit: 12 copies/mL; Qiagen, Courtaboeuf, France; Light Cycler 480; Roche, Boulogne-Billancourt, France) [15] or a commercially available PCR assay (COBAS Amplicor HBV Monitor, detection limit: 60 IU/mL; Roche Diagnostics, Meylan, France). To ensure comparability between assays, viral loads were reported in international units per milliliter (conversion factor: 1 IU/mL = 2.8 copies/mL [16]).

Statistical Analysis

The primary endpoint was all-cause mortality. The secondary endpoint was death or loss to follow-up (LTFU). LTFU was defined by whether patients did not attend their last quarterly scheduled visit and no further information on their vital status was available within the 6 months preceding the closing date.

Patients were grouped as HIV monoinfected (all HBsAg-negative participants) or HIV/HBV coinfecting (all

HBsAg-positive participants), the latter of which was further stratified on plasma HBV DNA <2000 IU/mL (low HBV viral load) and plasma HBV DNA ≥2000 IU/mL (high HBV viral load) at inclusion. The threshold of 2000 IU/mL was chosen based on levels corresponding to active infection and treatment indication among HBV-monoinfected individuals [17]. Mantel-Haenszel χ^2 or Fisher exact tests were used to compare baseline characteristics between these groups. The distribution of continuous variables was compared using Kruskal-Wallis test.

While stratifying on these groups, we used the Kaplan-Meier method to estimate the cumulative probability of death and death or LTFU, and estimated the incidence rates by dividing the number of first events by cumulative time at-risk. The time at-risk began at randomization and ended at death, LTFU, or 5 January 2015, whichever occurred first.

Cox proportional hazards models were used to compare hazards of achieving each endpoint between HBsAg-negative and HBsAg-positive patients (2-group analysis), and between HBsAg-negative, HBsAg-positive patients with HBV DNA <2000 IU/mL, and HBsAg-positive patients with HBV DNA ≥2000 IU/mL (3-group analysis). In multivariable analysis, hazard ratios (HRs) were adjusted a priori for the following variables: Temprano ART strategy (immediate vs deferred ART), Temprano IPT strategy (IPT vs no IPT), baseline CD4 cell count, sex, and baseline plasma HIV-1 RNA. Interactions between variables were tested. The proportional hazards assumption was examined.

All reported *P* values were 2-sided and no adjustments for multiple comparisons were applied. Statistical analyses were performed with SAS 9.4 software (SAS Institute, Cary, North Carolina).

Funder, Registration, and Ethics

The Temprano trial protocol, which included the PTP, was approved by the Côte d'Ivoire National Ethics Committee for Health Research. It was registered at ClinicalTrials.gov (NCT00495651). Signed informed consent was provided prior to participating in the trial and PTP. The sponsor had no role in the conduct of the study or interpretation of the data.

RESULTS

Baseline and Follow-up Characteristics

Overall

Of the 2056 participants analyzed in the Temprano trial, 2052 (99.8%) were included in this updated analysis. Median CD4 count was 464 (interquartile range [IQR], 369–573) cells/ μ L and median plasma HIV RNA was 4.7 (IQR, 4.0–5.3) log₁₀ copies/mL. Five hundred sixteen patients were randomized to immediate ART and IPT, 514 to immediate ART and no IPT, 511 to deferred ART and IPT, and 511 to deferred ART and

no IPT. There was no difference in baseline characteristics between arms.

Total follow-up time was 9394 person-years (PY), with a median of 58.3 (IQR, 40.3–68.9) months per participant. At study closing date, 1830 (89%) participants had started ART (including 1030 at baseline and 800 during follow-up). The cumulative time spent on ART was 7136 PY, accounting for 76% of the total follow-up time. The percentage of treated patients who declared having missed ≥ 1 antiretroviral drug intake during the previous 4 days anytime between study visits was 73% (*n* = 1313/1796).

By Hepatitis B Virus Status

At baseline, 1862 (91%) patients were HIV monoinfected and 190 (9%) HIV/HBV coinfecting. Of the latter, 135 (71%) had plasma HBV DNA <2000 IU/mL (including 64 with undetectable HBV DNA) and 55 (29%) had HBV DNA ≥2000 IU/mL (Figure 1 and Table 1). Compared to patients with HIV monoinfection, coinfecting patients were more frequently male (13% vs 8% female; *P* = .003). Coinfecting patients with HBV DNA ≥2000 IU/mL tended to have higher HIV RNA viral load, lower CD4 count, and higher rates of abnormal plasma ALT values compared with other patients. There was no difference between HBsAg-negative and HBsAg-positive patients in terms of follow-up time, proportion initiating ART, and time spent on ART (Table 1).

Among patients who received ART once during follow-up, the percentage who declared having missed ≥1 antiretroviral drug intake during the previous 4 days anytime between study visits was 73% in HIV monoinfection (*n* = 1188/1627), 74% in coinfection with low HBV DNA viral loads (*n* = 89/120), and 73% in coinfection with high HBV DNA viral loads (*n* = 36/49) (*P* = .96).

Outcomes

At study closing date, 1760 participants were alive and in active follow-up, 206 were lost to follow-up, and 86 were known to have died. Of the 86 deaths, 47 (54.6%) occurred during the trial and 39 (45.4%) during the PTP. Of the 206 lost to follow-up, 57 (27.7%) occurred during the trial and 149 (72.3%) during the PTP (Figure 1). The number of deaths was 74 (4.0%) in HIV-monoinfected patients, 5 (3.7%) in HIV/HBV-coinfecting patients with low HBV DNA, and 7 (12.7%) in HIV/HBV-coinfecting patients with high HBV DNA. The number lost to follow-up was 183 (9.8%) in HIV-monoinfected patients, 15 (11.1%) in HIV/HBV-coinfecting patients with low baseline HBV DNA, and 8 (14.5%) in HIV/HBV-coinfecting patients with high baseline HBV DNA (Table 1).

A total of 25 causes of death were documented. Documented causes of death included tuberculosis (*n* = 8), cancer (*n* = 5), bacterial diseases (*n* = 3), renal insufficiency (*n* = 3), cardiovascular diseases (*n* = 2), cryptococcosis (*n* = 1), firearm injury

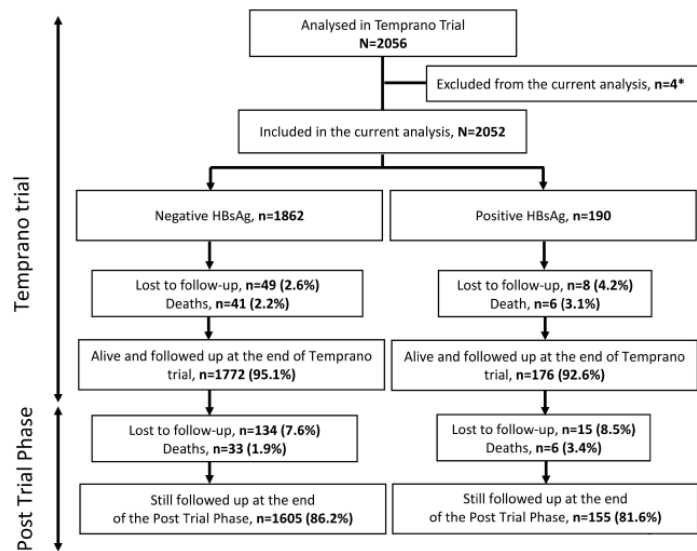


Figure 1. Flowchart. *Missing plasma hepatitis B virus DNA value. Abbreviation: HBsAg, hepatitis B surface antigen.

($n = 1$), and liver diseases ($n = 2$). The lattermost cause of death included 1 case of liver cirrhosis in an HBsAg-negative patient who died after 39 months of follow-up and spent 6 months on ART, and another case of fulminant hepatitis in an HBsAg-positive patient with high baseline HBV DNA. This patient was randomized to deferred ART and no IPT. Death occurred 84 days after inclusion and was due to cotrimoxazole-related toxicity.

Association Between Outcomes, Hepatitis B Virus Status, and Early Antiretroviral Therapy

In univariable analysis, the risk of death and of death or LTFU was similar in HIV-monoinfected and -coinfected patients with low HBV DNA viral load, and significantly higher in coinfecting patients with high HBV DNA viral load (hazard ratio [HR], 3.28 [95% CI, 1.51–7.11] for death and 2.00 [95% CI, 1.19–3.36] for death or LTFU, compared with monoinfected patients). In multivariable analysis adjusting for Temprano ART strategy (immediate vs deferred) and other key factors, the adjusted HR (aHR) slightly decreased but significance remained (aHR, 2.74 [95% CI, 1.26–5.97] for death and 1.85 [95% CI, 1.10–3.13] for death or LTFU) (Table 2). There was no interaction between ART strategy and HBV status for mortality ($P = .9$). These results were unchanged in sensitivity analysis including cotrimoxazole as a time-dependent covariate in the multivariable model (data not shown).

Overall, the 60-month probability of death was 11.8% (95% CI, 5.4%–24.5%) in coinfecting patients with high HBV DNA viral load, 4.4% (95% CI, 1.9%–10.4%) in coinfecting patients

with low HBV DNA viral load, and 4.2% (95% CI, 3.3%–5.4%) in HIV-monoinfected patients (Figure 2A). The 60-month probability of death or LTFU was 26.6% (95% CI, 16.3%–41.7%) in coinfecting patients with high HBV DNA viral load, 16.8% (95% CI, 11.0%–25.3%) in coinfecting patients with low HBV DNA viral load, and 14.1% (95% CI, 12.4%–16.0%) in HIV-monoinfected patients (Figure 2B). When considering only patients randomized to immediate ART, the 60-month probability of death was 13.7% (95% CI, 4.6%–37.2%), 4.7% (95% CI, 1.5%–13.9%), and 3.6% (95% CI, 2.5%–5.3%) in coinfecting patients with high HBV DNA viral load, coinfecting patients with low HBV DNA viral load, and HIV-monoinfected patients, respectively. When considering only patients randomized to deferred ART, the 60-month probability of death was 10.3% (95% CI, 3.4%–28.6%), 4.0% (95% CI, 1.0%–15.5%), and 4.8% (95% CI, 3.5%–6.6%) in coinfecting patients with high HBV DNA viral load, coinfecting patients with low HBV DNA viral load, and HIV-monoinfected patients, respectively (Figure 3).

DISCUSSION

In this large trial assessing the benefits of early ART in West African HIV-infected adults, we found a higher risk of mortality in HIV/HBV-coinfecting patients with high HBV DNA viral loads compared to other patients. Similar findings have been observed in previous observational studies with an average follow-up of up to 2 years [5, 18]. We extend these findings to a median of 55 months.

Table 1. Baseline and Follow-up Characteristics

Characteristic	HIV Monoinfected (n = 1862)	HIV/HBV Coinfected		P Value ^a
		HBV Viral Load <2000 IU/mL (n = 135)	HBV Viral Load ≥2000 IU/mL (n = 55)	
Baseline				
Age, y, median (IQR)	35 (30–42)	35 (30–42)	35 (28–40)	.56
Female	1478 (79)	90 (67)	43 (78)	.002
Schooling				.93
Primary school level or less	1012 (54)	68 (50)	32 (58)	
Secondary school level or more	850 (46)	67 (50)	23 (42)	
BMI, kg/m ² , median (IQR)	23 (20–25)	23 (20–26)	22 (19–24)	.11
Alcohol consumption, >1 glass/d	26 (1)	1 (1)	0 (0)	.99
WHO clinical stage				.42
1	1202 (65)	85 (63)	31 (56)	
2	485 (26)	35 (26)	16 (29)	
3	166 (9)	13 (10)	8 (15)	
4	9 (0)	2 (1)	0	
CD4 cell count				
Median cells/μL (IQR)	465 (372–575)	461 (357–564)	425 (322–538)	.11
≥500 cells/μL	772 (41)	56 (41)	18 (33)	.31
<500 cells/μL	1090 (59)	79 (59)	37 (67)	
Plasma HIV-1 RNA, log ₁₀ copies/mL, median (IQR)	4.6 (4.0–5.2)	4.8 (4.0–5.2)	5.0 (4.3–5.7)	.02
Positive HBeAg ^b	...	1 (1)	16 (39)	<.01
Positive anti-HBeAb ^b	...	81 (96)	24 (58)	<.01
Creatinine clearance <50 mL/min	25 (1)	2 (1)	1 (2)	.62
Plasma ALT, median (IQR)	18 (13–24)	19 (15–29)	25 (19–39)	<.01
Plasma ALT >2.5 × ULN	6 (0)	1 (1)	3 (5)	<.01
Hemoglobin <95 g/L	230 (12)	14 (10)	8 (15)	.97
Follow-up				
Follow-up, mo, median (IQR)	58.0 (41.0–68.9)	59.4 (38.8–69.0)	60.2 (37.3–70.3)	.94
Lost to follow-up	183 (10)	15 (11)	8 (15)	.24
Deaths	74 (4)	5 (4)	7 (13)	.016
Ever started CTX	1800 (97)	132 (98)	54 (99)	.82
Months spent on CTX, median (IQR)	33 (18–51)	34 (18–53)	30 (21–57)	.99
Ever started ART ^c	1656 (89)	124 (92)	50 (91)	.33
First-line ART regimen				
TDF-FTC + EFV	1169 (70)	78 (63)	37 (74)	.52
TDF-FTC + LPV/r ^d	362 (22)	33 (27)	10 (20)	
Other ^e	125 (8)	13 (10)	3 (6)	
Time spent on ART, person-years	6457	489	191	
Ever started IPT ^f	840 (46)	63 (49)	21 (42)	.15
Completed 6-mo course ^g	789 (94)	58 (92)	20 (95)	.85

Data are presented as No. (%) unless otherwise indicated. This included 516 patients randomized to immediate ART and IPT, 514 to immediate ART and no IPT, 511 to deferred ART and IPT, and 511 to deferred ART and no IPT.

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; BMI, body mass index; CTX, cotrimoxazole; EFV, efavirenz; FTC, emtricitabine; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HIV-1, human immunodeficiency virus type 1; IPT, isoniazid preventive therapy; IQR, interquartile range; LPV/r, lopinavir/ritonavir; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; WHO, World Health Organization.

^aP value for comparison between 3 groups (or 2 groups when first column is empty), using Mantel-Haenszel χ^2 or Fisher exact test for categorical variables and Kruskal-Wallis test for continuous variables.

^bAmong 125 patients (missing data, n = 65).

^cTwo hundred twenty-two patients never started ART because their CD4 cell count remained >500 cells/μL during the entire follow-up.

^dMain ART regimen was TDF-FTC + EFV. Among the 80 patients who started ART with TDF-FTC + LPV/r, the reason for not receiving an EFV-based regimen was dual HIV-1/2 infection, previous nevirapine use for preventing mother-to-child transmission, declining to use effective contraception, and other.

^eOther regimens were TDF-FTC-zidovudine (ZDV) (n = 81), ZDV-lamivudine (3TC)-LPV/r (n = 29), ZDV-3TC-nevirapine (n = 15), ZDV-3TC-EFV (n = 8), didanosine-3TC-EFV (n = 2), 3TC-abacavir-LPV/r (n = 2), stavudine (D4T)-3TC-EFV (n = 1), D4T-3TC-LPV/r (n = 1), TDF-FTC-nevirapine (n = 1), and TDF-FTC-3TC-D4T (n = 1).

^fOne hundred three patients did not take IPT. Reasons for not starting IPT were the presence of signs suggestive of tuberculosis on chest radiographs obtained at baseline (n = 16), presence of clinical signs suggestive of tuberculosis at the 1-month visit (n = 47), nonattendance at the 1-month visit (n = 24), elevated aminotransferase levels at baseline (n = 6), pregnancy (n = 4), death before 1 month (n = 1), and other (n = 5).

^gReasons for stopping IPT prematurely were death from an unknown cause (n = 1), discontinuation by patients for personal, nonmedical reasons (n = 22), discontinuation by physician because of signs or symptoms suggestive of tuberculosis (n = 10, 3 of whom were later confirmed to have tuberculosis), pregnancy (n = 13), and the following adverse events (n = 12): elevated aminotransferase levels, psychiatric side effects, and pruritus. None of the episodes of elevated aminotransferase levels led to death.

Table 2. Association Between Hepatitis B Virus Infection Status and Outcomes

Infection Status and Outcome	No. of Patients	No. of Events	Rate (per 100 PY)	Univariable ^a		Overall <i>P</i> Value	Multivariable ^b		Overall <i>P</i> Value
				HR (95% CI)	<i>P</i> Value		aHR (95% CI)	<i>P</i> Value	
Death									
2-group analysis									
HBsAg negative	1862	74	0.87	REF	...		REF	...	
HBsAg positive (irrespective of HBV DNA)	190	12	1.38	1.60 (.87–2.94)	.13		1.49 (.80–2.74)	0.21	
3-group analysis									
HBsAg negative	1862	74	0.87	REF	...		REF	...	
HBsAg positive, HBV DNA <2000 IU/mL	135	5	0.81	0.93 (.38–2.30)	.87	.01	0.90 (.36–2.24)	.82	.04
HBsAg positive, HBV DNA ≥2000 IU/mL	55	7	2.85	3.28 (1.51–7.11)	.002		2.74 (1.26–5.97)	.01	
Death or loss to follow-up									
2-group analysis									
HBsAg negative	1862	257	3.01	REF	...		REF	...	
HBsAg positive (irrespective of HBV DNA)	190	35	4.04	1.33 (.94–1.90)	.11		1.30 (.91–1.86)	.14	
3-group analysis									
HBsAg negative	1862	257	3.01	REF	...		REF	...	
HBsAg positive, HBV DNA <2000 IU/mL	135	20	3.22	1.07 (.68–1.68)	.78	.03	1.06 (.67–1.68)	.79	.07
HBsAg positive, HBV DNA ≥ 2000 IU/mL	55	15	6.10	2.00 (1.19–3.36)	.009		1.85 (1.10–3.13)	.02	

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HR, hazard ratio (Cox proportional hazards analysis); PY, person-years; REF, reference group.

^a*n* = 2052.

^b*n* = 2044 (plasma human immunodeficiency virus type 1 [HIV-1] RNA missing in 8 patients). Multivariable analyses are adjusted for the following variables: Temprano antiretroviral therapy (ART) strategy (immediate ART vs deferred ART), Temprano isoniazid preventive therapy (IPT) strategy (IPT vs no IPT), baseline CD4 count, sex, and baseline plasma HIV-1 RNA. The other following factors associated with mortality in multivariable analysis were HIV RNA viral load (<5.00 vs ≥5.00 log₁₀ copies/mL, aHR, 0.51 [95% CI, .33–.79]) and IPT strategy (IPT vs no IPT, aHR, 0.64 [95% CI, .42–.99]). ART strategy, sex, and baseline CD4 count were not significantly associated with mortality. There was no statistical evidence that these associations were different across HBV infection groups (*P* value for interaction: HIV RNA = .49; CD4 cell count = .93).

In our trial, first-line ART included tenofovir and emtricitabine. This combination is ideal for HIV/HBV-coinfected patients due to its potent anti-HIV and anti-HBV activity [5, 19]. As coinfecting patients with high HBV DNA and HIV RNA replication continue without antiviral treatment, their risk for liver-related complications increases [20]. Furthermore, greater HBV replication affects immune function [21], which potentially leads to increased risk of non-liver-related complications [22]. Therefore, it could be expected that initiating ART earlier would provide coinfecting patients with an increased benefit in terms of mortality reduction. This was not what we observed. In our study, the higher rate of mortality was maintained after adjusting for ART strategy, while the 60-month probability of death appeared similar in patients randomized to immediate ART or deferred ART, particularly in the subgroup of coinfecting patients with high HBV viral load. These findings suggest that other strategies should be combined with early ART to reduce mortality in patients with high HBV replication [23].

Higher mortality rates in coinfecting patients have been observed in several studies from the United States and Tanzania [24–26]. Some previous studies have suggested that death due to liver disease could increase in the ART era because of the

decrease in HIV-related diseases [27]. Recent reports from the United States and Europe have indeed shown increased mortality related to liver disease in HIV/HBV-coinfected patients [26, 28]. However, other research, such as in the French mortality 2000 study, have suggested that AIDS-related diseases remain a frequent cause of death in coinfecting patients [10, 27], highlighting the role of HBV infection in increased HIV virulence and acceleration towards AIDS [6]. The main differing characteristics of these studies compared to our trial, besides geographical location, were the extent of severe immunosuppression (with median CD4⁺ T-cell counts ranging from 200 to 250 cells/μL) and longer follow-up periods.

In our study, the most frequently documented causes of death were HIV-related infections or tumoral diseases. However, because of the high rate of undocumented causes and lack of liver fibrosis assessment, our data do not add to the debate on the preponderance of HIV- and HBV-related diseases attributing to death among coinfecting patients. Causes of deaths are oftentimes difficult to document in trials enrolling HIV-infected individuals and conducted in limited-resource countries, where the majority of patients die at home or in hospital settings with inadequate facilities to document morbidity compared to those

HCV infection

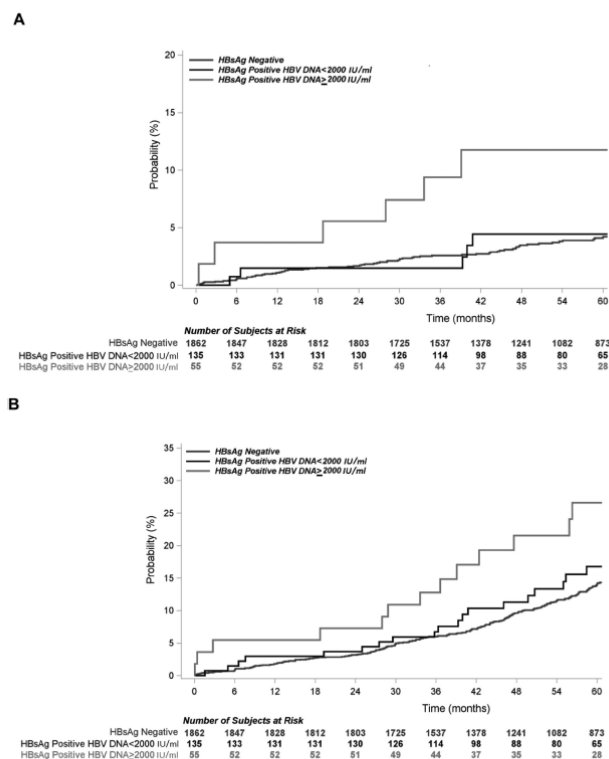


Figure 2. Probability of death and death or loss to follow-up, according to hepatitis B virus (HBV) status. Cumulative probability calculated by the Kaplan-Meier method is depicted for death (A) and death or loss to follow-up (B) as endpoints, while stratifying on human immunodeficiency virus (HIV) monoinfected, HIV/HBV coinfecting with HBV DNA viral load <2000 IU/mL, and HIV/HBV coinfecting with HBV DNA viral load ≥2000 IU/mL. Abbreviations: HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IU, international units.

in resource-rich countries. Furthermore, follow-up was not frequent enough to document the incidence of hepatic diseases, compared to other cohorts [29]. Finally, patients with severe liver diseases or high aminotransferase levels were not included in the Temprano trial, which likely diminished the risk of mortality from liver diseases.

Our study has several other limitations. First, HCV infection was not documented. However, its prevalence was probably low in the overall trial population, and even lower in HIV/HBV-coinfecting patients [30]. Second, we did not document occult HBV infection. The risk of liver-related disease and mortality is purportedly similar in HBsAg-negative patients with occult HBV infection and HBsAg-positive patients with low HBV DNA viral load. The inability to document occult HBV infection would, therefore, likely have no impact on our main result [31]. Third, 34% of HBsAg-positive patients had missing data on HBsAg serology. Fourth, healthcare was free of charge when

morbidity events occurred during the Temprano trial, whereas patients had to pay out-of-pocket during similar events in the posttrial phase. LTFU could have increased, thereby underestimating mortality rates during the posttrial phase. However, follow-up time and percentage of patients with LTFU were similar in HIV-monoinfected patients and coinfecting patients with high or low HBV DNA levels. It is then unlikely that mortality was more frequently underestimated in one group compared to others. Finally, we lacked longitudinal HBV and HIV virologic data, including data on resistant variants. It should be mentioned, however, that 97% of coinfecting participants undergoing ART received a tenofovir-containing regimen and no study to date has identified HBV variants resistant to this agent [19].

In conclusion, sub-Saharan African HIV-infected adults with chronic hepatitis B remain a population at heightened risk of mortality in the ART era, even for those at an early stage of HIV infection. Further studies are needed to assess whether other

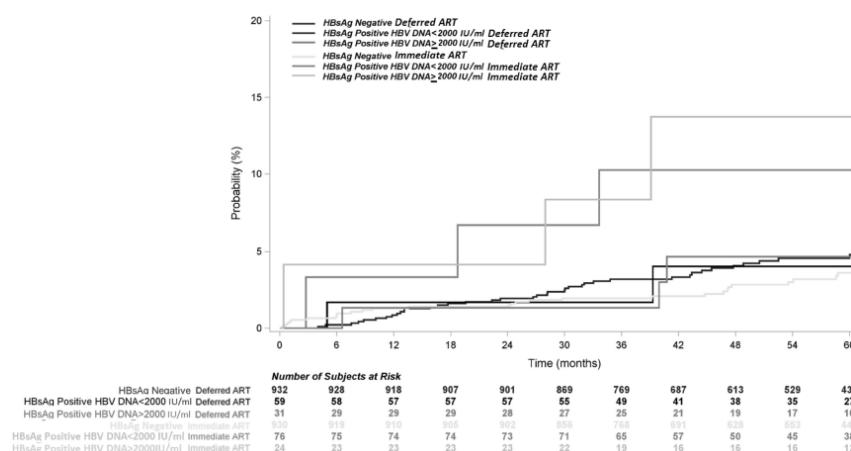


Figure 3. Probability of death, according to hepatitis B virus (HBV) status and antiretroviral therapy (ART) strategy. Cumulative probability calculated by the Kaplan-Meier method is depicted for death, while stratifying on human immunodeficiency virus (HIV) noninfected, HIV/HBV coinfected with HBV DNA viral load <2000 IU/mL, and HIV/HBV coinfected with HBV DNA viral load ≥2000 IU/mL; and for immediate and deferred ART within each of these groups. Log-rank *P* values for immediate vs deferred ART: among HBsAg-negative patients, *P* = .16; among HBsAg-positive patients with HBV DNA <2000 IU/mL, *P* = .92; among HBsAg-positive patients with HBV DNA ≥2000 IU/mL, *P* = .93. Abbreviations: ART, antiretroviral therapy; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IU, international units.

interventions should be combined with early ART to decrease mortality in HIV/HBV-coinfected patients with high HBV DNA viral load. Considering that HIV and HBV infections are acquired at different timepoints in life, early ART for HIV is not tantamount to early antiviral treatment for HBV. It would be recommended to treat HBV-monoinfected patients demonstrating active replication prior to becoming coinfected, noting that tenofovir use could additionally protect against HIV infection.

Notes

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2.4. Immune response in HIV-HBV co-infected individuals in the Temprano study

A large body of evidence suggests that there is no difference in the rates of virological response after the initiation of combined ART between HIV-positive individuals with and without chronic HBV infection (311). Nevertheless, there have been studies that have described slower immunorecovery in HIV-HBV co-infected patients (312,313). For example, the Swiss HIV cohort recently observed a significantly slower increase in mean CD4 cell count in HBsAg-positive and isolated-HBcAb antibody positive patients than in those with HBsAg-negative serology or with resolved HBV infection (314).

This question has aroused particular interest in SSA, with conflicting evidence. Some studies have reported no difference in the increase in CD4 cell counts between HBV co-infected and non-HBV co-infected individuals living with HIV (315,316), while others indicate that such a difference does in fact exist (297,298,317). The problem with these studies is that consistent data on HBV DNA are missing or have only been obtained at baseline, with follow-up typically extending up to 72 weeks. In addition, many studies in these contexts are limited to HIV-positive individuals with severe immunosuppression (i.e., a baseline CD4+ cell count of less than 100 cells/mm³). It would therefore be important to know whether the timing of ART plays a role in immune responses.

Furthermore, the role of immunosuppression on mortality might be different for HIV-HBV co-infected individuals. In HIV-HBV co-infected patients, higher HBV DNA is associated with lower CD4+ T cell counts (318). Interestingly, end stage liver disease in HIV-HBV co-infected individuals has been shown to be related to high HBV-DNA levels mainly as a result of low CD4+ cell counts and poor immunological control of HBV replication (319).

As described in Chapter 2.3, we observed that HIV-HBV co-infected individuals with HBV DNA viral loads >2,000 IU/mL had a significantly higher rate of mortality and loss to follow-up than HIV mono-infected individuals (320). Curiously, this effect was present regardless of whether ART was initiated early or deferred until reaching previous WHO recommendations. This result is highly concerning and deserves further elaboration. One possibility is that (i) HIV-HBV co-infected individuals are at higher risk of having poorer immunity, as determined by CD4+ cell counts, both prior to and during ART and (ii) HIV-HBV co-infected individuals more prone to mortality when their CD4+ cell counts are lower. The literature addressing either of these questions in a study population with relatively high CD4+ cell counts, which were consistently and prospectively measured, is virtually non-existent.

We again used data from the Temprano study to specifically address these two possibilities and address this gap in research. We assessed both immunorecovery and risk of mortality according to different CD4 count thresholds between the same co-infected groups as described in Chapter 2.3. The results have been drafted in a manuscript, which has been submitted to *BMC Infectious Diseases* and is presented on the following page.

Higher risk of mortality in HIV-HBV co-infected patients from sub-Saharan Africa is observed at lower CD4+ cell counts

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Running head : CD4+ and death in HIV-HBV coinfection

ABSTRACT

Background : Hepatitis B virus (HBV) co-infection in human immunodeficiency virus (HIV)-positive individuals increases the risk of overall mortality, especially when HBV-DNA levels are high. The role of CD4+ cell counts in this association is poorly defined. We aimed to determine whether HIV-HBV co-infection influences changes in CD4+ cell count before and during antiretroviral therapy (ART) and whether it affects mortality risk at levels of CD4+.

Methods : 2052 HIV-positive participants from Côte d'Ivoire in a randomized-control trial assessing early or deferred-ART were included. HBV-status was determined by hepatitis B surface antigen (HBsAg). Changes in CD4+ cell levels were estimated using a mixed-effect linear model. The incidence rates of all-cause mortality were estimated at CD4+ counts ≤ 350 , 351-500, $>500/\text{mm}^3$ and were compared between HBV-status groups as incident rate ratios (IRR).

Results : At baseline, 190 (9%) were HBsAg-positive [135 (71%) with HBV-DNA <2000 IU/mL, 55 (29%) ≥ 2000 IU/mL]. Follow-up was a median 58 months (IQR=40-69). Between co-infection groups, there were no differences in CD4+ decline before ART-initiation and no differences in CD4+ increase after ART-initiation. After adjusting for sex, age, baseline HIV-RNA level and early/deferred-ART arm, mortality rates were not significantly different between HBsAg-positive versus HBsAg-negative participants across strata of CD4+ levels. However, HBsAg-positive individuals with HBV-DNA ≥ 2000 IU/ml versus HBsAg-negative individuals had increased mortality rates at $\leq 350/\text{mm}^3$ (adjusted-IRR=3.82, 95%CI=1.11-9.70) and 351-500/ mm^3 (adjusted-IRR=4.37, 95%CI=0.98-13.02), but not $>500/\text{mm}^3$ (adjusted-IRR=1.07, 95%CI=0.01-4.91).

Conclusions : Despite no effect of HBV-infection on CD4+ levels, HIV-HBV co-infected individuals with high HBV-replication are at higher risk of mortality when CD4+ is $<500/\text{mm}^3$.

INTRODUCTION

Co-infection with chronic hepatitis B virus (HBV) is found in approximately 8% of individuals living with human immunodeficiency virus (HIV) infection (1). HIV-HBV co-infection is known to have broad consequences on the immunity of HIV-positive individuals (2). HIV-positive individuals with both resolved and chronic HBV infection have been shown to have an increased risk in progression to AIDS-defining illnesses in the absence of effective treatment (3). With the initiation of potent antiretroviral therapy (ART), most studies have demonstrated that although HIV-HBV co-infection is no longer likely to affect progression to AIDS (4), co-infection is associated with slower immunoreconstitution, leading to lower CD4+ cell counts during long term ART (5–7).

Poor levels of immunity in HIV-positive individuals have severe clinical consequences. The relationship between lower CD4+ cell counts and overall death during the natural history of HIV-infection has been clearly established (8). During treatment with ART, faster increases in CD4+ cell counts immediately after ART initiation have been associated with long-term immunoreconstitution (9), which lends to a lower risk of opportunistic infections and reduced short-term mortality (10–12). Given the association between HBV-infection and immunosuppression, HIV-HBV co-infection could increase the risk of overall mortality.

Indeed, several studies have shown an increased risk of overall mortality in individuals with HIV-HBV co-infection compared to HIV mono-infection despite treatment with effective anti-HBV and anti-HIV agents, although this association is inconsistent (2). In a recent secondary analysis of a randomized-clinical trial evaluating early and deferred-ART in Côte d'Ivoire, HIV-HBV co-infected patients with high HBV DNA levels were at higher risk of death and lost to follow-up compared to HIV-positive individuals without HBV co-infection, regardless of treatment arm (13).

It was unclear, however, how immunosuppression was related to this finding. One hypothesis could be that HIV-HBV co-infected individuals with high HBV DNA levels may have had faster decreases in CD4+ cell count while not receiving ART and/or may have had slower increases in CD4+ cell count after ART initiation. Increased immunosuppression in these individuals could then have led to a higher risk in mortality. Another hypothesis could be that the association between HIV-HBV co-infection with high HBV replication and overall mortality may have been accentuated when CD4+ cell counts were lower.

We took advantage of prospectively collected data from the Temprano study (14) to determine whether there were any differences in CD4+ decline while not receiving ART and CD4+ immunoreconstitution after ART initiation between HIV-HBV co-infected and HIV mono-infected patients. We also aimed to evaluate the relative risk of mortality in HIV-HBV co-infected and HIV mono-infected patients according to particular levels of CD4+ cell count.

METHODS

Study design and procedures

We included participants enrolled in the Temprano ANRS 12136 trial. In brief, the Temprano Trial was a randomized controlled, 2x2 factorial, superiority trial, conducted in nine clinics in Côte d'Ivoire. From March 2008 to July 2012, we included individuals based on the following criteria : HIV infection, aged ≥ 18 years, CD4+ count $< 800/\text{mm}^3$, absence of active TB or severe liver diseases, and no criteria for starting ART according to concurrent World Health Organization (WHO) guidelines. We excluded individuals based on the following criteria with respect to liver disease : plasma aspartate aminotransferase (AST), alanine aminotransferase

(ALT) levels >4 times the upper limit of normal (ULN) or any other severe liver disease as assessed by the physician. Full description of the trial design is reported elsewhere (14).

We randomly assigned participants to one of the following arms : two “deferred ART” arms (arms 1 and 2), in which ART initiation was deferred until patients met criteria for initiation ART according to concurrent WHO guidelines ; and two “immediate ART” arms (arms 3 and 4), in which ART was immediately initiated at inclusion. Participants assigned to arms 2 and 4 additionally received 6-month isoniazid prophylaxis for tuberculosis. Participants assigned to all arms received ART containing tenofovir (TDF)/emtricitabine as the first-line regimen with the third agent being efavirenz, zidovudine or lopinavir/ritonavir.

We followed participants for 30 months in the Temprano trial. We completed 30-month follow-up of the first Temprano study participant in September 2010. After this date, we asked all patients who reached the 30-month visit to continue follow-up in a post-trial phase (PTP). We continued this phase until the last patient completed their 30-month trial visit (closing date : 5 January 2015). Procedures of the Temprano study closely followed those of the PTP. Patients assigned to the deferred ART arms who had not started ART during the trial commenced ART during the PTP according to concurrent WHO criteria. The data analyzed in this study were collected between March 2008 to January 2015.

Included patients

For the present study, we considered all patients enrolled in the Temprano trial and PTP who had an available plasma hepatitis B surface antigen (HBsAg) and for those participants who were HBsAg-positive, an available plasma HBV-DNA level.

The markers of HBV replication obtained in Temprano have been summarized elsewhere (13). In brief, HBsAg serology was performed at baseline using an ELISA-based test (Monolisa® Bio-Rad, Marnes la Coquette, France). At inclusion, HBV DNA viral loads were quantified using an in-house polymerase chain reaction (PCR)-based assay (QuantiFast SYBR® Green PCR kit, Qiagen, Courtaboeuf, France ; Light Cycler 480 ; Roche, Boulogne-Billancourt, France ; detection limit : 12 copies/mL) (15) or a commercially-available PCR assay (COBAS®Amplicor HBV Monitor, Roche Diagnostics, Meylan, France; detection limit=60 IU/mL). Viral loads were reported in IU/mL in order to ensure comparability between assays [conversion factor : 1 IU/mL=2.8 copies/mL (16)].

Statistical analysis

Patients were regrouped as HIV mono-infected (all HBsAg-negative participants) or HIV/HBV co-infected (all HBsAg-positive participants), the latter of which was further stratified on plasma HBV DNA <2000 IU/mL and plasma HBV DNA ≥2000 IU/mL at inclusion. The threshold of 2000 IU/mL was chosen based on levels that, along with ALT levels, differentiate chronic “infection” and chronic “hepatitis” among HBeAg-negative HBV mono-infected individuals, according to guidelines from the European Association for the Study of the Liver (17).

We first determined whether there were any differences between HBV-infection groups with respect to CD4+ cell count changes over time, that is, while not receiving ART (i.e. “off-ART”) and after ART initiation (i.e. “on-ART”). Using mixed-effect non-linear regression, we parameterized a model whereby the decrease in CD4+ cell count off-ART was a linear function over time and the increase in CD4+ cell count on-ART was a square-root function over time. Follow-up in this analysis ended at death, LTFU, or 5 January 2015, whichever occurred first. Estimates specific to each HBV-infection group were obtained from an interaction term between

HBV-infection group and follow-up times for each period. A Wald χ^2 test of this interaction term was used to determine whether the slopes of CD4+ cell counts were different between HBV-infection groups. A random-intercept and random-coefficient for time were used to account for variation between individuals with respect to CD4+ T-cell count at the beginning of each time period and during follow-up, with an identity covariance structure between random-intercept and random-coefficient. Models were both unadjusted and adjusted a priori for CD4+ cell count at the beginning of each time period, HIV RNA level at inclusion (>5.0 versus ≤ 5.0 log₁₀ copies/mL), age (>35 versus ≤ 35 years), sex, and early versus deferred ART.

We then determined whether there were any differences between HBV-infection groups with respect to the incidence rate (IR) of all-cause mortality while at specific strata of CD4+ cell count. The time at-risk in this analysis began at randomization and ended at death, LTFU, or 5 January 2015, whichever occurred first. We defined three levels of CD4+ cell count at $\leq 350/\text{mm}^3$, $351-500/\text{mm}^3$, and $>500/\text{mm}^3$. We determined the time spent in a given CD4+ cell count stratum, assuming CD4+ to be constant between 2 measures of CD4+. We estimated the time-updated CD4+ cell count-specific IR of all-cause mortality per 100 person-years by dividing the number of events that occurred in each CD4 cell count stratum by the time spent in the corresponding stratum (for non-deceased patients) or the time between entry in the stratum and event (for deceased patients). 95% confidence intervals (CI) of IRs were calculated assuming a Poisson distribution if the number of events was lower than 50 and normal approximation otherwise. IR were compared between HBV-infection groups within CD4+ cell count strata by an Exact Poisson regression model using median unbiased estimates (with the mid-P-value rule) and log follow-up time as an offset. Incidence rate ratios (IRR) were estimated from this model and were given as both unadjusted and adjusted a priori for HIV RNA level at inclusion (>5.0 versus ≤ 5.0 log₁₀ copies/mL), age (>35 versus ≤ 35 years), sex, and early versus deferred ART.

All reported p-values were two-sided and no adjustments for multiple comparisons were applied. Statistical analyses were performed using SAS (v9.4, Cary, North Carolina) and STATA (v15.0, College Station, Texas).

Funder, registration, and ethics

The Temprano trial protocol was approved by the Côte d'Ivoire National Ethics Committee for Health Research. It was registered at Clinical Trials.gov (NCT00495651). Signed informed consent was provided prior to participating in the trial. The sponsor had no role in the conduct of the study and interpretation of the data.

RESULTS

Description of the study population

Of the 2056 participants analyzed in the Temprano trial, 4 did not have data on HBsAg-status and hence 2052 (99.8%) were included in this updated analysis. At baseline, HBsAg-negative and HBsAg-positive patients did not have any differences in proportions at CD4+ count levels ($p=0.58$). HBsAg-positive patients were slightly more likely to have a baseline CD4+ count $\leq 350/\text{mm}^3$ when HBV DNA levels were ≥ 2000 IU/mL (26%) or < 2000 IU/mL (23%) compared to HBsAg-negative patients (21%, $p=0.37$ and $p=0.83$, respectively). As shown in Table 1, higher levels of ALT ($p=0.002$) and higher proportion ever starting cotrimoxazole therapy ($p<0.001$) were observed as baseline levels of CD4+ count decreased.

Patients were followed for a median 58 months (IQR=40-69). Median follow-up was no different between HBsAg-negative (58 months, IQR=41-69) and HBsAg-positive patients (60 months, IQR=38-69) ($p=0.77$), even with baseline HBV DNA viral load <2000 IU/mL (60 months, IQR=39-69, $p=0.89$) or ≥ 2000 IU/mL (60 months, IQR=37-70, $p=0.87$).

No difference in CD4+ cell count changes during follow-up between HIV-HBV co-infection and HIV mono-infection

Off ART

Of the 1022 individuals randomized to receive deferred ART, 971 had at least 2 measures of CD4+ cell counts while not receiving ART. Off-ART median follow-up was 18 months (IQR=11-31) in this group. In HBsAg-negative patients, mean CD4+ count was 477/mm³ (95%CI=467-486) at baseline ($n=890$), decreasing to 426/mm³ (95%CI=414-437) after 12 months without ART ($n=729$) and 372/mm³ (95%CI=359-386) at the end of off-ART follow-up ($n=602$). In HBsAg-positive patients, mean CD4+ count was 452/mm³ (95%CI=421-482) at baseline ($n=81$) and similarly decreased to 395/mm³ (95%CI=364-425) after 12 months without ART ($n=65$) and 358/mm³ (95%CI=312-403) at the end of off-ART follow-up ($n=50$). Based on the mixed-effect non-linear regression model, there were no significant differences in CD4+ cell decrease while not receiving ART between HBsAg-negative and HBsAg-positive patients, both unadjusted (p for interaction=0.63) and adjusted for baseline CD4+ level, HIV RNA level, age, sex, and early versus deferred ART (p for interaction =0.73) (Figure 1A).

When separating HBsAg-positive patients based on HBV DNA viral load <2000 IU/mL and ≥ 2000 IU/mL, respectively, mean CD4+ count was 460/mm³ (95%CI=424-496) and 435/mm³ (95%CI=376-493) at baseline ($n=54$ and $n=27$), decreasing to 400/mm³ (95%CI=361-439) and 380/mm³ (95%CI=330-431) at 12 months without ART ($n=47$ and $n=18$), and 351/mm³

(95%CI=310-391) and 378/mm³ (95%CI=231-525) at the end of off-ART follow-up ($n=37$ and $n=13$). There were no significant differences in CD4+ cell decrease between HBsAg-negative patients and HBsAg-positive patients with HBV DNA viral load <2000 IU/mL (unadjusted $p=0.24$ and adjusted $p=0.38$) or with HBV DNA viral load ≥ 2000 IU/mL (unadjusted p for interaction=0.71 and adjusted p for interaction=0.49) (Figure 1B).

On ART

1729 patients-initiated ART and had at least 2 measures of CD4+ cell counts during ART. On-ART median follow-up was 55 months (IQR=37-61) in this group. In HBsAg-negative patients, mean CD4+ count was 405/mm³ (95%CI=397-413) at ART initiation ($n=1564$) increasing to 588/mm³ (95%CI=578-599) after 12 months of ART ($n=1404$) and 694/mm³ (95%CI=679-709) at the end of on-ART follow-up ($n=1371$). In HBsAg-positive patients, mean CD4+ count was 392/mm³ (95%CI=369-414) at ART initiation ($n=165$) and similarly increased to 577/mm³ (95%CI=542-612) after 12 months of ART ($n=142$) and 673/mm³ (95%CI=630-715) at the end of on-ART follow-up ($n=139$). Based on the mixed-effect non-linear regression model, there were no significant differences in CD4+ cell increase during treatment between HBsAg-negative and HBsAg-positive patients, both unadjusted (p for interaction=0.33) and adjusted for baseline CD4+ level, HIV RNA level, age, sex, and early versus deferred ART (p for interaction=0.30) (Figure 2A).

When separating HBsAg-positive patients based on HBV DNA viral load <2000 IU/mL and ≥ 2000 IU/mL, respectively, mean CD4+ count was 401/mm³ (95%CI=373-429) and 369/mm³ (95%CI=329-408) at ART initiation ($n=117$ and $n=48$), increasing to 577/mm³ (95%CI=536-619) and 576/mm³ (95%CI=506-647) after 12 months of ART ($n=99$ and $n=43$), and 682/mm³ (95%CI=633-731) and 650/mm³ (95%CI=562-737) at the end of on-ART follow-up ($n=99$ and $n=40$). There were no significant differences in CD4+ cell increase between HBsAg-negative

patients and HBsAg-positive patients with HBV DNA viral load <2000 IU/mL (unadjusted $p=0.17$ and adjusted p for interaction=0.20) or with HBV DNA viral load ≥ 2000 IU/mL (unadjusted $p=0.76$ and adjusted p for interaction=0.78) (Figure 2B).

Higher incidence of all-cause mortality in HIV-HBV coinfecting patients with high HBV-DNA levels is only observed at CD4+ below 500/mm³

During follow-up, there were 86 deaths (IR=0.92/100 person-years, 95%CI=0.72-1.11). As shown in Table 2, adjusted incidence of mortality was comparable between HBsAg-positive versus HBsAg-negative individuals when CD4+ cell counts were >500 (adjusted-IRR=0.85, 95%CI=0.13-2.94). An increased risk of mortality, albeit not significant, was observed when CD4+ counts reached 351-500/mm³ (adjusted-IRR=1.51, 95%CI=0.34-4.46) or ≤ 350 /mm³ (adjusted-IRR=2.10, 95%CI=0.84-4.53). This increased risk was even more pronounced in HBsAg-positive patients with baseline HBV DNA ≥ 2000 IU/mL versus HBsAg-negative patients : at 351-500/mm³ CD4+ count, adjusted-IRR=4.37 (95%CI=0.98-13.02), and at ≤ 350 /mm³ CD4+ count, adjusted-IRR=3.82 (95%CI=1.11-9.70).

DISCUSSION

Using data from a randomized clinical trial, we did not demonstrate any difference in decrease in CD4+ cell count while not receiving ART or in immunorecovery after ART-initiation between HIV-HBV coinfection and HIV mono-infection. Even when HBV DNA levels were above 2,000 IU/mL in co-infected patients, for whom risk of AIDS-related morbidity and mortality is particularly high (13,18), changes in CD4+ cell counts were no different compared to HIV mono-

infected patients. These data provide reassuring information on at least the immunologic outcomes of HIV-HBV co-infected individuals with relatively mild immunosuppression.

HIV-HBV co-infected individuals with higher HBV DNA levels at baseline began follow-up with slightly lower CD4+ cell counts compared to HIV-monoinfected individuals (13). Estimates from the mixed-effects model additionally showed that while not receiving ART, the declines in CD4+ count ran parallel between HBV-infection groups. Chronic HBV infection does contribute to immunodysfunction, specifically with regards to depletion of HBV-specific cytotoxic lymphocytes and impaired proliferative capacity of B-cells, similar to most chronic viral infections (19, 20). However, it is uncertain whether these HBV-induced immune deficiencies would have any influence on CD4+ T-cell counts. Our results would suggest that HBV infection does not affect CD4+ cell counts in untreated HIV-HBV co-infected patients, at least not when CD4+ levels are above 250/mm³.

During ART, CD4+ increases were rapid in the first 6 months and began to wane in the months thereafter, as expected (8), while these increases were also parallel between co-infection groups. This finding was also observed in a previous analysis of the Trivacan study (21), as well as other studies from Europe and South Africa (4,22,23). In contrast, poorer immunorecovery has been observed for HIV-HBV co-infected versus HIV mono-infected patients in studies from Switzerland and Nigeria (5,6). The discrepancy between studies could be partly explained by the fact that most have included individuals with severe immunosuppression and higher prevalence of liver disease, both of which are associated with reduced CD4+ cell counts during ART (8,24). In our study, all patients had a substantially higher CD4+ cell count and, per exclusion criterion, did not have liver impairment as established by transaminase levels. In addition, almost all patients in our study received ART containing tenofovir, which has potent

anti-HBV activity (25). Any purported effect of HBV on immunorecovery would have been effectively reduced.

In a previous analysis, we observed a higher mortality rate in HIV-HBV co-infected individuals with high HBV DNA (13). In our multivariable analysis, we additionally found that HIV-HBV co-infected individuals with high HBV DNA viral are at significantly higher risk of all-cause mortality, compared to others, when their CD4+ counts are $\leq 350/\text{mm}^3$. This excess risk is still high as CD4+ levels reach between 351-500/ mm^3 and is no longer apparent as levels reach above 500/ mm^3 . Given that HIV-HBV co-infected individuals do not have accelerated declines in CD4+ cell counts while not receiving ART and that they are able to exhibit immunorecovery comparably as quick as in those with HIV mono-infection, these data would not support the hypothesis that more severe immunosuppression over time in HIV-HBV co-infected individuals with high HBV DNA levels was responsible for a higher risk in mortality. Rather, these individuals simply have a more pronounced susceptibility to mortality when CD4+ levels are below 500/ mm^3 . Our observations stress the need to immediately treat co-infected patients with high HBV replication and to closely monitor them until CD4+ levels return above 500/ mm^3 .

The underlying explanation for these findings is somewhat unclear. Most deaths in the Temprano study were due to infectious diseases (14). Co-infected patients in sub-Saharan Africa with elevated HBV-replication at ART-initiation are more susceptible to HIV-related morbidity, especially invasive bacterial diseases (13,18,26). These causes of morbidity are in contrast to other studies in European settings, where liver-related disease appears to bear more influence on mortality rates in HIV-HBV co-infected individuals (27–29). The liver is known to carry an important immunological function, orchestrating immune responses against pathogens entering via gastrointestinal tract (30,31). Perhaps co-infected individuals with high levels of HBV DNA had more liver damage and as a result, were unable to clear HIV-related infections as

CD4+ cell counts were lower. Information on liver fibrosis would be needed to support this hypothesis and were unfortunately not collected in this study.

Interestingly, these data bring support for a previous modeling study calibrated to sub-Saharan Africa, in which a more deleterious impact on mortality would be observed in HIV-HBV co-infected patients if ART were delayed until CD4+ <500 (32). However, this model was based on assumptions that progression of liver fibrosis would lead to death in these individuals and that this progression would become faster as CD4+ counts decreased. Considering its cause for concern in the HIV-HBV co-infected population of sub-Saharan Africa, future models should consider the role of infections on mortality.

Other limitations of our study need to be addressed. First, data were derived from a clinical trial designed to assess the benefits of early treatment in HIV-positive individuals. There could be a potential selection bias for individuals randomized to deferred ART who initiated ART later (i.e. at lower CD4+ cell counts). Second, despite the large numbers of individuals recruited in the Temprano study, the HIV-HBV co-infected subgroups included small sample sizes. Third, individuals with grade 3-4 liver enzyme elevations and severe liver disease were excluded. These exclusion criteria made it difficult to recognize hepatic flares or decompensation following immune reconstitution in those with liver cirrhosis, which could contribute to mortality. Fourth, we did not have any data on HDV serostatus or HDV RNA replication at baseline, while HDV infection is known to be fairly prevalent among HBsAg-positive individuals in sub-Saharan Africa and contribute to an excess in mortality (33). Finally, as TDF-containing ART was given to the vast majority of participants, HBV DNA replication was likely controlled in >95% of co-infected individuals, as shown in a previous sub-analysis of the Temprano study (14), and HBeAg- and HBsAg-seroclearance were rather rare (34). As such, we were unable to assess whether changes in CD4+ count were associated with persistent HBV replication or seroconversion. In

addition, some of the agents used in this study are no longer part of first-line ART regimens and immunorestitution could be different with other current first-line antiretroviral agents, such as integrase strand transfer inhibitors.

In conclusion, we observed that HIV-HBV co-infected and HIV mono-infected patients did not have differences in CD4+ decline while not receiving ART or in immunorestitution after initiating ART. Importantly, the risk of mortality associated with HIV-HBV co-infection at high HBV DNA levels was only evident when CD4+ counts were below 500/mm³. In order to improve the quality of care for HIV-HBV co-infected individuals in sub-Saharan Africa, a deeper understanding of the causes of morbidity/mortality is still needed in this population.

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DISCLOSURE STATEMENT

The authors report no conflicts of interest.

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TABLES

Table 1. Baseline and follow up characteristics

	CD4+ cell count strata (/mm ³)			p-value*
	<350	[350-500]	>500	
	N=438	N=771	N=843	
Baseline				
Age in years, median (IQR)	36 (31, 42)	34 (29, 42)	35 (29, 42)	0.05
Female, n (%)	336 (77)	620 (80)	655 (78)	0.24
Schooling, n (%)				0.58
Primary school level or less	228 (52)	420 (54)	464 (55)	
Secondary school level or more	210 (48)	351 (46)	379 (45)	
BMI, kg/m ² , median (IQR)	22 (20, 25)	22 (20, 25)	23 (20, 26)	0.32
WHO clinical stage, n (%)				0.15
1	296 (68)	477 (62)	545 (65)	
2	96 (22)	212 (27)	228 (27)	
3	42 (10)	79 (10)	66 (8)	
4	4 (1)	3 (0)	4 (0)	
Median CD4 cell count/mm ³ (IQR)	301 (261, 328)	434 (401, 461)	598 (541, 675)	<0.001
Plasma HIV-1 RNA, log ₁₀ copies/ml, median (IQR)	4.8 (4.2, 5.4)	4.7 (4.0, 5.3)	4.5 (3.8, 5.2)	<0.001
Positive HBsAg	46 (11)	70 (9)	74 (9)	0.58
Plasma HBV DNA ≥2000 IU/mL	15 (3)	22 (3)	18 (2)	0.67
Positive HBeAg [‡] , n (%)	8 (22)	4 (8)	5 (13)	0.16
Positive anti-HBeAb [‡] , n (%)	27 (75)	45 (88)	33 (87)	0.24
Creatinine clearance <50 ml/min, n (%)	8 (2)	14 (2)	6 (1)	0.11
Plasma ALT, median (IQR)	19 (15, 27)	18 (13, 24)	18 (13, 24)	0.002
Plasma ALT >2.5 × ULN, n (%)	2 (0)	5 (1)	3 (0)	0.72
Hemoglobin <95 g/liter, n (%)	64 (15)	87 (11)	101 (12)	0.24
Follow-up				
Total time of follow-up, persons-years	2377	3620	3397	
Lost to follow-up, n (%)	58 (13)	69 (9)	79 (9)	0.04
Deaths, n (%)	26 (6)	37 (5)	23 (3)	0.01
Ever started cotrimoxazole (CTX), n (%)	438 (100)	765 (99)	783 (93)	<0.001
Months spent on CTX, median (IQR)	45 (30, 62)	34 (22, 53)	26 (6, 42)	<0.001

Table 1 (con't).

	CD4+ cell count strata (/mm ³)			<i>p</i> -value*
	<350	[350-500]	>500	
	<i>N</i> =438	<i>N</i> =771	<i>N</i> =843	
Ever started ART [€] , n (%)	426 (97)	715 (93)	689 (82)	<0.02
First-line ART regimen, n (%)				<0.01
TDF-FTC plus EFV	304 (71)	499 (70)	481 (70)	
TDF-FTC plus LPV/r [‡]	79 (19)	153 (21)	173 (25)	
TDF-FTV plus ZDV	28 (7)	37 (5)	16 (2)	
Other [§]	15 (4)	26 (4)	19 (3)	
Time spent on ART, persons-years	2069	2807	2260	
Ever started IPT, n (%)	191 (44)	366 (47)	379 (45)	0.38

Footnotes to Table 1

This included 516 patients randomized to immediate-ART and IPT, 514 to immediate-ART and no IPT, 511 to deferred-ART and IPT and 511 to deferred-ART and no IPT.

N: number in population; n: number in groups; IQR: interquartile range; BMI: body mass index; IPT: Isoniazid Preventive Therapy;

WHO: World Health Organization; ART: Antiretroviral Therapy; TDF: tenofovir; FTC: emtricitabine; ZDV: zidovudine; LPV/r:

lopinavir/ritonavir; ALT: alanine transaminase; ULN: upper limit of normal. BMI: body mass index; Ag: antigen; Ab: antibodies.

HBsAg: hepatitis B surface antigen.

**p*-value for comparison between three groups (or two groups when first column is empty), using Pearson χ^2 or Fisher Exact test for categorical variables and Kruskal-Wallis test for continuous variables.

[€]222 patients never started ART because their CD4 cell count remained >500/mm³ during the entire follow-up.

*Main ART regimen was TDF–FTC plus EFV. Among patients who started ART with TDF–FTC plus LPV/r, the reason for not receiving an EFV-based regimen was dual HIV-1/2 infection, previous nevirapine-use for preventing mother-to-child transmission, declining to use effective contraception, and other.

§Other regimens were ZDV–lamivudine (3TC) –LPV/r (n=29), ZDV–3TC–nevirapine (n=15), ZDV–3TC–EFV (n=8), 3TC–abacavir–LPV/r (n=2), DDI 3TC EFV (n=2), stavudine (D4T) –3TC–EFV (n=1), D4T–3TC–LPV/r (n=1), TDF-FTC-3TC-D4T (n=1), TDF-FTC-NVP (n=1).

£Among 125 patients (missing data, n=65).

Table 2. Incidence of death according to hepatitis B virus infection status within strata of CD4+ cell count

CD4+ cell count/mm ³ strata	Infection status	Deaths, <i>n</i>	PY at risk	IR, per 100 PY (95%CI)	IRR ¹ (95%CI)		
					Unadjusted	Adjusted ²	
Two-group analysis							
	<350	HBsAg-negative	31	1363	2.27 (1.47-3.08)	Ref	Ref
		HBsAg-positive	7	141	4.96 (1.99-10.23)	2.25 (0.90-4.85)	2.10 (0.84-4.53)
	350-500	HBsAg-negative	20	2306	0.87 (0.53-1.34)	Ref	Ref
		HBsAg-positive	3	239	1.26 (0.26-3.67)	1.50 (0.34-4.40)	1.51 (0.34-4.46)
	>500	HBsAg-negative	23	4858	0.47 (0.30-0.71)	Ref	Ref
		HBsAg-positive	2	486	0.41 (0.05-1.49)	0.93 (0.14-3.16)	0.85 (0.13-2.94)
Three-group analysis							
	<350	HBsAg-negative	31	1363	2.27 (1.47-3.08)	Ref	Ref
		HBsAg-positive, HBV DNA <2000 IU/mL	3	96	3.13 (0.64-9.14)	1.48 (0.34-4.16)	1.33 (0.31-3.78)
		HBsAg-positive, HBV DNA ≥2000 IU/mL	4	46	8.70 (2.37-22.26)	3.98 (1.16-10.11)	3.82 (1.11-9.70)
	350-500	HBsAg-negative	20	2306	0.87 (0.53-1.34)	Ref	Ref
		HBsAg-positive, HBV DNA <2000 IU/mL	0	162	0 (0-2.28)	0.50 (<0.01-2.28)	0.52 (<0.01-2.40)
		HBsAg-positive, HBV DNA ≥2000 IU/mL	3	78	3.85 (0.79-11.24)	4.68 (1.06-13.74)	4.37 (0.98-13.02)
	>500	HBsAg-negative	23	4858	0.47 (0.30-0.71)	Ref	Ref
		HBsAg-positive, HBV DNA <2000 IU/mL	2	364	0.55 (0.07-1.98)	1.24 (0.18-4.22)	1.16 (0.17-4.02)
		HBsAg-positive, HBV DNA ≥2000 IU/mL	0	123	0 (0-3.00)	1.21 (<0.01-5.52)	1.07 (<0.01-4.91)

Footnotes to Table 2

¹Calculated from an Exact Poisson regression model using median unbiased estimates with the mid-P-value rule.

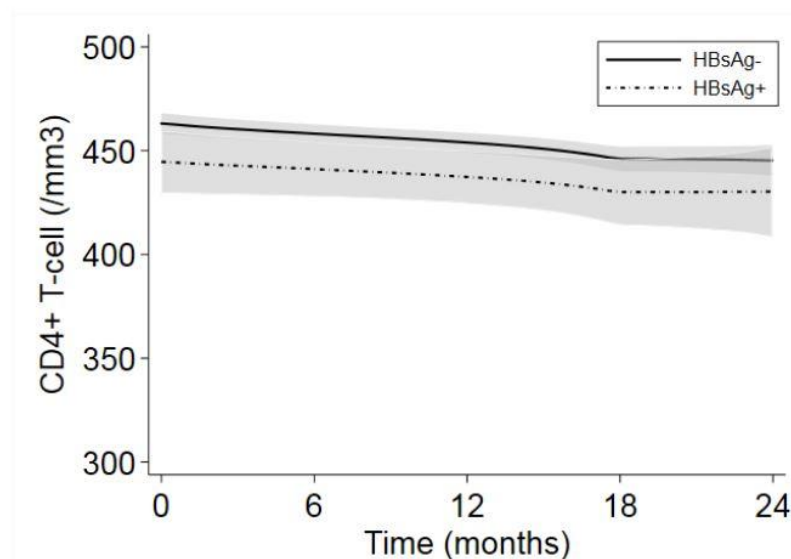
²Adjusted for sex, age (<35 versus ≥35 years), baseline HIV-RNA (<5.00 versus ≥5.00 log₁₀ copies/mL), and early or deferred ART arm.

Abbreviations: HBsAg, Hepatitis B surface antigen; HBV DNA, Hepatitis B virus deoxyribonucleic acid; CD4, CD4+ T lymphocytes;

PY, person-year; CI, confidence interval

FIGURE LEGEND

A



B

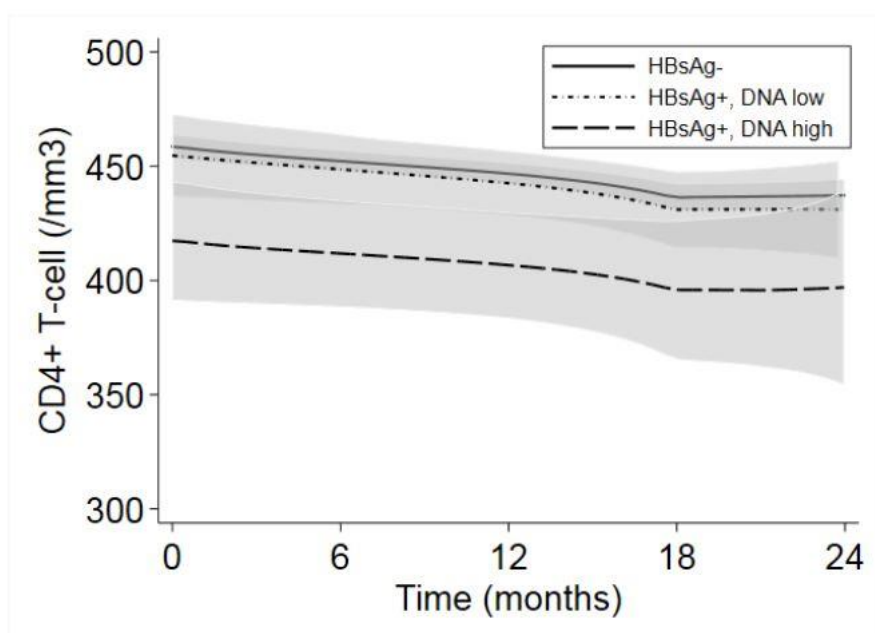
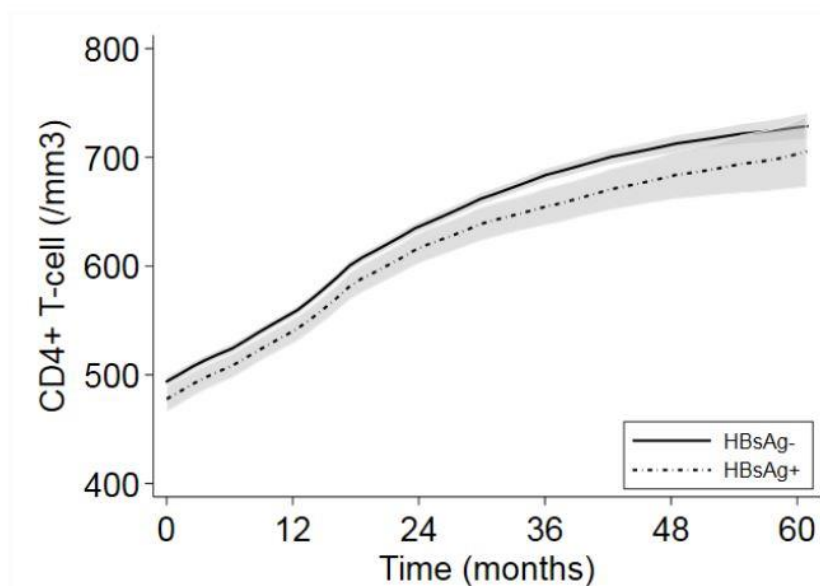


Figure 1. Modeled CD4+ T cell count decrease while not receiving antiretroviral therapy (ART) Mean CD4+ T cell counts estimated as linear decrease off ART over time (lines) along with their 95% confidence intervals (shaded) using a mixed-effect regression model. Estimates are adjusted for baseline CD4+ level, HIV RNA level, age and sex. Curves

are stratified by hepatitis B surface antigen (HBsAg)-status (**A**) or HBsAg-status and baseline HBV DNA at low (<2000 IU/mL) or high (≥ 2000 IU/mL) levels (**B**).

A



B

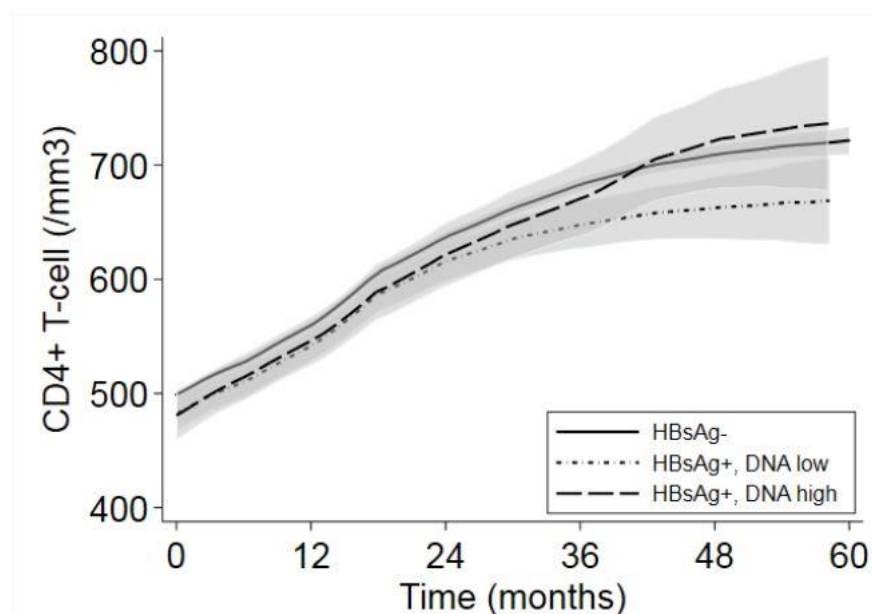


Figure 2. Modeled CD4+ T cell count increase after initiating antiretroviral therapy (ART)

Mean CD4+ T cell counts estimated as root-square increase on ART over time (lines) along with their 95% confidence intervals (shaded) using a mixed-effect regression model.

Estimates are adjusted for baseline CD4+ level, HIV RNA level, age and sex. Curves are stratified by hepatitis B surface antigen (HBsAg)-status (**A**) or HBsAg-status and baseline HBV DNA at low (<2000 IU/mL) or high (\geq 2000 IU/mL) levels (**B**).

2.5 Natural history of HBV infection in HIV-positive individuals who are not receiving ART in the Temprano study

In SSA, HBeAg-negative chronic infection, as determined by EASL guidelines, constitutes the predominant patient group with chronic hepatitis B nowadays. The formally named “inactive carrier” state may persist indefinitely or progress to HBeAg-negative chronic hepatitis after years of controlled HBV infection. The differentiation of “inactive carriers” from HBeAg-negative chronic hepatitis B patients is important, as the former is known to coincide with low incidence of cirrhosis and hepatocellular carcinoma, while the latter is associated with a high risk of developing cirrhosis and HCC and, therefore, may benefit more from timely initiation of antiviral treatment (321).

Few studies have longitudinally evaluated HBV activity in HBeAg-negative infection in HBV mono-infection (322) and almost no studies exist in HIV-HBV co-infection. As described in Chapter 1.1, HBeAg-negative chronic infection results from losing HBeAg-positive status and usually acquisition of anti-HBeAb. Individuals in this state are considered to be in an immunologically controlled phase of infection. This phase can be followed by HBeAg-negative chronic hepatitis, which results in increased HBV replication and transaminase levels (formally called the “immune reactive” phase) (48). As we have already mentioned, HBV is usually acquired during early childhood in SSA. It would then be assumed that as HIV-HBV co-infected individuals without ART develop weaker immunity with a drop in CD4+ cell counts, HBeAg-negative chronic infection could more rapidly progress to the HBeAg-negative chronic hepatitis phase. This could have immediate consequences of accelerated liver disease progression, as shown by Thio et al in the Multicenter AIDS Cohort Study (304).

In this section, we took advantage of data from the Temprano study among HIV-HBV co-infected individuals who were not, and had not, initiated ART. We first identified the HBeAg-status of HIV-HBV co-infected participants at inclusion. Among them, we continuously measured HBV DNA viral loads and ALT levels. This information allowed use to not only

characterize the evolution of HBV DNA viral load, but also progression to more active forms of HBeAg-negative infection without ART, thereby providing a snapshot of the natural progression of HBV disease during increasing immunosuppression. The results of our analysis were published in the journal, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, and are presented on the following page.



Hepatitis B virus activity in untreated hepatitis B e antigen–negative human immunodeficiency virus–hepatitis B virus co-infected patients from sub-Saharan Africa

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Background: In human immunodeficiency virus (HIV) and hepatitis B virus (HBV) co-infected patients from sub-Saharan Africa with hepatitis B e antigen (HBeAg)-negative status, data are limited on the evolution of HBV activity when antiretroviral treatment (ART) is absent.

Methods: A total of 43 HBeAg-negative co-infected patients not indicated for ART (per concomitant World Health Organization recommendations) were followed during participation in a randomized controlled trial in Côte d'Ivoire. Chronic HBeAg-negative phases were classified at yearly visits and defined as 'infection' (HBV DNA $\leq 10\,000$ copies/mL and normal alanine aminotransferase [ALT]) or 'hepatitis' (HBV DNA $> 10\,000$ copies/mL and/or above normal ALT). Dispersion in HBV DNA and ALT levels during follow-up was assessed using interquartile range (IQR) regression.

Results: During a median 25 months (IQR 19–31), 17 (40%) patients consistently had 'infection', 5 (12%) consistently had 'hepatitis' and 21 (48%) fluctuated between phases. Wider dispersion in HBV DNA over time was associated with higher baseline HIV RNA ($p=0.02$) and higher baseline HBV DNA levels ($p=0.008$), while wider dispersion in ALT was associated with higher baseline HIV RNA ($p<0.001$), higher baseline ALT levels ($p=0.02$) and baseline hepatitis surface antigen $> 4.0 \log_{10}$ IU/mL ($p=0.02$).

Conclusions: HBV activity is common with HBeAg-negative status, whose variation is partly linked to HIV replication. Fluctuations in disease phase make it difficult to assess the risk of morbidity and mortality after ART initiation.

Keywords: chronic hepatitis B, genetic variability, HBeAg negative, natural history, surface gene

Introduction

Among human immunodeficiency virus (HIV)-infected individuals in sub-Saharan Africa (SSA), roughly 5–10% are co-infected with chronic hepatitis B virus (HBV).¹ In a number of studies conducted in Europe, the United States and Australia,

HIV–HBV co-infection is known to increase the risk of morbidity and mortality compared with HIV mono-infection.² The increased risk in overall morbidity and mortality during HIV–HBV co-infection has been largely confirmed in patients from SSA.^{3–5}

In HBV mono-infection, patients begin with hepatitis B e antigen (HBeAg)-positive serology after infection and become negative

as they mount immune responses against the virus.⁶ When patients progress to HBeAg-negative disease, HBV is suppressed and transaminase and liver fibrosis levels are low. This phase of HBV is termed HBeAg-negative chronic 'infection'.⁷ Over time, some patients enter a more active form of disease, termed HBeAg-negative chronic 'hepatitis', whereby HBV DNA and transaminase levels are much higher and liver fibrosis is more pronounced. These HBeAg-negative phases help differentiate the degree of HBV activity and, since the risk of developing hepatocellular carcinoma (HCC) or liver-related morbidity is significantly increased during HBeAg-negative hepatitis, guide clinicians in the initiation of antiviral treatment.⁷

Considering that anti-HBV responses are needed to control HBV activity and could be impaired due to HIV-induced immunosuppression,² HIV-HBV co-infected patients could exhibit substantially different evolution of HBeAg-negative disease than HBV mono-infected patients. However, there are few studies on the natural history of HBV infection during co-infection, which for the most part can only be inferred from studies in patients on antiretroviral therapy (ART) not containing an anti-HBV agent.⁴ Repeat assessments of HBV DNA and alanine aminotransferase (ALT) in HBeAg-negative co-infected individuals without ART could provide insight on the progression of HBeAg-negative 'infection' to 'hepatitis' in this population.

In the study herein, we used unique data from a randomized controlled trial in Côte d'Ivoire,⁸ allowing prospective longitudinal follow-up in patients without ART and hence representing a small portion of the natural history of HIV and HBV infection. The aim was to examine the extent and risk factors of HBV activity over time, as determined by chronic 'infection' and 'hepatitis', among HBeAg-negative co-infected patients who have never received or have not yet initiated ART. Given that these phases are defined by recommended thresholds, we also assessed determinants of dispersion in HBV DNA and ALT levels in order to further understand reasons for changes in the HBeAg-negative phase.

Materials and methods

Study population

Patients were selected from the National Agency for Research on AIDS and Viral Hepatitis (ANRS) 12136 Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults (TEMPRANO) trial.⁸ Briefly, this study was a multicentre, randomized, open-label trial aimed at assessing the benefits and risks of initiating early ART versus concurrent recommendations from the World Health Organization (WHO), with or without 6-month isoniazid prophylaxis for tuberculosis (TB). Inclusion criteria were as follows: provided signed, informed consent; age >18 y; had HIV-1 infection or HIV-1/HIV-2 dual infection; had no ongoing active TB; had no ongoing pregnancy and/or were not breastfeeding; had a CD4⁺ T-cell count <800 cells/mm³ and did not meet criteria for ART initiation according to the most recent WHO guidelines. Participants were randomly assigned to one of four arms: two 'standard ART' arms (arms 1 and 2), in which ART was delayed until patients met concurrent WHO starting criteria; and two 'early ART' arms (arms 3 and 4), in which ART was initiated immediately on inclusion. In arms 2 and 4,

participants received 6-month isoniazid prophylaxis for TB. All participants gave written informed consent and the protocol was approved by the ethics committee of the Ministry of Health of Côte d'Ivoire and by the institutional review board of the ANRS (Paris, France). The study has been registered under clinicaltrials.gov identifier NCT00495651.

In this analysis, we selected patients testing hepatitis B surface antigen (HBsAg) positive and HBeAg negative at study inclusion (Mini Vidas assay, Biomerieux, Marcy l'Etoile, France), confirmed by the Architect i2000 assay (Abbott Laboratories, Rungis, France), who did not start ART at randomization (study arms 1 and 2) and continued follow-up with at least one visit while not receiving ART.

HBV virological, serological and biochemical data

HBV-related parameters were obtained from frozen samples stored at -80°C and were quantified at baseline and at every 12-month follow-up visit. HBV DNA was quantified from an in-house quantitative polymerase chain reaction (PCR) assay (Light Cycler 480, Roche Diagnostics, Meylan, France) with a detection limit of <12 copies/mL.⁹ HBeAg and anti-HBe antibodies were detected using a qualitative assay (Elecys, Roche Diagnostics). Quantitative HBsAg (qHBsAg) was measured using the Elecys assay with the Modular E170 analyser (Roche Diagnostics).¹⁰ Plasma ALT levels were quantified using standard methods.

We established chronic HBeAg-negative phases based on definitions from the European Association of the Study of the Liver (EASL).⁷ Since data on liver fibrosis were not obtained, infection phase could only be assessed using HBV DNA and ALT levels. HBeAg-negative 'infection' was defined as HBV DNA ≤10 000 copies/mL and normal ALT (<40 IU/mL) and HBeAg-negative 'hepatitis' as HBV DNA >10 000 copies/mL and/or above normal ALT (≥40 IU/mL).

Determining HBV genotype

Genotypic analysis was performed at baseline and during follow-up for all patients with an HBV viral load >1000 copies/mL.⁹ Direct sequencing after nested PCR amplification of the reverse transcriptase (rt) and surface antigen (s) encoding regions was used to obtain aa sequences of the *pol* and *S* genes (between rt107–rt385 and s99–s226, respectively), as well as amplification of the preC/C region to obtain basal core promoter (BCP) and pre-core (pc) nucleotide (nt) sequences (nt1743–2362). Individual sequences were aligned using the ClustalW full multiple alignment program with 1000 bootstraps in BioEdit (version 7.0.5.3; Ibis Therapeutics, Carlsbad, CA).

HBV genotypes were determined via phylogenetic analysis conducted on aligned sequences of the *pc* region (nt1814–2452), which were compared with several referent sequences of HBV genotypes A–H (GenBank accession numbers listed in Supplementary Table 1). The neighbour-joining method was employed with 1000 bootstrap replications using a Kimura two-parameter substitution model that included transitions and transversions (d). A discrete gamma model with a mean of 1 was also used to incorporate rate variation among sites. The resulting phylogenetic tree was constructed using Molecular

Evolutionary Genetics Analysis (version 6) software and is presented in Supplementary Figure 1.

Detection of HBV mutations

Individual aa sequences were compared with a genotype-specific consensus sequence of the polymerase and small hepatitis B surface protein retrieved from the Hepatitis B Virus Database¹¹ (defined in the Supplementary materials). If an aa at a given position was different than the consensus sequence, a mutation was considered present at this position. Antiviral resistance mutations on the *pol* gene were defined as the function of the associated agent: lamivudine (rtV173L, rtL180M, rtM204V/I), adefovir (rtA181T/V, rtN236T), entecavir (rtT184S/A/I/L/G/C/M, rtS202C/G/I, rtM250I/V). A pc mutation was defined as an adenine instead of guanine nucleotide at position 1896 on the pc region.

HIV virological and immunological data

CD4⁺ cell counts (True Count technique on FACScan, Becton Dickinson, Aalst-Enembogem, Belgium) and plasma HIV-1 RNA (real-time PCR on TaqMan, ABI Prism 7000, Applied Biosystems, Courtaboeuf, France; detection threshold 300 copies/mL) were measured at baseline and every 6 months during follow-up.¹²

Statistical analysis

The inclusion study visit was defined as the baseline. Follow-up began at baseline and continued until the last follow-up visit, study termination, ART initiation or death, whichever occurred first.

Longitudinal profiles of HBV activity were established in relation to whether patients consistently exhibited HBeAg-negative 'infection', fluctuated between HBeAg-negative 'infection' and 'hepatitis' or consistently exhibited HBeAg-negative 'hepatitis'. Baseline and follow-up characteristics were compared between HBV activity groups using the Kruskal-Wallis test for continuous variables and Pearson χ^2 test or Fisher's exact test for categorical variables.

In order to study determinants of dispersion in the two markers defining HBV activity, we used interquartile range (IQR) regression. In brief, two quantile models are used to regress determinants on the 75th and 25th percentiles of HBV DNA and ALT levels across time points. The difference between the two regressed percentiles, $\text{diff}(p75, p25)$, is given per unit increase in risk factor and 95% confidence intervals (CIs) were calculated from standard errors obtained using 200 bootstrapped samples. Only baseline determinants were used in this analysis. All analyses were performed using STATA version 12.1 (StataCorp, College Station, TX, USA) and significance was determined by a p -value <0.05 .

Results

Description of the study population

Between 18 March 2008 and 30 March 2011 (when inclusions for this substudy were terminated), 148 of 1625 patients enrolled in the TEMPRANO study were identified as HBsAg positive at inclusion. Among them, 105 were not included because

they were randomized to receive early ART ($n=66$), had only one follow-up visit ($n=10$), did not have confirmed HBsAg-positive serology ($n=8$), had suspected acute HBV infection ($n=1$), had HBeAg-positive serology ($n=2$) or did not have available HBV DNA ($n=17$) or qHBsAg ($n=1$) levels at inclusion. In total, 43 patients were analysed.

Baseline demographic and HIV- and HBV-related characteristics of included patients are provided in Table 1. The median HBV DNA ($3.41 \log_{10}$ copies/mL [IQR 2.38–4.25]) and ALT levels (20 IU/mL [IQR 17–29]) were low. According to EASL 2017 guidelines, patients began follow-up with HBeAg-negative chronic 'infection' ($n=30$ [69.8%]) or HBeAg-negative chronic 'hepatitis' ($n=13$ [30.2%]). All patients were anti-HBe antibody positive. Among patients with available preC/C sequences ($n=25$), 21 patients harboured HBV genotype E, 3 genotype C and 1 with possible recombinant genotype A/D (Supplementary methods, Supplementary Figure 2). The pcG1896A mutation was found in 18 patients (72.0%).

Profiles of HBeAg-negative HBV activity during follow-up

The median follow-up was 25 months (IQR 19–31), corresponding to a median of 5 visits (IQR 4–6) per patient. The distribution of longitudinal profiles of HBeAg-negative HBV activity was as follows: consistently HBeAg-negative chronic 'infection' ($n=17$), fluctuating between HBeAg-negative chronic 'infection' and 'hepatitis' ($n=21$) and consistently HBeAg-negative chronic 'hepatitis' ($n=5$). In patients with fluctuating HBV activity profiles, HBeAg-negative chronic 'infection' and 'hepatitis' were identified in 45.8% and 54.2% of total study visits, respectively. No patient became HBeAg positive during follow-up.

As shown in Figure 1A, the median within-patient range (difference between minimum and maximum) of HBV DNA levels observed during follow-up was largest in patients fluctuating between HBeAg-negative chronic 'infection' and 'hepatitis' ($3.11 \log_{10}$ copies/mL [IQR 2.63–3.97]), followed by patients consistently classified with HBeAg-negative chronic 'infection' (2.59 [IQR 0.52–3.02]) and consistently with HBeAg-negative chronic 'hepatitis' (1.67 [IQR 1.00–2.32]) ($p=0.03$). Only 3 (7.0%) patients had undetectable HBV DNA levels at all follow-up time points. qHBsAg levels were stable during follow-up for most patients, regardless of the HBeAg-negative HBV activity profile (Figure 1B). ALT was highly variable during follow-up (Figure 1C), with the majority of ALT flares greater than two times the upper limit of normal (>70 IU/L) occurring in patients consistently classified with HBeAg-negative chronic 'hepatitis' (60.0%) or those fluctuating between HBeAg-negative chronic 'infection' and 'hepatitis' (38.1%).

Table 1 compares baseline characteristics across HBeAg-negative HBV activity profiles. As profiles went from those consistently classified with HBeAg-negative chronic 'infection' to those consistently with chronic 'hepatitis', baseline HIV RNA levels were increasingly higher ($p=0.02$) and the baseline percentage of CD4⁺ cells was increasingly lower ($p=0.03$). Body mass index was also significantly lower in patients consistently classified with HBeAg-negative chronic 'hepatitis' compared with all other groups (21 vs 25 kg/m², respectively; $p=0.02$). Finally,

Table 1. Description of the study population

Characteristics	Total (n=43)	HBeAg-negative phase			p-Value ^a
		Consistently chronic 'infection' (n=17)	Fluctuating (n=21)	Consistently chronic 'hepatitis' (n=5)	
Baseline					
Male/female (% males)	8/35 (18.6)	3/14 (17.7)	4/17 (19.1)	1/4 (20.0)	0.9
Age (years), median IQR	33 (30–39)	33 (31–37)	34 (30–42)	34 (32–37)	0.9
Body mass index (kg/m ²), median (IQR)	24.3 (20.7–27.2)	24.4 (20.7–26.0)	24.7 (21.9)	21.1 (18.6–21.7)	0.05
Current smoker, n (%)	1 (2.3)	0 (0)	1 (4.8)	0 (0)	0.9
WHO clinical stage, n (%)					0.7
Stage I	28 (65.1)	10 (58.8)	14 (66.7)	4 (80.0)	
Stage II	10 (23.3)	5 (29.4)	5 (23.8)	0 (0)	
Stage III	5 (11.6)	2 (11.8)	2 (9.5)	1 (20.0)	
HIV RNA >300 copies/mL, n (%)	41 (95.4)	16 (94.1)	20 (95.2)	5 (100)	0.9
HIV RNA (log ₁₀ copies/mL, median (IQR))	4.48 (3.91–5.08)	4.02 (3.55–4.83)	4.49 (3.97–5.08)	5.14 (5.08–5.38)	0.02
CD4 ⁺ cell count (per mm ³), median (IQR)	473 (381–574)	490 (445–661)	473 (382–548)	377 (356–386)	0.15
CD4 ⁺ cell count (%), median (IQR)	20.6 (16.6–26.6)	21.7 (20.6–28.3)	19.9 (16.1–23.7)	15.6 (12.5–18.1)	0.03
HBV genotype (N=25), n (%)					0.5
E	21 (84.0)	5 (71.4)	11 (84.6)	5 (100)	
C	3 (12.0)	1 (14.3)	2 (15.4)	0 (0)	
A/D recombinant	1 (4.0)	1 (14.3)	0 (0)	0 (0)	
Precore mutation (N=25), n (%)	18 (72.0)	4 (57.1)	9 (69.2)	5 (100)	0.3
qHBsAg (log ₁₀ IU/mL) (N=40), median (IQR)	3.58 (3.11–3.98)	3.54 (3.11–3.87)	3.61 (3.03–3.94)	4.01 (3.55–4.14)	0.5
Follow-up characteristics					
Duration (months), median (IQR)	25 (19–31)	25 (20–31)	25 (19–31)	15 (12–21)	0.17
Total HBV viral load, n (%)	5 (4–6)	5 (4–5)	5 (4–6)	4 (3–5)	0.3
Change in qHBsAg from baseline, median (IQR)	−0.05 (−0.18 to −0.01)	−0.06 (−0.18 to −0.02)	−0.05 (−0.08 to −0.01)	−0.43 (−0.52 to 0.17)	0.7

Chronic 'infection' defined as HBV DNA <10 000 copies/mL and ALT <35 IU/mL and chronic 'hepatitis' as HBV DNA ≥10 000 copies/mL and/or ALT ≥35 IU/mL.

^aSignificance between replication groups determined using Kruskal-Wallis test for continuous variables and Pearson χ^2 test or Fisher's exact test for categorical variables.

follow-up was slightly lower in those consistently classified with HBeAg-negative chronic 'hepatitis' compared with all others (15 vs 25 months, respectively; $p=0.06$).

HBV genetic variability and HBeAg-negative HBV activity during follow-up

Table 2 describes genotypic findings on the HBV *pol* and *S* genes for patients with available data. There were no noteworthy differences in the genetic variability between HBeAg-negative HBV activity groups. No lamivudine resistance mutations on the *rt* domain were observed in the entire study population. Eight mutations on the 'a' determinant of the *S* gene were observed: sI110L ($n=3$), sP120T ($n=1$), sT126I ($n=1$), sQ129H ($n=2$) and

sF134L ($n=1$). One other *S* gene mutation at a position conventionally associated with antiviral-selective pressures was observed (sE164G); however, it did not appear to correspond to a resistance mutation on the *pol* gene (as is the case with the sE164D mutation). For patients having more than one study visit with HBV genetic information ($n=6$) (Supplementary Figure 3), two exhibited changes in dominant HBV variants during follow-up, whereas four demonstrated no such changes.

Determinants of HBV DNA and ALT dispersion over time

Table 3 summarizes baseline determinants of increased diff (p75, p25) in HBV DNA and ALT levels over time. Baseline HIV RNA levels were associated with greater dispersion of both

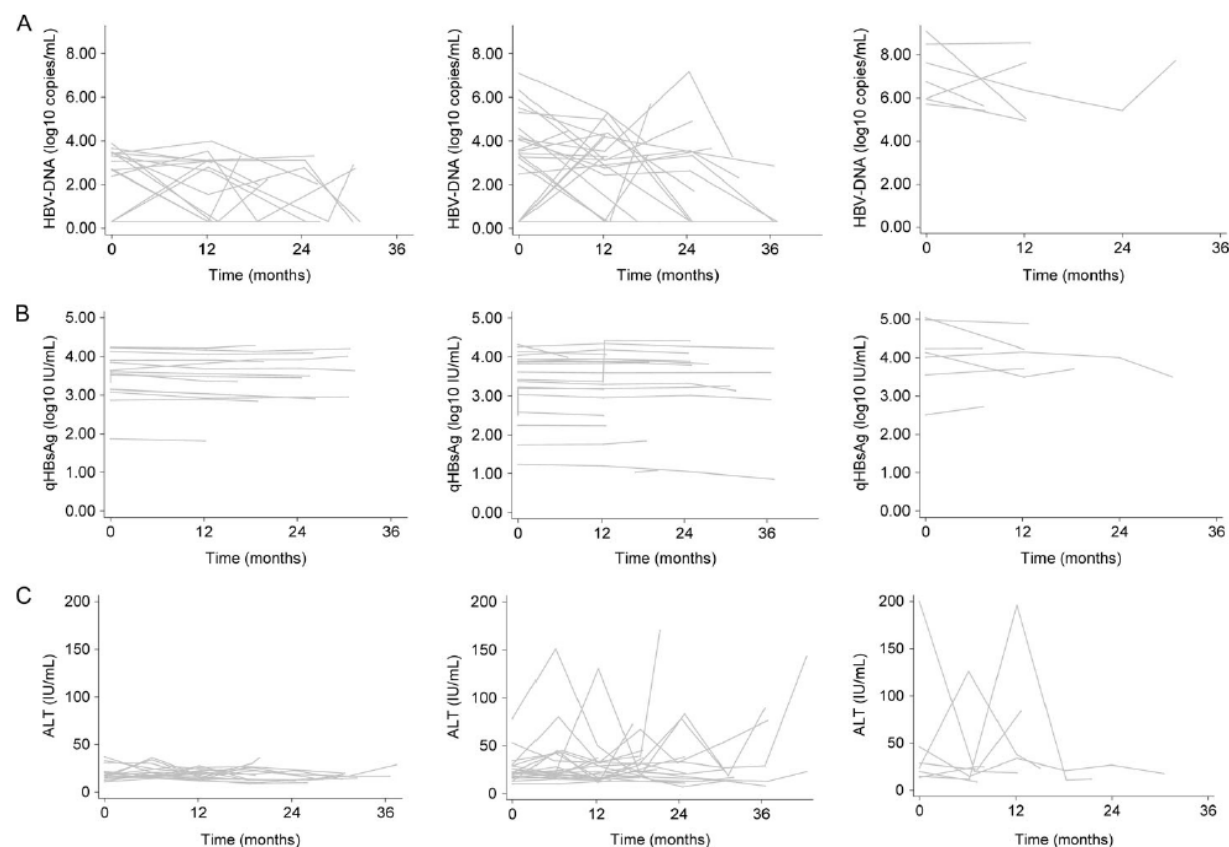


Figure 1. Markers of HBV replication during follow-up. Individual lines (in grey) are given for (A) HBV DNA, (B) qHBsAg and (C) ALT during untreated infection with HIV-HBV. Figures are presented according to HBeAg-negative HBV activity profile: consistently chronic 'infection' (left panels), fluctuating between chronic 'infection' and 'hepatitis' (centre panels) and consistently chronic 'hepatitis' (right panels).

HBV DNA ($p=0.02$) and ALT ($p<0.001$). Greater dispersion of HBV DNA over time was found specifically with higher baseline HBV DNA viral loads ($p=0.008$), whereas greater dispersion of ALT levels over time was observed specifically in baseline qHBsAg levels $>4.0 \log_{10}$ IU/mL ($p=0.02$) and higher baseline ALT levels ($p=0.02$). Multivariable analysis was precluded by the low number of patients.

Discussion

The vast majority of individuals chronically infected with HBV in SSA are HBeAg negative. Nevertheless, HBV activity during HBeAg-negative disease is unclear for both HBV mono-infected and HIV-HBV co-infected patients on the continent. By longitudinally examining HBV DNA and ALT levels in a group of treatment-naïve co-infected patients from Côte d'Ivoire who did not receive ART, we demonstrate that roughly half of patients exhibit fluctuations between HBeAg-negative chronic 'infection' and 'hepatitis'.

As expected, higher baseline levels of HBV DNA or ALT levels were associated with greater dispersion of their individual markers during follow-up. Lower baseline qHBsAg, which in general is a strong predictor of consequent viral inactivity,¹³ was only associated with lower ALT dispersion. However, qHBsAg distributions were rather narrow and did not substantially change over time in our study population, making it difficult to compare with other studies wherein individuals had much lower qHBsAg levels.

Importantly, both instability of the HBeAg-negative phase or remaining with HBeAg-negative chronic 'hepatitis' were strongly linked to more advanced HIV infection at baseline, as reflected by the higher HIV RNA levels and lower percentage of CD4⁺ T cells. It could be that the progression of HIV infection observed until baseline led to fluctuation between HBeAg-negative phases or consistently having chronic 'hepatitis', relative to the group consistently classified as chronic 'infection'. The pathophysiological link between the HBeAg-negative phase of chronic HBV and HIV infection is somewhat difficult to explain. As ongoing HIV replication causes a decrease in CD4⁺ T-cells, co-infected patients begin to exhibit more pronounced deficiencies

Table 2. HBV phase consistency and genotypic analysis of patients with available data

ID	Follow-up (months)	HBV DNA (log ₁₀ copies/mL)		n ^a	Genotypic findings	
		M0	End of follow-up		pol gene	S gene
Consistently HBeAg-negative chronic infection						
NS002	13	3.89	<0.3	1	wt	wt
HB036	37	2.38	2.73	1	rtT128N	sP120T, sY206C, sV209W
Fluctuating						
LP042	31	5.30	<0.3	2	wt	wt
HB083	31	4.10	3.28	2	wt	sE164G, sS193L
CF228	21	7.09	3.90	2	rtV266K	wt
CF277	25	<0.3	<0.3	1	wt	wt
HB170	19	<0.3	5.69	1	wt	wt
HB150	26	4.56	<0.3	1	rtI269L	sI110L, sT126I, sK160R, sI213L, sF219S, sF220C, sV224A
AB069	37	2.48	<0.3	1	rtQ316H	sV190A, sS204N, sV209W, sY225F
LP064	19	3.60	4.45	1	rtK333Q	sS204N, sL215 ^b
NS259	25	3.14	4.90	1	rtV142A	sI110L, sF134L, sV184G, sT189I, sS204N
NS092	17	3.44	3.29	1	rtS219A	sQ129H, sS193L, sS210R
Consistently HBeAg-negative chronic hepatitis						
ST073	7	5.72	5.42	2	rtN337T	wt
AB023	21	5.98	7.65	2	rtS117P ^b , rtS219A ^b , rtC332Y ^b	sS210R ^b , sL215 ^a
HB061	31	7.64	7.74	4	rtK333Q, rtV266K ^c	sI110L ^c
NS025	12	9.08	5.05	1	rtS219A	sQ129H, sS193L, sS210R
ST114	15	5.95	4.94	1	rtS213T, rtL311I, rtK333Q	sY200F, sS204R

Values for HBV DNA are given for baseline (M0) and at the last follow-up visit. It should be noted that these values do not necessarily represent the maximum and minimum during follow-up.

^aNumber of available samples with HBV sequences.

^bMutation was not observed at the last follow-up visit.

^cOnly one visit at which rtK333Q was no longer the dominant quasispecies and rtV266K (with sI110L mutation) was observed.

in anti-HBV responses, such as Kupffer and stellate cell activation in the liver, and regulation of intrahepatic apoptosis.^{14,15} The resulting loss of HBV control likely increases intrahepatic HBV DNA replication¹⁶ and thus could allow for higher plasma HBV DNA and ALT levels. Chronic HBV infection itself also contributes to immunodysfunction, specifically with regards to depletion of HBV-specific cytotoxic lymphocytes and impaired proliferative capacity of B-cells.^{17,18} It is unknown whether these HBV-induced immune deficiencies have any direct or indirect influence on CD4⁺ T-cell counts or HIV replication. Taken together, the progression towards HBeAg-negative chronic hepatitis most likely reflects the consequences of HIV-induced immunosuppression and possibly altered immunoregulation from chronic HBV.

Although most co-infected patients are expected to initiate ART immediately after HIV diagnosis, these results are still pertinent to this population for two important reasons. First, HBV DNA at baseline has been repeatedly useful in estimating the risk of overall mortality in HIV-HBV co-infected patients from SSA,^{19,20} even after early initiation of ART,²¹ while it is assumed that assessing the phase of HBeAg-negative chronic HBV would be comparably valuable. Fluctuations in HBeAg-negative phases

indicate that, if evaluated once, assessments could misrepresent HBV activity and thus complicate risk stratification after ART initiation. The results from our study population suggest that this occurs in roughly a quarter of all assessments. Second, data from health care centres in similar settings suggest that co-infected patients are more likely to default on care and discontinue ART compared with HIV mono-infected individuals.²² Our findings underscore the potentially unfavourable consequences of uncontrolled HIV replication when no longer in care.

With repeated measures taken as part of participating in a clinical trial, these data are uncommon for both HBV mono-infected and HIV-HBV co-infected patients in SSA. It is clinically well known that HBV mono-infected patients can exhibit fluctuations in markers of replication.⁷ We observed that the dispersion in our study population was due in part to HIV-related factors, making it difficult to extrapolate to HBV mono-infected patients. Nevertheless, a recent analysis among HBeAg-negative inactive carriers (i.e. HBeAg-negative chronic infection) showed that HBV activity can be observed in 35% of patients after 1 y without antiviral therapy,¹³ indicating that fluctuation between

Table 3. Determinants of dispersion in markers of HBV replication during follow-up (IQR regression analysis)

Baseline characteristics	HBV DNA (log ₁₀ copies/mL)		ALT (IU/mL)	
	Diff(p75, p25) (95% CI)	p-Value	Diff(p75, p25) (95% CI)	p-Value
Age (per year)	-0.01 (-0.12 to 0.10)	0.8	0.0 (-0.2 to 0.3)	0.8
Female vs male	-0.36 (-2.24 to 1.52)	0.7	-6.0 (-19.5 to 7.5)	0.4
Body mass index (per kg/m ²)	-0.06 (-0.22 to 0.10)	0.4	0.0 (-0.6 to 0.6)	0.9
WHO stage III or IV	1.79 (-1.85 to 5.44)	0.3	-1.0 (-10.0 to 8.0)	0.8
HIV RNA (per log ₁₀ copies/mL)	0.94 (0.13 to 1.76)	0.02	5.1 (3.0 to 7.3)	<0.001
HIV RNA >10 000 copies/mL	1.54 (-0.65 to 3.73)	0.17	7.0 (2.7 to 11.3)	0.001
CD4 ⁺ (per 100/mm ³)	-0.35 (-0.91 to 0.21)	0.2	-0.6 (-2.9 to 1.8)	0.6
CD4 ⁺ >350 cells/mm ³	1.86 (-0.82 to 4.53)	0.17	0.0 (-19.9 to 19.9)	0.9
HBV DNA (per log ₁₀ copies/mL)	0.46 (0.12 to 0.80)	0.008	0.4 (-1.2 to 2.0)	0.6
ALT (per 10 IU/mL)	0.00 (-0.36 to 0.37)	0.9	9.9 (1.8 to 18.0)	0.02
ALT >40 IU/mL	2.68 (-1.48 to 6.83)	0.2	20.0 (-6.0 to 46.0)	0.13
qHBsAg (per log ₁₀ IU/mL)	0.27 (-0.59 to 1.13)	0.5	2.5 (-0.8 to 5.8)	0.14
qHBsAg >4.0 log ₁₀ IU/mL	-0.05 (-2.76 to 2.65)	0.9	16.0 (2.1 to 29.9)	0.02
Follow-up time	-0.05 (-0.13 to 0.02)	0.15	0.1 (-0.3 to 0.4)	0.7

The difference between the two regressed percentiles, diff(p75, p25), is given per unit increase in risk factor and 95% CIs calculated from standard errors obtained using 200 bootstrapped samples.

HBeAg-negative chronic 'infection' and 'hepatitis' is not entirely exclusive to co-infected patients.

The clinical implications of fluctuations between HBeAg-negative phases are uncertain. When focusing on HBV DNA replication specifically, longitudinal profiles of HBV replication have been assessed in the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus study among Asian HBV mono-infected patients.²³ Individuals with consistently higher HBV DNA replication over the course of up to 10 y had a significantly higher incidence rate of HCC, underscoring the clinical importance of persistent replication. We were unable to confirm these results in our study because of the small numbers of patients and limited follow-up time. Other studies on the continent linking HBV phase or, at the very least, HBV DNA replication and morbidity are needed to bring clearer information on disease trajectories.

No remarkable HBV mutations emerged in patients with fluctuating HBeAg-negative phases or in those consistently classified with HBeAg-negative chronic 'hepatitis'. Nonetheless, other interesting observations with regards to genetic variability during untreated infection could be made. First, dominant variants would appear stable for most patients, yet some exhibited changes in aa at certain positions over time. This 'transition' could be explained by natural changes in levels of highly prevalent quasispecies. The viral diversity of such patients would be worthwhile to investigate in future research given its deleterious association with serological outcomes.²⁴ Second, mutations conferring resistance to lamivudine have been found both as majority and minority quasispecies in newly infected patients.²⁵ Due to the overlapping structure of the HBV genome, these mutations correspond to vaccine escape mutations on the S gene, which are known to affect immunogenicity and anti-HBs

antibody binding and have serious public health implications vis-à-vis HBV vaccination.²⁶ Similar to previous cross-sectional studies,^{9,27} it is reassuring that no lamivudine-resistant HBV variants developed during follow-up.

One limitation of our study was that patients consistently classified with HBeAg-negative chronic 'hepatitis' had shorter follow-up time, and consequently fewer study visits, compared with other profiles. In fact, these patients could have belonged to the fluctuating profile group. However, follow-up mostly ended as patients initiated ART, and since these patients had several risk factors associated with HBeAg-negative chronic 'hepatitis', it would be likely that their HBV DNA viral loads and ALT levels would persist regardless of whether follow-up was extended. Second, patients with severely elevated transaminases or clinical signs of severe liver disease at inclusion were excluded, while those with occult HBV infection were simply not evaluated. This may have resulted in a study population with a limited spectrum of HBV-related disease. Third, an evaluation of liver fibrosis is required to firmly establish the HBeAg-negative phase.⁷ As liver biopsies or other non-invasive measures of liver fibrosis were unavailable, we could only rely on HBV DNA and ALT levels, which may not necessarily reflect long-term liver disease. Fourth, changes in HBV DNA could be due to the inherent variability of HBV DNA quantification by using an in-house PCR assay. Finally, we did not collect data on HDV serostatus, which is expected to be positive in 7–10% of the study population.²⁸ This could have resulted in an increased proportion of patients with higher transaminase levels and lacking HBV DNA replication.²⁹

In conclusion, HBV activity is common with HBeAg-negative status in HIV-HBV co-infected individuals from SSA, whose variation is partly linked to HIV replication. The rather large proportion of patients fluctuating between HBeAg-negative phases of HBV is rather concerning, given that their risk of morbidity and

mortality after ART initiation is difficult to assess. Although the further clinical implications of these fluctuating profiles is uncertain, our findings stress the need for early and continued anti-HBV treatment containing ART for the co-infected patient population in order to sufficiently control HBV replication. Whether similar fluctuations are observed among HBeAg-negative HBV mono-infected patients in SSA deserves further study.

Supplementary data

Supplementary data are available at Transactions online (<http://trstmh.oxfordjournals.org/>).

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3. CONCLUSION

3.1. Key findings for HIV-HBV co-infected individuals in SSA initiating ART

With the data available on both HIV and HBV replication in HIV-positive individuals enrolled in the Temprano trial, we were first interested in studying the effect of overall mortality in HIV-HBV co-infected patients at an earlier stage of HIV infection. Prior to this thesis, there were a number of studies examining the excessive risk of mortality in HIV-HBV co-infected patients (219). Overall, HIV-HBV co-infection clearly leads to a greater risk of both overall and liver-related mortality in the absence of treatment, but under anti-HBV containing ART, this risk seems to be diminished. Our study is likely the first to evaluate this research question at an early stage of HIV infection and more importantly, early ART initiation. We observed that despite effective and early treatment for HIV, there was an excess in mortality among particularly co-infected patients with a high HBV viral load (i.e., >2,000 IU/mL) compared to all other infection groups (320).

Interestingly, the main regimen given to participants of this trial was based on TDF. TDF-containing ART is known to suppress replication of HBV and with this reduction, help buttress HBsAg-seroclearance for a small subset of HIV-HBV co-infected individuals (146,154). Data from the VarBVa study, which was a more extensive evaluation of virological and serological makers of HBV in individuals undergoing anti-HBV containing ART in the Temprano trial, demonstrated that HBV-DNA suppression was extensive during TDF-containing ART (146) and that almost 12% of HIV-HBV co-infected patients exhibited HBsAg-seroclearance (323). The role of HBV-disease was then likely limited in contributing to the higher risk of mortality in HIV-HBV co-infected patients with elevated HBV DNA at baseline. On the other hand, since participants of the Temprano trial were not tested for liver damage, it is difficult to confirm this assumption. Generally, in the Temprano trial, the most frequent cause of morbidity and mortality was related to bacterial diseases (13) and a previous sub-study of the Trivacan trial

also showed a higher risk of bacterial related diseases for HIV-HBV co-infected individuals with high baseline HBV DNA replication who underwent anti-HBV containing ART (324). This cause of morbidity and mortality needs to be further clarified.

These intriguing results led us to determine why such an excess in mortality would exist despite effective treatment against both HIV and HBV. We demonstrated that HIV-HBV co-infected and HIV mono-infected patients did not have differences in immune decline when they were not undergoing ART, nor did they have a significantly different rate in immunorestitution, as defined by the increase in CD4+ cell count, when they were undergoing ART. Consistent with results from others conducted in patients with relatively high CD4+ cell counts in SSA, chronic HBV co-infection does not appear to alter immune responses after initiating combined ART (311,316,325). Nevertheless, this finding is in contrast to other studies, where patients were more immunocompromised and there was a much higher prevalence of individuals with HBeAg-positive serology and higher levels of HBV DNA replication (312,317). It has been shown in HIV-positive individuals with severe immunosuppression that HIV-HBV co-infection is associated with increased apoptosis of CD4+ T cells through increased T cell activation compared to HIV mono-infection (326,327), hence problems of immunorestitution could be due to the impaired function of anti-HBV specific immunity when CD4+ cell counts are low. Importantly, we demonstrated, albeit with low numbers of deaths, that the risk of overall mortality associated with HIV-HBV co-infection at high HBV DNA levels was strongest when CD4+ counts were below 500/mm³. This is one of the first analysis to be able to stratify the excessive risk of mortality due to HIV-HBV co-infection on CD4+ cell counts.

Finally, when ART is not given to HIV-HBV co-infected individuals, it could be speculated that HBV activity would change with increased lessening of CD4+ cell counts. We then assessed the natural history, i.e., HBV DNA and ALT activity, of chronic HBV infection in ART-naïve participants randomized to the deferred ART arms of the Temprano trial. We demonstrated that roughly half of patients exhibited fluctuations between HBeAg-negative chronic infection"

and” hepatitis”, which emphasizes the high degrees of variation in HBV activity for these patients. The variation in both HBV DNA and ALT levels were partly linked to HIV replication (312).

3.2. Clinical application of these findings to HIV-HBV co-infected individuals in SSA

As would be expected for any research endeavor, we intended that these results be used to improve the care of individuals co-infected with HIV and HBV. It is therefore important to translate our results in terms of how they can be applied to clinical settings. Prior to this thesis, one of the major advances in HIV-related care was the universal recommendation that ART be initiated soon after HIV diagnosis. Although it was well known that anti-HBV containing ART would also help suppress HBV DNA to undetectable levels, it remained unknown how HIV, or even HBV-related care would be affected with early ART, especially when CD4+ cell counts are high. With the results from our study, we are able to more fully address the following questions:

- As co-infected patients with high HBV DNA viral loads are at increased risk of overall mortality, regardless of receiving deferred and early ART, how should follow-up be conducted in these individuals?

First, it is important to test for HBsAg serology and HBV DNA when enrolling patients in care in order to assess their risk of mortality. Given that HBV DNA viral load is correlated to the risk of mortality; closer follow-up might be warranted. This would include looking for signs of liver disease in these patients. Of course, recommendations already suggest performing liver blood tests every 3 months during the first year after ART initiation and every 6-12 months thereafter (143). Given the high incidence of bacterial diseases with higher HBV DNA viral loads, emphasis should also be placed on assessing invasive bacterial infections and immediately treating these infections. Nevertheless, since we were unable to verify the cause of mortality

in our studies, more attention to the causes of death in future investigations will help determine which diseases would require more frequent monitoring.

- As co-infected patients did not have difficulties in immunorecovery during treatment, but did have higher mortality at lower CD4+ cell counts, what are the implications of therapy and appropriate follow-up?

We found that there was no difference in developing immunosuppression off ART or in immunorecovery during ART between HIV-HBV co-infected and HIV mono-infected patients. These data provide reassuring information that co-infected patients, even with high HBV DNA viral loads, can be effectively treated without concerns of poor immune reconstitution. We did, however, observe that the risk of death was substantially higher in HIV-HBV co-infected patients when their CD4+ cell counts were below 500/mm³. This finding confirms the urgency to start ART as soon as possible, particularly in co-infected patients. However, when co-infected individuals are undergoing care at lower CD4+ cell counts, there should be extra monitoring for these individuals until they reach adequate levels of CD4+. Once again, more detailed studies on the causes of morbidity and mortality would help understand what types of extra monitoring would be required.

- How stable are markers of HBV replication during the natural course of HIV-HBV co-infection (i.e., when HIV-positive individuals are not on ART)?

In SSA, the vast majority of individuals chronically infected with HBV are HBeAg-negative (321,328,329). Inactivity with HBeAg-negative patients is not always the case, as they can display large fluctuations in HBV DNA replication. Higher levels of baseline HIV RNA replication is associated with higher degrees of variation of HBV DNA replication during follow-up. This could make stratification of mortality risk, on the basis of HBV DNA, more difficult for individuals with higher HIV RNA viral loads. Lower % of CD4+ cells were associated with being consistently in the HBeAg-negative chronic “hepatitis” phase. Hence, co-infection with HIV could steer patients into more active forms of HBV infection. Delaying HIV treatment for those

co-infected could worsen liver disease. These findings highlight the importance of HBV monitoring before and directly prior to initiating ART containing TDF.

3.3. Research gaps still needing to be addressed in HIV-HBV co-infected individuals in SSA

Since we demonstrated a higher risk of mortality, even when HIV-HBV co-infected patients with high HBV DNA viral loads initiated treatment early, there are a number of remaining questions that need to be clarified for the HIV-HBV co-infected population in SSA. Furthermore, as the landscape of ART is still evolving, there are certain challenges that HIV-HBV co-infected individuals might face in the future. In the last chapter of the thesis, these remaining gaps in research will be discussed in more detail.

3.3.1. HIV- and liver-related disease in HIV-HBV co-infected individuals

Mortality in HIV-HBV individuals co-infected might be related to HIV, HBV, or both. In the era of early ART, patients are starting ART without any clinical evidence of HIV infection. Thus, if all HIV-positive individuals are tested and immediately initiate ART, the incidence of HIV-related morbidity and mortality would be expected to be very low.

There is conflicting evidence on whether HBV influences the progression of HIV-related disease (75,325), which might be simply due to differences in the proportion on effective therapy or differences in CD4+ cell counts at ART-initiation. With earlier ART initiation, it could very well be that the types of HIV-related diseases encountered, or diseases related to HIV-associated immunosuppression, are rather different than in most of these previous studies. The susceptibility to bacterial infections in co-infected patients with high HBV DNA replication, as evidenced in previous research, might be associated with some HIV-related factor. Understanding the underlying causes of these diseases would help improve knowledge on what needs to be monitored precisely and how often.

Liver-related disease is the main concern for individuals chronically infected with HBV infection. Since HBV-infection is acquired earlier in childhood in SSA, co-infected individuals will have already had lived with HBV infection for long periods of time and might have had a certain level of liver damage by the time they are infected with HIV. Even more concerning is that HIV-HBV co-infection is associated with an increased risk of liver cirrhosis, HCC, and liver-related mortality versus HIV mono-infected individuals (65,304,330). With the potent HBV suppression offered by TDF-containing ART (146,154), the levels of liver fibrosis are expected to decrease in both HBV mono-infected and HIV-HBV co-infected individuals alike (331,332). The reduction in histological activity will in turn lessen the risk of HCC (333–336) and HBV-related mortality in HIV-positive individuals (337).

However, there exist very few studies that have given an ideal picture of liver fibrosis and cirrhosis in TDF-treated HIV-HBV co-infected individuals from SSA (331,338), and virtually no studies exist on the progression of HCC and ESLD in this patient population. The risk of HCC is known to substantially differ between HBV genotypes (339), ethnicity (340), and exposure to other hepatotoxic agents, such as aflatoxin B1. Furthermore, the studies conducted to date on the impact of HBV genotypes have mostly involved genotypes A, B, C, and D, and as genotype E is predominant in west Africa, the implications of this genotype on HCC are poorly understood. More involved cohorts of both HIV-HBV and HBV mono-infected cohorts would help fill many of the current research gaps and help define more efficient monitoring strategies for these patients.

3.3.2. Effect of previous HBV infection

Thus far, we have only described HBV infection as a function of HBsAg-serostatus and HBV DNA replication. As described in Chapter 1, it is difficult to reduce HBV infection to these parameters, particularly in settings where HBV vaccination rates are far from universal levels and a large proportion of individuals are likely to have had HBV infection during childhood or

adolescence. Indeed, several markers are related to HBV infection, which can allow identification of individuals with resolved HBV infection, isolated anti-HBcAb status and OBI. The risk of these forms of HBV infection are practically unknown in SSA and in treated HIV-HBV co-infected patients worldwide. If there are indeed differences in immunorecovery and mortality rates between these profiles, this could help identify individuals with HBsAg-negative who are at risk of developing severe disease.

3.3.3. Therapeutic implications for HIV-HBV co-infected individuals

Given that the treatment paradigms are also slowly changing in HIV-positive individuals; this does leave some questions regarding HBV infection in SSA:

- **Removing the TDF/TAF component of ART:** TDF-containing ART has been the most widely used treatment for much of SSA (341,342). This treatment has been known to offer prophylactic effects against HBV acquisition (279,297). Certain individuals may be forced to no longer use TDF-containing regimens due to bone or kidney toxicities. For these individuals, TAF-containing ART would be an ideal option and would help maintain their protection against HBV infection. Other individuals may develop resistance to TDF/TAF and will no longer be able to use this regimen to suppress HIV replication and hence will no longer be protected against HBV. In HBV vaccinated individuals, this would normally not be considered a problem. However, the rates of non-immunized individuals are still high for much of SSA (208,343,344) and HIV resistant to TDF has been recently shown to be high on the continent (345). It remains questionable whether HBV vaccination will become more important in the future and if so, how HBV vaccination can be rolled out for HIV-positive individuals. This would likely require increased testing to establish non-immunized status. Furthermore, individuals who have had exposure to HBV or those with OBI would have severe forms of HBV reactivation when discontinuing the anti-HBV component of their ART (346,347). The extent of this issue should also be evaluated in future studies.

- **Switching to dolutegravir (DTG)/3TC dual therapy:** There has been a substantial interest in using dual DTG/3TC therapy to treat HIV-positive individuals, which have now become a part of international guidelines (142,348). There is a risk that HIV-HBV co-infected patients, whose status may be unknown or forgotten by their treating physician, are switched from a TDF-containing regimen to one with an anti-HBV agent with a lower barrier to genetic resistance, i.e., 3TC. The risk of developing 3TC resistant HBV variants is substantially high in 3TC-treated co-infected individuals (349). On the other hand, individuals with low HBV DNA replication and HBeAg-negative serostatus, which are mostly found in SSA, have a very low risk of developing 3TC resistant strains (146). It could very well be that switching to DTG/3TC could be a viable option for some HIV-HBV co-infected individuals. This would require, however, more extensive evaluation.
- **The challenge of using long-lasting injectables of HIV treatment in HIV-HBV co-infected individuals:** Long-lasting injectables, such as cabotegravir, have given hope for more manageable anti-HIV treatment. Unfortunately, this treatment has no anti-HBV effect and makes it complicated for HIV-HBV co-infected patients to use (as TDF is still required) (350). Currently, this treatment option is not available in LMIC, but as rollout of innovative treatments could soon occur in SSA, where HBsAg-positive prevalence is high, understanding the implications for co-infected individuals is needed.

3.3.4. Implications for research in HBV mono-infection

The target population studied in this thesis was HIV-HBV co-infected individuals. It could be argued that as these individuals have certain immunological impairments due to HIV-infection, inference of any results from this population would be difficult to extend to HBV mono-infected individuals. Nevertheless, our studies pose interesting questions related to HBV mono-infection:

- **Disease progression:** In SSA, little is known on the progression of HCC and ESLD. Furthermore, there are few studies examining to what extent late presentation of HBV-

infection occurs on the continent, apart from the few cross-sectional studies on severity of liver disease in HBV mono-infected individuals (351). As HBV infection occurs in youth or earlier, patients usually present to care later during adulthood and sometimes with very evident symptoms of ESLD. Since there is no systematic care for HBV mono-infection, as is the case with HIV, and care and treatment are excessively expensive and patients must pay out-of-pocket, observational, longitudinal cohorts in this setting are difficult to put in place.

- **Frequency of monitoring markers of HBV activity:** Although there are already elaborate clinical practice guidelines for chronic HBV infection and given the high costs of assessing HBV-related parameters, the frequency of these assessments is difficult to achieve. There are no standard procedures to monitor HBV infection for serological, virological or histological markers in resource limited settings, particularly from a cost-benefit perspective, and it could be that repeated monitoring individuals from the HBeAg-negative chronic infection phase might not need to be followed so closely. Still, given the rather high HBV activity in HBeAg-negative patients observed in our study, a more suitable timeline for monitoring patients needs to be determined.
- **Initiating HBV treatment:** As TDF decreases liver fibrosis and contributes further to the reduced risk of HCC, chronically infected patients with advanced disease need to initiate treatment. For all other infection stages, there remains a “gray zone” in which the specific conditions needing to be met for NA-treatment initiation are unknown. Further clinical studies have addressed what is termed “treatment eligibility” in SSA (352), but have only relied on criteria from the EASL guidelines to determine this eligibility.

The information provided in this thesis has given a deeper understanding in the management and treatment of HIV-HBV co-infected individuals. However, there is still much research needed. Understanding the underlying causes, both HIV- and liver-related, will help inform clinicians on what types of co-morbidities should be examined in routine care. The implications

of other HBV infection profiles on mortality also needs to be considered. Meanwhile, the new treatment strategies for HIV-positive individuals cannot ignore the specificities required when treating HIV-HBV co-infected patients. Together with increasing protection against HBV infection (through anti-HBV containing ART or vaccination), we can further understand how to eradicate HBV in SSA for both HIV-HBV and HBV infected populations.

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Titre : Conséquences de l'infection par le VHB chez les personnes séropositives en Afrique subsaharienne à l'ère du traitement antirétroviral précoce

Introduction : En Afrique subsaharienne la co-infection VIH-VHB est encore un problème de santé publique, même à un moment où les ARV sont universelles. Nous avons étudié les conséquences de l'infection par le VHB chez les personnes VIH+ à l'ère du traitement antirétroviral précoce. **Méthodes :** À partir des données de l'essai Temprano ANRS 12136, nous avons effectué trois analyses pour évaluer chez les co-infectés VHB-VIH (1) le risque de mortalité, (2) la mortalité en fonction du taux de CD4 et (3) la répllication virale B et la fluctuation des ALAT chez les individus AgHBe négatifs naïfs de traitement. **Résultats :** 2052 (99,8%) ont été inclus dans cette analyse, 1862 (91%) étaient mono infectés par le VIH et 190 (9%) co-infectés par le VIH / VHB. Parmi ces derniers, 135 (71%) avaient une charge virale du VHB <2 000 UI / ml et 55 (29%) \geq 2 000 UI / ml. L'étude de la mortalité a montré que : Les patients co-infectés VIH-VHB qui ont une forte charge virale VHB > 2000 UI/ml ont une mortalité trois fois plus élevée comparée aux patients non co-infectés, ou avec une charge virale B VHB < 2000 UI/ml. L'étude de l'activité du virus de l'hépatite B chez les patients co-infectés naïfs de traitement a montré que la quantification de l'AgHBs était stable pendant le suivi pour la plupart des patients, quel que soit le profil d'activité AgHBe-négatif du VHB. Le taux d'ALAT était très variable au cours du suivi, la majorité des poussées d'ALAT supérieures à deux fois la limite supérieure de la normale (> 70 UI / L) survenant chez des patients systématiquement classés avec une « hépatite » chronique AgHBe négative (60,0 %) ou celles oscillant entre « infection » chronique AgHBe négatif et « hépatite » (38,1%). L'étude de la mortalité en fonction du taux de CD4 a noté que l'incidence ajustée de la mortalité était comparable entre les individus AgHBs positifs et AgHBs négatifs lorsque les CD4 étaient > 500/mm³ (RTI ajusté = 0,85, IC à 95% = 0,13-2,95). Cette différence est devenue plus apparente lorsque le nombre de CD4 atteignait 350-500 / mm³ (IRR ajusté = 1,51, IC à 95% = 0,34-4,46) ou <350 / mm³ (IRR ajusté = 2,10, IC 95% = 0,84-4,53). **Conclusion :** En Afrique subsaharienne, nous avons montré que les adultes infectés par le VIH et atteints d'hépatite B chronique restent une population à risque accru de mortalité malgré un traitement antirétroviral précoce, même pour ceux qui sont traités à un stade précoce de l'infection par le VIH.

Mots clés : co-infection VIH-VHB, réponse immunitaire, mortalité, Afrique subsaharienne

Title: Consequences of HBV infection in HIV-positive individuals in Sub Saharan Africa during the era of early antiretroviral therapy

Background: In Sub Saharan Africa HIV-HBV co-infection is still a public health concern, even at a time when ART are universal. We study the consequences of HBV infection in HIV-positive individuals during the era of early antiretroviral therapy. **Methods:** From the Temprano ANRS 12136 trial database, we conducted three analyses to evaluate in co-infected patients: (1) the risk of mortality, (2) the immune recovery, and (3) HBV DNA replication and ALT fluctuation in hepatitis B "e" antigen negative individuals and the dispersion of these two markers. **Findings:** 2052 (99.8%) were included in this analysis, 1862 (91%) were mono infected with HIV and 190 (9%) co-infected with HIV / HBV. Of these, 135 (71%) had an HBV viral load <2000 IU / ml and 55 (29%) \geq 2000 IU / ml. the study of mortality shown that HIV-HBV co-infected patients who have a high HBV viral load > 2000 IU / ml have a mortality three times higher compared to patients not co-infected, or with an HBV B viral load <2000 IU / ml. In the study of hepatitis B virus activity in co-infected treatment-naïve patients, the quantification of HBsAg was stable during follow-up for most patients, regardless of the HBeAg-negative activity profile HBV. The level of ALT was highly variable during follow-up, with the majority of ALT surges above twice the upper limit of normal (> 70 IU / L) occurring in patients consistently classified with "hepatitis" chronic HBeAg negative (60.0%) or those oscillating between chronic HBeAg negative "infection" and "hepatitis" (38.1%). In the study of mortality as a function of CD4 count, the adjusted incidence of mortality was comparable between HBsAg positive and HBsAg negative individuals when the CD4 + cell count was > 500 / mm³ (adjusted RTI = 0.85, 95% CI = 0.13-2.95). This difference became more apparent when the CD4 count reached 350-500 / mm³ (adjusted IRR = 1.51, 95% CI = 0.34-4.46) or <350 / mm³ (adjusted IRR = 2.10, 95% CI = 0.84-4.53). **Conclusion:** In sub-Saharan Africa, we have shown that adults infected with HIV with chronic hepatitis B remain a population at increased risk of death despite early antiretroviral therapy, even for those treated at an early stage of infection with HIV.

Key words: HIV-HBV co-infection, immune recovery, mortality, sub-saharan Africa